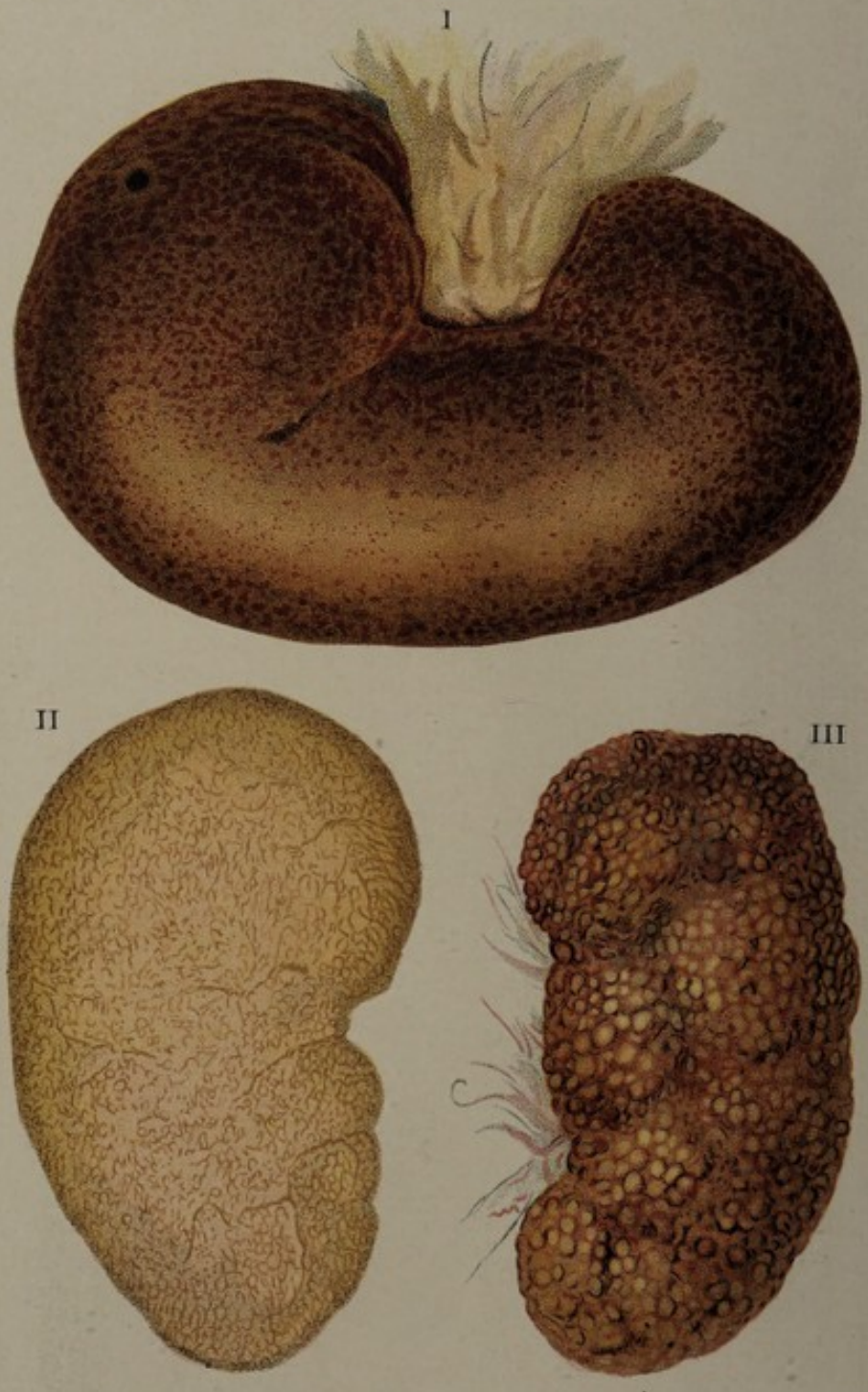
Diseases of the kidneys and of the spleen : hemorrhagic diseases / by Dr. H. Senator and Dr. M. Litten ; edited with additions by James B. Herrick ; authorized translation from the German, under the editorial supervision of Alfred Stengel.

PLATE I.



I. Acute hemorrhagic nephritis (see p. 187).
II. Chronic parenchymatous nephritis (see p. 231).
III. Chronic interstitial nephritis (see p. 266). (From Rosenstein, *Pathologie und Therapie der Nierenkrankheiten.*)

Nothnagel's Practice

DISEASES OF THE KIDNEYS AND OF THE SPLEEN

HEMORRHAGIC DISEASES

BY

DR. H. SENATOR

Professor of Internal Medicine, University of Berlin

AND

DR. M. LITTEN

Professor of Internal Medicine, University of Berlin

EDITED, WITH ADDITIONS

BY

JAMES B. HERRICK, M.D.

Professor of Medicine, Rush Medical College, University of Chicago

---

AUTHORIZED TRANSLATION FROM THE GERMAN, UNDER THE EDITORIAL SUPERVISION OF

ALFRED STENGEL, M.D.

Professor of Clinical Medicine in the University of Pennsylvania

---

PHILADELPHIA AND LONDON

W. B. SAUNDERS & COMPANY

1905

PRESS OF
W. B. SAUNDERS & COMPANY
PHILADELPHIA

PREFACE.

THE excellence of the series of monographs issued under the editorship of Professor Nothnagel has been recognized by all who are sufficiently familiar with German to read these works, and the series has found a not inconsiderable proportion of its distribution in this and other English-speaking countries. I have so often heard regret expressed by those whose lack of familiarity with German kept these works beyond their reach, that I was glad of the opportunity to assist in the bringing out of an English edition. It was especially gratifying to find that the prominent specialists who were invited to co-operate by editing separate volumes were as interested as myself in the matter of publication of an English edition. These editors have been requested to make such additions to the original articles as seem necessary to them to bring the articles fully up to date and at the same time to adapt them thoroughly to the American or English reader. The names of the editors alone suffice to assure the profession that in the additions there will be preserved the same high standard of excellence that has been so conspicuous a feature in the original German articles.

In all cases the German author has been consulted with regard to the publication of this edition of his work, and has given specific consent. In one case only it was unfortunately necessary to substitute for the translation of the German article an entirely new one by an American author, on account of a previous arrangement of the German author to issue a translation of his article separately from this series. With this exception the Nothnagel series will be presented intact.

ALFRED STENGEL.

WELLCOME INSTITUTE
LIBRARY
Coll.
Call
No.

EDITOR'S PREFACE.

SENATOR'S book on *Diseases of the Kidney* has always seemed to me a model. Clear in style, systematic in arrangement of facts, logical in reasoning, not prolix, and with a due sense of proportion, it leaves little to be desired. So when a Second Edition appeared, bringing the subject well up to date, I gladly consented to edit the volume. The immense literature of diseases of the kidney has been so carefully gone over by Senator and so well digested (he is so sensible and conservative in his own views—that are based on a careful study of this literature as well as on a vast personal experience) that one finds little to add and little to criticize. I have ventured, however, here and there to emphasize or enlarge upon certain points, especially such as are of value to the practitioner—points on Treatment, Diagnosis, Urinary Analysis, etc. I have referred briefly to the Surgical Treatment of Nephritis, though perhaps Senator's silence concerning this topic is a more forceful condemnation than my own spoken words. I have added also a few pages on the Theory and Value of Cryoscopy and Phloridzin Glycosuria, as aids in determining the functional power of the kidney. A few plates and figures have been inserted. The microphotographs are from preparations kindly made for me by Dr. E. R. LeCount.

As the volume on the kidney would, alone, be much smaller than the others in the series, I—somewhat reluctantly—consented to include the section on Diseases of the Spleen and the Hemorrhagic Diseases. While many views concerning the Anemias, Leukemia, Malaria, and other diseases here considered have changed since Litten wrote, it seemed wisest and best to let his words stand as he penned them. Brief additions had to be made regarding the more recent views concerning Malaria and the Relation of the Mosquito to its causation, regarding Splenic Anemia, Congenital Icterus with Splenomegaly, the *X*-ray in the Treatment of Leukemia, etc. Much more would have been said had it not been realized that the object of the volume was to present these diseases from the standpoint of the *spleen* and not the blood, and also that there was in preparation the volume on the *Blood*, edited by Dr. Stengel, in which the blood features would be gone into in detail. It

is important for the practitioner to study the spleen from the standpoint of diagnosis. The spleen is too often overlooked by the physician, even in his routine examinations. Litten's work will help one to appreciate the value of a study of this organ.

While no order has yet been brought out of the chaos we call the Hemorrhagic Diseases or the Purpuric Diseases, either by Litten or any one else, Litten's work on this topic is worth careful study and will be of great help in understanding these perplexing conditions. A short chapter on Infantile Scurvy has been added.

I desire to express my obligations to Dr. R. T. Woodyatt for great help in the preparation of the volume.

JAMES B. HERRICK.

CHICAGO, June 29, 1905.

CONTENTS

DISEASES OF THE KIDNEY

By Prof. Dr. H. Senator

DISEASES OF THE SPLEEN

By Prof. Dr. M. Litten

HEMORRHAGIC DISEASES

By PROF. DR. M. LITTEN

DISEASES OF THE KIDNEY.

By PROF. DR. H. SENATOR.

DISEASES OF THE KIDNEY.

GENERAL PORTION.

HISTORIC INTRODUCTION AND PRELIMINARY CONSIDERATIONS.

ALTHOUGH inspection and examination of the urine, the excretory product of the kidneys, had been practised by physicians since time immemorial, the knowledge of diseases of the kidney during the earlier ages of medicine and down to the nineteenth century continued to be incomplete and very defective. This knowledge possessed by the ancients was limited, so far as appears from the writings of Hippocrates, to injuries, suppuration of the kidney, the existence of renal calculi, and the doctrine that a diminution in the quantity of urine is a cause of dropsy. Later it was stated by Aëtius and Avicenna that dropsy develops in the course of induration of the kidney. Individual cases of kidney disease reported by Schenck, Bonet, Morgagni, J. P. Frank, Portal, and others added but little to the store of renal pathology, although observations in regard to the coincidence of dropsy with changes in the kidneys gradually became more and more numerous. But even Sauvages, while he knew that anasarca might occur as the result of vesical calculi, was not aware that ascites might be caused by kidney disease. Even Cotugno's[1] important discovery in 1770 of a substance coagulable by heat—albumin—in the urine of individuals suffering from dropsy and diabetes resulted merely in the subdivision of dropsy into a form with, and one without, albuminuria (Cruikshank).

Further progress was made when Brande,[2] and later Scudamore,[3] demonstrated that albuminous urine contains a very small amount of urea.

A decisive change was first introduced by R. Bright, a physician at Guy's Hospital. After Alison, of Edinburgh,[4] had announced in 1823 that he had found indurated nodular kidneys in a number of cases of dropsy with albuminuria, Bright made the definite statement in a series of papers,[5] the first of which appeared in 1827, that many forms of

[1] *De ischiade nervosa commentarius*, Vienna, 1770, p. 24.

[2] *An Account of Some Changes from Disease in the Composition of Human Urine*, London, 1807.

[3] *A Treatise on the Nature of Gout*, etc., London, 1823, p. 313.

[4] After P. Rayer, *Traité des maladies des reins*, 1, ii., Paris, 1840, p. 543.

[5] *Reports of Medical Cases*, i., 1827, ii., 1831; *Guy's Hosp. Rep.*, 1836, 1840, and 1843.

dropsy owe their origin to a disease of the kidney manifesting itself by the presence of albumin in the urine. The investigation of this class of diseases at once engaged the zealous attention of physicians, who eagerly availed themselves of the microscopic and chemical methods of examination which were being rapidly developed at that time. The knowledge of the minute structure of the kidneys and of their function expanded at a rate hitherto unheard of, and along with it the field of renal pathology.

The progress in the latter department served to increase our knowledge not only of the kidney diseases that were at first grouped under the name of "Bright's disease," and later divided into a number of different forms, but also of the other affections of the kidney, such as tumors, displacements, and the like. The pathology of the kidneys, which up to that time had been treated in a most step-motherly fashion, now began to form the subject of detailed essays and monographs. The first systematic treatise on diseases of the kidneys is found in P. F. O. Rayer's classic work in three volumes, entitled *Traité des maladies des reins*, etc., Paris, 1839–41. He was followed in England by G. Johnson, *On the Diseases of the Kidney*, etc., London, 1852; in Germany by Julius Vogel, "Krankheiten der harnbereitenden Organe," in *Virchow's Handbuch der speciellen Pathologie*, vol. vi., Erlangen, 1856–65; and especially by S. Rosenstein, *Die Pathologie und Therapie der Nierenkrankheiten*, ed. i., Berlin, 1863, and ed. iv., 1894.

These authors were followed by a large number of other workers, and to-day the literature on diseases of the kidneys in general is fully abreast of that pertaining to other diseases.

[It will well repay the student to read Bright's original papers and see how our later knowledge of diseases of the kidney really started. One is surprised to note the accuracy of the clinical observations and of the postmortem records. Bright's plates, too, showing pathologic conditions—like those in Rayer's Atlas—are faithful and artistic portraitures, the excellence of which has seldom been surpassed.—Ed.]

As the kidneys are hidden deep within the tissues, they are not readily accessible to direct examination by inspection and palpation or other physical methods, and the changes in the urine are therefore of the greatest importance for the recognition of renal disease. Some of these changes belong only to certain diseases, others are common to all, or, at least, a large number of renal affections. Thus the excretion of albumin or blood in the urine—*albuminuria*, *hematuria*—may occur in any disease of the kidneys; and certain phenomena and pathologic conditions, such as *urinary tube casts*, *dropsy*, *uremia*, and the *changes in the vascular apparatus*, are especially characteristic of kidney disease. In order to avoid repetition in the description of the individual diseases, I shall begin with a general description of these common symptoms or effects of renal disease, and shall then discuss a number of other morbid conditions which also manifest themselves by conspicuous changes in the urine, and which, while they do not bear the same causal relation to kidney disease as the above symptoms, cannot, in the present state of

our knowledge, be attributed with certainty to disease of any other organ, and are therefore regarded rather as independent forms of disease. The affections referred to are *hemoglobinuria*, *lipuria* and *chyluria*, *oxaluria* and *phosphaturia*.

ALBUMINURIA AND ALBUMOSURIA.

Albuminuria—that is, the occurrence in the urine of albumin in solution—may be due to the admixture of albumin or albuminous fluids, such as blood, pus, spermatic fluid or tumor juices, with the urine that was free from albumin as it came from the kidneys; or by the entrance of albumin into the urine within the uropoietic portions of the kidney, the glomeruli and uriniferous tubules, so that the urine already contains albumin when it escapes from the kidneys into the passages leading from the kidney. In the former case we speak of *spurious* or *false albuminuria* (*albuminuria spuria*, pseudo-albuminuria), while the second variety is designated *true* or *genuine albuminuria* (*albuminuria vera*, *renalis*) or simply "albuminuria." [The first variety might also be termed infrarenal, as the albumin enters the urine below the kidney proper.—Ed.]

The **distinction between spurious and true albuminuria** usually presents no difficulties; for fluids that enter the urine after it has left the tubules of the kidney, in addition to containing a variable quantity of cellular elements, usually settle at the bottom of the vessel on standing or on centrifugalizing, and the supernatant layer of urine, which is clear or can be rendered so by filtering, is either free from albumin or contains only a minute quantity, out of all proportion to the number of cellular elements found in the sediment.

According to Goldberg,[1] when the admixture consists only of pus, and the albumin present is mechanically mixed with the urine—in other words, when there is spurious albuminuria—the relation between the quantity of albumin, as determined with Esbach's albuminometer, and the number of pus corpuscles contained in 1 c.mm., as counted with the apparatus of Thoma-Zeiss, is less than about 1 : 50,000—that is to say, if there are 50,000 pus corpuscles in a cubic millimeter of the sediment, and the albumin contained in the clear fluid above is more than 1 part in 1000, the albuminuria is not due solely to the admixture of pus. (See also Hematuria.) This method is, of course, not exact, since the counting of the pus corpuscles itself is subject to inaccuracies and the pus cannot be uniformly distributed in the urine, and, finally, Esbach's albuminometer gives only an approximately accurate result; but in favorable cases the method is of some value in deciding whether the albuminuria is genuine or spurious.[2]

The kind of albuminuria present can also be determined by examining the sediment microscopically for the presence of cells and other tissue elements that do not belong to the kidney. It is to be remembered that the occurrence of true pus corpuscles (multinuclear leukocytes),

[1] *Centralbl. f. die med. Wissenschaften*, 1893, No. 36.
[2] S. K. Reinecke, *Berlin. klin. Woch.*, 1895, No. 49.

particularly in large numbers, is against a renal albuminuria; since, as the writer has shown, the sediment in simple uncomplicated nephritis, while it contains some leukocytes of a different variety, is devoid of true pus corpuscles, or contains only a negligibly small number of these elements.[1] A combination of true and false albuminuria—as, for example, when nephritis and cystitis are both present—is recognized, as will appear from what has been said, by the fact that the filtered urine contains a *large* quantity of albumin. When, however, the renal affection is attended by only slight albuminuria—as, for example, in certain cases of contracted kidney—its recognition when associated with some other disease, such as a cystitis, may present greater difficulties. But in such cases symptoms referable to other organs, the heart and blood-vessels or the retina, and other properties of the urine, such as increased quantity with lowered specific gravity and the presence of casts, will point to the presence of a kidney lesion. It will rarely be necessary for diagnostic purposes to resort to a method proposed by Thompson, which consists in thoroughly flushing out the bladder and collecting the urine from the kidneys, by means of the catheter, before it becomes mingled with the contents of the bladder. [In certain cases, however, ureteral catheterization might be of great help in showing whether the urine from the kidneys is free or not from pus and albumin.—Ed.]

In *true* or *renal albuminuria*, with which we are exclusively concerned in the present work, the albumin excreted in the urine is in the large majority of cases coagulable by heat, and cannot be distinguished from the albumin contained in blood-serum, *serum-albumin* (*serin*), *serum-globulin* (*paraglobulin*), and *nucleo-albumin*. The first usually predominates over the other two. In very rare cases only one of these three albuminous substances has been found in the urine, and such cases are therefore designated as simple *serinuria*, *globulinuria*, and *nucleo-albuminuria* respectively.[2]

The relation between the two substances in ordinary cases of albuminuria, which is designated by F. A. Hoffmann as the "albumin quotient" (serin-globulin), is extremely variable, and frequently differs not only from the quotient of *normal* blood-serum, which is 1.5–2, but also from the quotient of serum in disease and of the blood-serum of the same individual from whom the urine is obtained. There is nothing

[1] Senator, in *Virchow's Archiv*, cxxxi., 1893, p. 385. See also Reinecke, *loc. cit.*, and Diss. inaug., Jena, 1894.

[2] Serinuria was observed by F. A. Hoffmann in the case of a woman suffering from cancer of the stomach (*Virchow's Archiv*, vol. lxxxix., p. 271); by Pichler and Vogt after compression of the extremities (*Centralbl. f. inn. Med.*, 1894, No. 17); by F. D. Boyd (*Report of the Royal College of Physicians*, Edinburgh, 1894), in four cases of subacute and chronic nephritis, on occasional days; and by J. Strauss (Diss. inaug., Strassburg, 1895). Globulinuria was observed by Werner (*Deutsch. med. Woch.*, 1893, No. 46) in a case of acute nephritis; by Maguire (*Lancet*, 1886, p. 1082) in the case of a puerperal woman; and by M. Matthes in the case of a leukemic woman (*Berlin. klin. Woch.*, 1894, No. 24). Simple "nucleo-albuminuria" was observed by J. Strauss (*loc. cit.*) in chronic interstitial nephritis and in urine from a congested kidney in a case of emphysema. According to Estelle and Faveret (*Revue des sciences méd.*, 1882, No. 11), serinuria or globulinuria can be produced experimentally by injecting serin or globulin. The statements of earlier authors are untrustworthy, because they probably confounded globulin with nucleo-albumin.

wonderful about this, however, as aside from other causes it is to be remembered that all the albumin contained in the urine is not necessarily derived from the blood-serum.

Csatáry[1] believed that the velocity in the glomeruli of the kidneys lowers the percentage of globulin contained in the urine, and that accordingly the albumin quotient rises as the total quantity of urine is increased. On the other hand, it has been shown by Cloëtta[2] that the albumin quotient depends not on the pressure and velocity of the blood-stream, but on the structure of the membranes; if the latter are unusually dense, less globulin will pass through, and the quotient will accordingly be greater. Judging from our present stock of observations, the greatest percentage of globulin is found in the urine of acute nephritis, in the urine modified by circulatory engorgement, and among chronic renal diseases in amyloid degeneration (*q. v.*).[3]

Nucleo-albumin was formerly confounded with so-called "mucin" and even with globulin, and its occurrence in the urine has only within recent times become a subject of investigation. K. Mörner[4] has shown that the substance found by the usual methods to be "nucleo-albumin" is really albumin in combination with substances that precipitate albumin. It is probable, therefore, that everything that has been written about "nucleo-albuminuria" refers to such combinations of albumin, and not to true nucleo-albumin.

As, however, nucleo-albumin is one of the principal constituents of cells and is also present in large quantities in the kidneys, it is to be presumed *à priori* that nucleo-albumin occurs chiefly during active destruction of the renal epithelium, as in certain forms of acute (desquamative) nephritis.

F. Obermayer[5] also found nucleo-albuminuria regularly in jaundice and after the ingestion of substances that are capable of injuring the renal epithelium; K. Pichler and V. Vogt,[6] after the renal artery had been compressed for a short time, sometimes in association with ordinary albumin. In jaundice the "nucleo-albumin" in the urine may exceed in quantity the other forms of albumin. A. Kossler[7] observed a true "nucleo-albuminuria" with casts in a number of renal affections, and correctly refers its origin to the renal epithelium. (See Urinary Casts.) "Nucleo-albumin," however, also occurs in the blood, as J. Strauss has shown[8]; and, as he and the author have demonstrated, it is also found in transudates. It is therefore quite possible that, like other forms of albumin, it passes from the blood into the urine. However, a very marked "nucleo-albuminuria," and even more so an exclusive

[1] *Deutsch. Archiv f. klin. Med.*, 1891, xlvii. and xlviii.

[2] *Arch. f. exper. Path.*, etc., xlii.

[3] F. D. Boyd (*loc. cit.*) also found relatively large quantities of globulin in the albumin of a pregnant woman; very little more, however, than is found in amyloid disease. He does not state the cause of the albuminuria.

[4] *Skandin. Arch. f. Physiol.*, vi., 1895, p. 332.

[5] *Centralbl. f. klin. Med.*, 1892, No. 1. See also D. Sarzin's dissertation on the "Excretion of Nucleo-albumin in the Urine," Berlin, 1894, written at the author's suggestion.

[6] *Centralbl. f. klin. Med.*, 1894, No. 17.

[7] *Berlin. klin. Woch.*, 1895, No. 14.

[8] *Loc. cit.*

"nucleo-albuminuria," indicates active destruction of renal epithelium. (See also Albuminuria in the Newborn.)

Ad. Ott[1] considers "nucleo-albumin" a constant constituent of urine; but, as the author has already said, K. Mörner no doubt correctly interprets this finding as applying to the albumin which normally occurs in the urine in combination with substances that have the power of precipitating albumin. In catarrh of the renal passages, the mucus of the urine probably contains true nucleo-albumin in many instances.[2]

In addition to the forms of albumin that have been referred to, and which coagulate on boiling, other albuminous substances occur either alone or in conjunction with other forms of albumin that do not coagulate on boiling, and in this respect, as well as in certain other properties, more nearly resemble the albumins elaborated during digestion. As all the albumins of the latter class were formerly designated "peptones," the term *peptonuria* was applied to the excretion in the urine of such forms of albumin as resemble peptones. Since, however, W. Kühne's investigations taught us to distinguish the last product of albumin digestion from the first and intermediary products, *propeptones* or *albumoses*, and the term *peptone Kühne* was applied to true peptone, the excretion of the latter body in the urine was distinguished under the term *peptonuria* in a narrow sense from propeptonuria or *albumosuria*.

I. **Peptonuria** in the narrow sense, or the excretion of peptone Kühne, occurs practically only in extremely rare cases, except after experimental injection, as numerous investigations[3] have demonstrated. The substance which was regarded as true peptone (Kühne) was in all probability one of the albumoses, the varieties of which are difficult to distinguish from one another and from peptone Kühne. It is asserted by Midori Ito,[4] however, that he found true peptone in very small quantities in association with albumoses in various diseases, more particularly in croupous pneumonia.

II. **Albumosuria** or **propeptonuria,** also called peptonuria in the older sense. Two varieties are to be distinguished. The first consists in the excretion of a peculiar substance, first found in the urine by Bence-Jones,[5] which, according to the investigations of A. Magnus-Levy,[6] differs from the albumoses in certain essential points and more closely resembles the albumins, although it also shows some difference from the latter which precludes its being included in the same group. In the second form, which is much more common, substances that are unquestionably albumoses and usually possess the properties of deutero-albumose are excreted.

(*a*) *Bence-Jones Albumosuria or Albuminuria.*—This condition has

[1] *Prager Zeits. f. Heilk.*, 1895, xvi.

[2] See H. Citron's dissertation, "Ueber Mucin im Harn," written under the author's direction, Berlin, 1886, and J. Strauss, *loc. cit.*

[3] *E. g.*: E. Stadelmann, "Untersuchungen über die Peptonurie," Wiesbaden, 1894; H. Senator, *Deutsch. med. Woch.*, 1895, No. 14; Sior, *Jahrb. f. Kinderheilk.* xxxvii.

[4] *Deutsch. Arch. f. klin. Med.*, 1901, lxxi.

[5] *Philos. Trans. of the Royal Soc.*, 1848, i.

[6] Hoppe-Seyler's, *Zeits. f. physiol. Chem.*, 1900, xxx.

been observed in only a dozen cases up to the present time.[1] So far as autopsy and clinical symptoms show, all the patients concerned were suffering from a grave disease of the osseous system, usually associated with marked anemia; this disease was first regarded as osteomalacia, but later was found to be of the nature of myeloma, or lymphoma and lymphosarcoma. The occurrence of this form of albuminuria in osteomalacia was recently[2] observed in a single case. At all events, it may be concluded from existing observations that the occurrence of the Bence-Jones albuminous body in the urine indicates some grave disease of the bones.

G. Zülzer succeeded in producing experimentally a severe anemia with transitory Bence-Jones albumosuria by poisoning a dog with pyrodin.

The quantity of Bence-Jones albumin in the urine varies between ¼ in 1000 to almost 7 per cent., and the quantities excreted during twenty-four hours vary between 30 and 36 gm. (Magnus-Levy) and 70 gm. (Bence-Jones). The fact that excretion is very active is against the assumption that the substance is derived from diseased bone, and rather suggests that it is an abnormal metabolic product of the albumin ingested with the food (Noël Paton, Magnus-Levy).

(*b*) *True albumosuria* consists in the excretion of albuminous bodies practically identical with true albumoses—that is, the substances preceding peptone in the digestion evolution of albumin, especially deutero-albumoses. As early as 1882 the writer[3] called attention to the fact that it occurs not so very infrequently in various morbid conditions, although before that time the occurrence in the urine of a form of albumin not coagulable by boiling had been noticed in a few isolated cases. Since then albumoses have often been demonstrated in the urine; and in this respect this true albumosuria is distinguished from that of Bence-Jones's, which, as has been stated, is extremely rare. The quantity of albumoses excreted in the urine is in general much less than the quantity of Bence-Jones albumin. The albumoses contained in fresh urine before decomposition has set in may be derived from the blood like albumin itself, or from substances containing albumose that enter the urine after it has left the kidney proper, such substances, for example, as spermatic fluid, pus, and the products of tissue degeneration.

The consideration of this form, called *albumosuria spuria* in analogy to albuminuria, need not be discussed in this place.

[F. Parkes Weber,[4] in 1903, was able to collect 28 cases that he regarded, upon critical analysis, as undoubted instances of Bence-Jones albumosuria. Abstracts of most of these cases had been previously

[1] To the cases collected by Magnus-Levy down to the year 1900 a case of L. Hugounenq (*Lyon méd.*, 1901, No. 3) is to be added. It is that of a physician, fifty-five years of age, who was taken ill with severe anemia, and, according to the author's informant, developed a tumor on the chest about two and a half months before death. The urine did not become cloudy on the application of heat, but in many other respects was identical with the urine in Bence-Jones albumosuria.

[2] Jochmann and Schumm, *Münch. med. Woch.*, 1901, No. 34.

[3] H. Senator, *Die Albuminurie*, 1st ed., Berlin, 1882, p. 10.

[4] "Multiple Myeloma with Bence-Jones Proteid in the Urine," *Am. Jour. Med. Sci.*, vol. cxxvi., No. 4, Oct., 1903.

given in a paper by C. E. Simon.[1] Weber concludes that Bence-Jones albumosuria is always the result of disease of the bone-marrow, the large number of instances of its association with multiple myeloma being striking. Secondary or metastatic tumors in the bone-marrow appear not to cause it. The association of certain nervous phenomena and the appearance of the Bence-Jones body in the urine has been several times noted (*cf.* Anders and Boston, London *Lancet*, Jan. 10, 1903).

Another interesting observation in connection with this peculiar substance has been made by Coriat,[2] who found the Bence-Jones body in the pleuritic effusion from a patient with alcoholism, polyneuritis, delirium, tenderness over the ribs, and anemia. The urine failed to show the Bence-Jones albumose.—Ed.]

True albumosuria (*albumosuria vera*) occurs principally when the blood is flooded with albumoses; and the latter substances in turn are due to one of two causes: (1) the abnormal passage of albumoses from the gastro-intestinal tract into the blood—*alimentary* or *enterogenous albumosuria*, and (2) the disintegration of cells, particularly of leukocytes, in the blood itself, in the parenchyma of the tissues, or in hemorrhagic and purulent exudates from which the albumoses make their way into the blood—*hematogenous* and *histogenetic albumosuria*.

1. *Alimentary* or *enterogenous albumosuria* has been observed after the administration of large quantities of artificial foodstuffs given as substitutes for albuminous food, and usually containing an abundance of albumoses. When an ulcerative process is going on in the digestive tract, Chvostek and Stromayer[3] assert that the ingestion of small quantities—from 40 to 60 gm. (say from 1–2 oz.)—of albumose suffice to produce an albumosuria. Hence, if such a test turns out positive and other symptoms are present this would be in favor of the existence of an ulcerative process in the gastro-intestinal canal, although a negative result cannot be regarded as a proof of the contrary.

2. It is probable the term *hematogenous* or *histogenetic albumosuria* should be applied to the form which occurs in a great variety of febrile diseases, especially in fibrinous pneumonia, purulent meningitis, empyema, and pyemic and other similar processes.[4] [The albumose in these diseases is by some regarded as due to the direct influence of the microorganism upon the body (*cf.* Harris, *Amer. Jour. Med. Sci.*, cxi.).—Ed.] L. Krehl and M. Matthes[5] go so far as to assert that the urine of a febrile individual always contains albumose, which disappears as the fever subsides; but the investigations by Finigan in the author's clinic failed to confirm the observation that albumoses occur constantly in the urine of febrile individuals.[6] This form of albumose, like the deutero-

[1] "Observations on the Nature of the Bence-Jones Albumin," *Am. Jour. Med. Sci.*, vol. cxxiii., No. 6, June, 1902.

[2] "The Occurrence of the Bence-Jones Albumin in a Pleuritic Effusion," *Am. Jour. Med. Sci.*, vol. cxxvi., No. 4, Oct., 1903.

[3] *Wien. klin. Woch.*, 1896, No. 47.

[4] S. Robitschek, *Zeits. f. klin. Med.*, xxiv., p. 566; Stadelmann, *loc. cit.*; H. Senator, *Deutsch. Med. Woch.*, 1895, No. 14; Br. Leick, *ibid.*, No. 2. Ito, *loc. cit.*

[5] *Deutsch. Arch. f. klin. Med.*, liv., p. 501.

[6] Diss. inaug., Berlin, 1902.

albumoses produced during digestion, causes fever when injected subcutaneously into guinea-pigs.

This group includes also the albumosuria which occurs in various *febrile and non-febrile infections and intoxications*, such as septicopyemia, acute yellow atrophy of the liver, gangrene, phosphorus-poisoning, after the injection of tuberculin, and in other similar conditions. "Peptonuria" or albumosuria, which, according to Fischel, occurs during pregnancy, and especially during the puerperium as a result of involution of the uterus, as well as the albumosuria that is occasionally observed in leukemia, scurvy, and other grave diseases of the blood, also belongs in this category.[1]

Albumosuria, with or without albuminuria, has further been observed by Köppen and by Meyer and Meine[2] in various acute and chronic *psychoses;* and probably has the same origin and significance as the albumosuria which occurs in nephritis, and which will be discussed presently. In some cases, however, the albumosuria appears to be independent of any renal disease, and must be attributed to an overloading of the blood with albumoses, which in turn is probably the result of the intestines being flooded with albuminous material (in polyphagia?) or of a functional disturbance of the intestine.

In *disease of the kidney*, especially in acute and chronic nephritis, albumosuria occurs not infrequently either as a concomitant or as a precursor of albuminuria; and when the renal condition clears up it sometimes persists after the albuminuria has subsided. The phenomenon is difficult to explain. As in such cases the greater part of the albumin is derived from the blood, it is justifiable to assume that, as the blood always contains small quantities of albumoses, some of the latter escape along with the albumin. The presence of albumosuria without albuminuria may be explained by the fact that albumoses are more readily dialysable. Yet, on that hypothesis, it is difficult to understand why albumosuria is on the whole not a common occurrence. The possibility that the kidneys themselves are the source of the albumosuria through the disintegration of the tissue, as in the case of nucleo-albuminuria (see above), or the conversion of the albumin or part of it into albumoses, should also be remembered.

Secondary conversion of albumin into albumoses or "peptones" may also occur in the urine under the influence of digestive ferments such as pepsin (Sehrwald[3]), or ferments similar in their action present within the urinary passages or developing outside of the body during the decomposition of the urine (Ter Grigoriantz[4]). Generally, however, this digestive action is prevented by the saline constituents of the urine (Stadelmann, *loc. cit.*).

Finally, the fact that the albumin in an albuminous urine may give rise to the formation of albumoses after prolonged boiling, to which the writer called attention a long time ago, must not be overlooked.[5]

[1] A. Löwy and P. Fr. Richter (*Berlin. klin. Woch.*, 1897, No. 47), found albumoses in the blood after inducing artificial leukocytosis.

[2] Köppen, *Arch. f. Psychiatrie*, etc., xx., p. 825; Meyer and Meine, *ibid.*, xxvii., p. 614.

[3] *Deutsch. med. Woch.*, 1890, No. 24.

[4] *Zeits. f. physiol. Chem.*, vi. and Diss. inaug., Dorpat, 1882; Sior, *loc. cit.*

[5] Senator, in *Virchow's Archiv*, lx., 1874; Stadelmann, *loc. cit.;* Löwy and Richter, *loc. cit.*

Tests for Albumin.—In order to demonstrate the presence of any form of albumin, the urine must be perfectly clear. Turbid urine must therefore be filtered before an analysis is made, and, if necessary —that is, if simple filtering does not clear it up sufficiently—must be shaken up with a little burnt magnesia. If the urine is very concentrated, it is advisable, in order to obtain more trustworthy results, to dilute it with water.

The oldest method, the one by which Cotugno discovered albumin in the urine, consists in boiling the urine, which must be acid in reaction. It is not very reliable, because it produces turbidities that are not due to the presence of albumin, and if the quantity of albumin is very small the test is not to be depended upon. If a little nitric acid is added to the boiled urine the test is somewhat more reliable, as the nitric acid clears up the other turbidities which are due to earthy salts; but small quantities of albumin may escape detection because they are destroyed by boiling with nitric acid, and the albumoses are altogether overlooked because they remain in solution at high temperatures.

The writer recommends the following methods as trustworthy and at the same time sufficiently sensitive in every instance for the requirements of general practice.

1. *Nitric Acid Test.*—While the urine is cold, pure (officinal) nitric acid is added—best by means of a pipet—by carefully allowing it to flow down along the side of the test tube held at an angle, so that the acid, which is heavier than the urine, collects at the bottom of the tube, where it forms a plainly visible layer, ½ to 1 cm. (about ½ in.), in thickness. In the presence of albumin or albumoses a white precipitate of varying thickness is formed *at the plane of contact of the two fluids and spreads upward;* if the quantity of albumin is very small, the cloud forms only after one or two minutes. When the urine contains a great deal of pigment a brown or violet pigmentation may appear between the urine and the layer of albumin; but this does not interfere with the recognition of the albuminous cloud. When the urine is very concentrated the addition of nitric acid not infrequently produces a cloud, which is due to urates, and which might possibly be mistaken for albumin. If, however, the nitric acid is added exactly as the writer has indicated above, the turbidity due to urates, which is delicate like a veil and may appear crystalline to the naked eye, spreads from above downward and disappears when the urine is slightly warmed; these two points serve to distinguish it from the turbidity due to albumin. In doubtful cases the test may be repeated after diluting the urine, as the urates then remain in solution. Finally a cloud may appear on the addition of nitric acid when the urine contains certain excretory products which occur after the ingestion of resins or balsamics; but these substances are dissolved by alcohol or ether.

If by this test a precipitate is formed that is not due to uric acid or acids derived from resins, it may indicate ordinary albumin (serin and globulin) or albumoses or both. If the precipitate disappears on the application of heat, it is composed of albumoses. It is advisable to take another specimen of urine and repeat the test in the inverse order—that is, the urine, which must be acid in reaction, is first boiled and then treated with nitric acid—by this procedure a cloud due to phosphates is dissolved while the albumin remains undissolved. If the precipitate should first form after the urine cools, it would indicate the presence of albumoses.

When the urine contains a very minute quantity of albumin a precipitate is sometimes formed on boiling, which disappears wholly or in part after the addition of nitric acid. In this case a greater part of the precipitate is due to phosphates, and the quantity of albumin is so small that it is recognized only after the urine has completely cooled and the albumin has settled to the bottom of the test tube.

2. *Potassium Ferrocyanid Test.*—If the urine has an acid reaction a few drops of *acetic acid*, or if it is alkaline, enough acetic acid to make the specimen distinctly acid, are added, and then drop by drop a solution of *potassium ferrocyanid.* In the presence of albumin or albumoses a cloud or precipitate occurs, either at once or after a few seconds, depending on the quantity present. When the urine is highly concentrated it is well, for this test also, to dilute the specimen with water. If the addition of acetic acid alone produces a cloud—from urates, uric acid or nucleo-albumin—the urine must be filtered before the ferrocyanid is added. In this test also any albumoses that may be precipitated are dissolved by heat.

3. *Sodium Chlorid or Sodium Sulphate Test.*—The urine is treated with *acetic acid* until the reaction is markedly acid, when an equal quantity of a *saturated solution of sodium chlorid* or *sodium sulphate* is added and the specimen heated until it boils. If a precipitate forms before heat is applied, it may be due to albumin or albumoses. The latter are dissolved by heat and reprecipitate on cooling. If the specimen contains a very small quantity of coagulable albumin, no precipitate occurs until after the specimen has been boiled.

Finally the writer will mention, on account of its great convenience, the test with *metaphosphoric acid* recommended by Hindenlang. A small piece of the solid (molten) acid, which may be carried in the pocket, is previously dissolved in a little water and used instead of nitric acid, as in test 1.

[From the fact that positive results are usually so readily obtained in testing albuminous urines, physicians, in the hurry of their routine examinations, often grow careless and fall into error. Thus, the precaution to acidulate the urine with acetic acid after heating may be neglected and a cloud of phosphates be regarded as albumin. Or the whole test tube of urine is heated rather than the upper stratum of the well-filled tube, and the contrast effect between the clear, cool, lower stratum and the heated upper stratum that is cloudy from the precipitated albumin is lost. The heat test should, as has been said, always be controlled by some other. An error is sometimes made by failing to remember that with small amounts of albumin the ring at the point of contact of the urine and nitric acid may be formed only after one to two minutes. A rough quantitative test for albumin, that of Brandberg, is based on this fact, the time of appearance of the ring in successive measured dilutions of the urine being noted, and from these data the amount of albumin estimated from comparison with tables prepared from observations on the time of appearance of the ring in urines with known percentages of albumin. The cloud from urates should be thought of especially in the concentrated urines. The dilution of the urine or the application of heat will, as has been said, help one to avoid this error, as in the diluted and in the heated urine the urates will not cause this cloud. The fact should also be remembered that the cloud of urates forms above and works downward, differing in this respect from the cloud of albumin.—Ed.]

These tests, by means of which 0.04 to 0.05 parts in 1000[1] of albumin can be detected in the urine, suffice for all practical purposes; and if the result is negative, "albuminuria" may be excluded. Even smaller quantities of albumin occur in the urine, however, and require for their demonstration more delicate tests. Many such tests have been given, but they are not all free from fallacies. The *sulphosalicylic*

[1] In pure solutions of albumin they are even more sensitive.

acid test of G. Roch, by which it is possible clearly to demonstrate 1 part of albumin in 50,000, may be recommended. The acid may be used in solution, or, according to Mankiewicz,[1] by adding a piece as large as a pea to 10 c.c. of urine and shaking the mixture. The precipitate is formed either at once or in the course of a minute, depending on the quantity of albumin present. Another very delicate reagent, which is recommended by Ed. Spiegler,[2] consists of 8 parts of bichlorid of mercury, 4 parts of tartaric acid, 20 parts of glycerin, and 200 parts of distilled water. This reagent is said to detect albumin or albumoses in the proportion of 1 : 350,000, a whitish ring being formed at the plane of contact of the two fluids. In order to eliminate any nucleo-albumin ("mucin") in performing these tests, the urine is to be diluted and treated with acetic acid, and the resulting precipitate, if there be one, removed by filtering. Ad. Jolles[3] recommends the following mixture: 5 parts of bichlorid of mercury, 10 parts of succinic acid, 5 parts of sodium chlorid, and 250 parts of distilled water. An equal part of this mixture is added to the urine after it has been acidulated with dilute acetic acid.

The occurrence of such minute traces of albumin in the urine, as has been said before, is of no practical importance; it possesses some theoretic significance, however, to which the writer shall return later on.

As regards the demonstration of the individual varieties of albumin—*serum-albumin*, *globulin*, *nucleo-albumin*, *albumoses*, and *peptone*—the presence of all of them, with the exception of peptone (Kühne), can be determined by inference if the tests given above under 1, 2, and 3 are properly employed. Serum-albumin and globulin, which usually occur in conjunction (see above) and are thrown down before the specimen is heated, especially by tests 1 and 2, are not redissolved by heat; hence, if the precipitate is completely dissolved, the presence of albumoses (propeptone) may be inferred; and if it is only partially dissolved, albumoses in conjunction with coagulable albumin may be suspected. A cloud produced by the addition of acetic acid (2 and 3) may be due to globulin, or more particularly to nucleo-albumin; globulin would be dissolved by a small excess of the acid, while nucleo-albumin would not be so dissolved.

A more trustworthy method of demonstrating *globulin* consists in diluting a quantity of clear urine in a long test tube with a large quantity of distilled water until the specific gravity falls to 1001 or 1002—when a globulin cloud not infrequently develops—and adding a drop of diluted acetic or boric acid. After a time the globulin precipitate settles at the bottom of the tube as a loose white powder, which may be tested by additional reactions. When it is desired to precipitate all the globulin contained in the specimen, the urine should be rendered faintly *alkaline* by the addition of ammonium hydrate, filtered an hour later, and then treated with a quantity of *neutral* ammonium sulphate solution equal to the volume of urine. The filtrate from this mixture, freed from globulin, contains serum-albumin, as may be demonstrated by acidulating and boiling or by any of the ordinary tests for albumin (see above). The presence of "*nucleo-albumin*" may be demonstrated by diluting a clear specimen of urine with three times the quantity of water and rendering it strongly acid by the addition of a considerable quantity of acetic acid. After filtering, the precipitate, which is insoluble in acetic, but readily soluble in hydrochloric, acid, may be, for purposes of greater accuracy, dissolved again in an alkaline solution and then reprecipitated by the

[1] Mankiewicz in Casper and Lohnstein's *Monatsbericht über Krankh. des Harnapparats*, 1899, No. 11.

[2] *Centralbl. f. klin. Med.*, 1893, No. 3.

[3] *Therap. Woch.*, 1896, No. 5.

addition of magnesium sulphate. In contradistinction to mucin,[1] this precipitate, when boiled for some time with some dilute mineral acid (hydrochloric or sulphuric), does not yield a reducing substance that reacts (with copper sulphate) in an alkaline solution.

Albumoses (*propeptones*) are recognized, as the writer has already said in connection with the above tests, by the fact that the precipitate which forms after the addition of the respective reagent to the cold urine dissolves on the application of heat and reappears when the specimen has again cooled. If greater accuracy is desired, test 3 is used, but the urine is afterward heated and filtered while hot, so that the coagulated albumin remains on the filter paper. In the presence of albumoses, the filtrate on cooling will show a precipitate of varying density, which may be intensified by the addition of concentrated ammonium sulphate, and which also gives the biuret reaction.

In order to obtain the albumoses as free as possible from admixture, particularly with urobilin, which also gives the biuret reaction, it is advisable to adopt the following method, devised by v. Aldor:[2] The urine is first acidulated with hydrochloric acid, and, if necessary, freed from albumin by the addition of a 15 per cent. solution of trichloracetic acid; it is then treated rapidly with a 5 per cent. solution of phosphotungstic acid until no more precipitate is produced; the specimen is then centrifugated, and the precipitate is taken up rapidly in alcohol and again centrifugated until it ceases to take up pigment. The precipitate is then taken up in water and tested for the biuret reaction.

The presence of *Bence-Jones albumin* is recognized by the appearance of a cloud in acid urine immediately after warming, the interval depending on the saline content; the cloud entirely or nearly disappears at the boiling-point and reappears again on cooling. Alcohol precipitates the albuminous body; the *fresh* precipitate is soluble in water, gives the biuret reaction, and responds to reagents in the same way as the albumoses, although in individual cases some differences are observed.

In order to demonstrate the true *Kühne peptone* (see p. 22), the urine must be free from albumin. If necessary, therefore, coagulable albumin must first be removed, preferably by method 3, which at the same time removes any nucleoalbumin that may be present. A large quantity (500 c.c.) of acid urine is then placed in a water bath at 60° to 70° C. and saturated with ammonium sulphate; after it has cooled it is filtered, the filtrate is rendered faintly alkaline with sodium carbonate and again treated with ammonium sulphate as before. This second filtrate is then accurately neutralized with acetic acid, and then precipitated for the third time with ammonium sulphate in the presence of heat. The filtrate obtained after this third precipitation is then boiled down, treated with a tannin solution, and allowed to stand until all the precipitate has settled at the bottom. The precipitate, after being dried, is heated for a few minutes with baryta (barium oxid) water and a little caustic baryta in boiling water, filtered after one or two hours, and the filtrate tested for the biuret reaction. If the filtrate is very highly colored, it may be previously decolorized by the addition of a little neutral lead acetate.

To make an accurate *quantitative* determination of albumin, the latter must be carefully precipitated and washed and the dried precipitate weighed; but this method is very circumstantial and time-consuming. A similar procedure would also be necessary to determine the individual forms of albumin, some of which cannot be completely precipitated. Other methods for quantitative analysis, such as polarization and colorimetry, are more convenient but less accurate. In practice accurate quantitative determination may be dispensed with, the proportion of albumin being estimated approximately by comparing the height of the precipitate in test tubes of the same size when the same quantities of urine are used. A very convenient, but by no means accurate, instrument is *Esbach's albuminimeter*. A definite quantity of urine is mixed with a definite quantity of a solution of picric and citric acids (10 parts of picric acid, 20 parts of citric acid, and 1000 of water) in a test tube empirically graduated in units per thousand,

[1] According to J. Strauss (*loc. cit.*), mucin is sometimes found in cystitis. In this condition, and perhaps in many cases of renal albuminuria, the mucus is derived from the mucous membrane of the urinary bladder or the mucous glands in the pelvis of the kidney.

[2] *Berlin. klin. Woch.*, 1890, Nos. 35 and 36.

and allowed to stand for twenty-four hours. The height of the precipitate (albumin) depends, among other conditions, on the external temperature; hence, in order to obtain comparable readings, the temperature should be as uniform as possible. Highly concentrated urine should first be diluted, as uric acid and coloring-matter will be precipitated in addition to the albumin if this precaution is neglected.

As the scale of this albuminimeter is not carried beyond 7 parts in 1000, the urine must be diluted with a definite quantity of water if the proportion of albumin exceeds that amount, when the proportion of albumin for the original urine can be calculated. The following procedure, recommended by Th. Lohnstein,[1] has the advantage of being more accurate, and it is at the same time comparatively simple. The specific gravity of the urine is determined to 5 decimals by means of a special areometer devised by the originator of the method; the albumin is then removed by boiling if necessary, the addition of a little acetic acid, and after enough water has been added to the filtrate to restore the original volume, the specific gravity is taken again. The difference between the two readings multiplied by 720 gives the proportion of albumin contained in the specimen.

[In practice, besides the Esbach method and the rough estimate made by noting the height of the column of albumin that forms after precipitation and standing for several hours, there may be mentioned the estimation made by noting the thickness, density, and quickness of formation of the albumin ring at the point of contact of the urine and nitric acid. This is, of course, only an approximate estimate, and is of value only after one has had experience. In attempting a quantitative estimate by this method, the same reagent glass, preferably a conical sediment glass, should always be employed, the same amount of urine and acid, and the same conditions, so far as possible, as to light. It is remarkable how one, by training, can in this way approximate the amount of albumin in a specimen of urine. Also by the use of the centrifuge, employing graduated tubes, such as the Purdy tubes, and previously diluting when the percentage of albumin is seen to be high, a quite accurate and rapid quantitative examination can be made.

Much confusion often arises, at least in the United States, because some physicians make these approximate quantitative examinations in one way, others in another, and because percentages are sometimes stated according to the weight standard and again according to that of volume. It should always be made clear when reference is made to a volume percentage. Thus, a statement that there is 3 per cent. albumin in a urine would mean an exceedingly large amount if a weight percentage is meant; a much smaller amount if a percentage by volume is implied.—Ed.]

The quantity of albumin excreted in the urine usually varies from a mere trace to several grams in a thousand. An albuminuria of more than 10 parts in 1000 is rare; in exceptional cases larger quantities (6 to 8 per cent.) have been observed. The writer made such an observation for several consecutive days in a case of subacute nephritis.

Physiologic Albuminuria.—For a long time the doctrine prevailed that normal urine is absolutely free from albumin, so that the most minute excretion of albumin was regarded as pathologic and as a sign of "Bright's disease of the kidneys." Later, however, when analyses were made with greater frequency and more delicate methods were employed, albumin was found in cases in which no renal affection, or even any other disease, could be demonstrated; and this excretion of albumin was therefore regarded as a purely functional disturbance. This discovery cast a shadow of doubt on the importance of albuminuria as a symptom of disease, especially as albumin continued to be found with ever-increasing frequency in normal urine obtained from healthy individuals as the tests employed increased in delicacy and sensitive-

[1] *Pflüger's Archiv*, lix. and lx.

ness.[1] It was at first believed that the substance thus demonstrated in normal urine was not the ordinary coagulable albumin, but nucleo-albumin, formerly regarded as mucin. The experiments of H. Winternitz,[2] Petersson and Paykull,[3] however, and especially the numerous experiments of Ed. Spiegler,[4] make it impossible to doubt that not only nucleo-albumin but also ordinary albumin may occur in normal urine. Indeed, Spiegler, using the extremely sensitive test devised by himself (see p. 28), found traces of albumin so frequently in persons of the better class that he sometimes experienced some difficulty in obtaining urine absolutely free from it.

Finally, it has been proved by K. Mörner,[5] beyond the possibility of a doubt, that albumin (serum-albumin) is a *normal* constituent of urine, in quantities of 22 to 78 mgm. in the liter (.0022 to .0078 per cent.). The substance formerly described as the nucleo-albumin (mucin) of normal urine, Mörner believes to be a combination of albumin with substances that precipitate albumin (especially chondroitin-sulphuric acid).

Incidentally, it may be mentioned that, as P. Simader[6] has shown, traces of albumin are constantly present in the urine of the lower animals as well as in that of human beings.

Albumin therefore resembles many other substances which were formerly regarded as abnormal constituents of the urine, and which later by means of improved methods of analysis have been demonstrated to be normal constituents, although present only in minute quantities; as, for example, sugar, inosit, oxalic acid, urobilin, indican, fat, and the like. These bodies cannot be found in every specimen of normal urine; but under certain *physiologic* conditions they make their appearance in increased quantities and become more readily demonstrable. The condition is then termed "physiologic glycosuria, oxaluria," and the like. The same observation applies in the case of albumin. Although the substance can be discovered in normal urine only by the most delicate reactions, and then not invariably, it appears in considerable quantities *under certain conditions that are fully within the limits of health*, and its presence can then be recognized by the usual tests for albumin that have been given above. The condition is therefore called "*physiologic albuminuria*," just as we may speak of physiologic emphysema and the like.

The theory of certain authors, among them v. Noorden and Malfatti,[7] that in physiologic albuminuria the substance is not true serum-albumin but *nucleo-albumin* has now been completely disproved. Under

[1] For further discussion of this point and for the literature relating to albuminuria in general the reader is referred to Senator: *Albuminurie*, 2d ed., Berlin, 1890; and his article entitled "Albuminurie," in *Eulenburg's Realencyklopädie der gesammten Heilkunde*, 3d ed., vol. i., 1894; and the article "Functionelle Albuminurie," by L. Goldstein, in *Zülzer's and Oberländer's klin. Handb. der Krankh. der Harn- und Sexualorgane*, Part I., Leipzig, 1893, p. 383.

[2] *Zeits. f. physiol. Chemie*, xv., 1891.

[3] "Upsala läkareförnings," etc., cited in *Virchow's Jahresber.*, 1893, ii., p. 284.

[4] *Loc. cit.*

[5] *Loc. cit.*

[6] *Zeits. f. Thiermed.*, N. F. 1. 6., 1897.

[7] v. Noorden, *Deutsch. Arch. f. klin. Med.*, xxxviii.; Malfatti, *Wien., klin. Woch.*, 1891, No. 24.

normal conditions *nucleo-albumin* does not occur in the urine; for, as the writer has just said, Mörner has demonstrated that the substance which was formerly regarded as nucleo-albumin is really albumin that has been precipitated in an acetic acid solution by the substances capable of precipitating albumin which are also present in the urine. If the latter substances do not suffice to precipitate all the albumin its presence can be demonstrated by the usual reactions.

Since, therefore, albumin is a normal constituent of urine, it is evident that it may become augmented under normal conditions. In other words, *physiologic albuminuria* is quite conceivable, just as other normal constituents of the urine, of which a mere trace that is very difficult to detect is present under ordinary conditions, may become increased and susceptible of being demonstrated by means of the ordinary reagents (see p. 30.), though the conditions producing this increase do not overstep the physiologic limit.

It goes without saying that it is impossible to draw a sharp line between physiologic and pathologic albuminuria, just as it is difficult to say where health ends and disease begins. Just as in cases of glycosuria it is sometimes difficult or even impossible to tell whether the condition is still within the limits of the physiologic or has entered the domain of the pathologic, so there are cases of albuminuria which occupy the borderland between health and disease, and do not become pathologic unless the causal factors of the albuminuria continue to exert their influence on the organism.

An albuminuria can be called physiologic with absolute certainty only when *very small quantities of albumin are found in the otherwise normal urine of a healthy individual not beyond middle age, and then only at intervals and after certain definite extraordinary but physiologic causes.* Such causes are severe muscular exertion, an unusually hearty meal, especially one consisting of food rich in albumin; a cold bath, emotional excitement and mental overexertion. Unless at least one of these causes is present in association with the above-named conditions, the writer regards the verdict as, to say the least, doubtful.

If several of these conditions are present at the same time there is, of course, a proportionately greater tendency to albuminuria. *Hard muscular labor* at first produces albuminuria in persons unaccustomed to it; although later, after the hardening process is completed, the albumin disappears from the urine. Albuminuria is observed in recruits after long marches; after all kinds of athletic exercises, especially those involving exertion of the muscles of the pelvis and leg, such as bicycling, riding, snow-shoeing, mountain-climbing, foot-ball, and the like. As the albumin disappears after a time if the exercises are kept up, it is evident that the albuminuria is due to a *physiologic* and not to a morbid process in the kidneys.

It is impossible to say with any degree of positiveness how much should be regarded as a "small" quantity of albumin. Personally, the writer is not inclined to regard an albuminuria that exceeds 0.4 to 0.5 in 1000 as "physiologic," even when everything else in the case

favors that view.[1] Nor should the fact that albuminuria occurs repeatedly in an apparently healthy individual as a temporary symptom be regarded as a proof that the albuminuria is "physiologic." For, like any other symptom, even a pathologic albuminuria is subject to *remissions* or if it is very slight, to complete *intermissions*. Nothing is more common than to find the excretion of albumin showing marked fluctuations in the course of twenty-four hours; thus, with rare exceptions, less albumin is excreted during the morning hours after a night's rest, and the albuminuria may even disappear altogether, to increase again some time in the course of the day, and reach its maximum sooner or later, according to the individual's condition.

When albumin disappears for a time in the course of a day and the remaining functions of the organs are normal or show but slight disturbance, the condition has been called "*cyclic albuminuria*," after Pavy. But this "cycle" depends altogether on external conditions, and can, as a rule, be modified by changing these conditions. The causes include, in addition to the same influences that have just been enumerated as producing so-called "physiologic" albuminuria, sexual excitement, coitus, masturbation, pollution, and a number of other stimuli of which individuals are not conscious, and which exert their influence during the day and during the waking state, but not at night. If these influences and stimuli are suppressed as much as possible during the day and transferred to the night, remissions and intermissions in the albuminuria usually occur in the inverse order.

Cyclic albuminuria is distinguished from *physiologic* albuminuria in that it does not require for its production the operation of any extraordinary exciting cause that is, however, still within physiologic limits; the normal biologic functions—in fact, the ordinary needs of everyday life—suffice to bring about cyclic albuminuria. The most frequent form, which occurs while the subject is in the erect position, standing, walking, sometimes also sitting and kneeling, has attracted most attention and has received a special name, probably because it is observed more frequently than any other. Stirling[2] calls it albuminuria of posture or "orthostatic" albuminuria; Heubner[3] recently proposed the term "orthotic" albuminuria, and regards this particular form as identical with Pavy's "cyclic" albuminuria. In this, however, he is wrong, as the "cyclic" appearance of albumin, as the writer has said, may be due, although more rarely, to influences other than the erect posture. The writer has seen cases in which the albuminuria did not occur after assuming the erect posture, but appeared *after a meal;* and others in which only the morning urine, passed before arising, contained albumin, the albuminuria being due to nightly *masturbation*, and ceasing when measures were taken to prevent the abuse. To be consistent, therefore, we should have to adopt the terms *digestive*, *masturbatory*

[1] It appears from numerous publications that careless readers have misunderstood this statement and concluded that the author asserts that an albuminuria not exceeding 5 in 1000 is physiologic if the urine otherwise appears to be normal.

[2] *Lancet*, 1887, p. 1159.

[3] *Ueber chron. Nephritis und Albuminurie im Kindesalter*, Berlin, 1897, p. 60.

albuminuria, and the like, in addition to orthostatic or orthotic albuminuria, which would be a useless overloading of the nomenclature. Because edema may develop while a patient is walking about and disappear when the recumbent position is assumed, this form has not received the designation of orthostatic or orthotic, to distinguish it from other forms of edema.

The *causes* of the intermittent appearance of physiologic or pathologic (cyclic) albuminuria probably vary in accordance with the various exciting circumstances. In *muscular exertion*, which is by far the most common exciting cause, two factors are to be considered: the circulation in the kidneys, and the irritation of the kidneys, by the metabolic products generated during muscular activity.

As regards the circulatory conditions, there can be no doubt that when the body is in the erect posture, as during walking and standing, and to some extent in the sitting and kneeling postures, the circulation is impeded in the entire territory of the inferior vena cava, which, of course, also includes the kidneys, and retardation of the blood-stream with stasis is therefore more likely to develop than when the body is in the horizontal position. If the renal parenchyma is only slightly affected and the heart at the same time is weak, the occurrence of albuminuria on assuming the erect posture is quite conceivable as an expression of congestion, just as edema appears in the ankles and feet and disappears again when the patient lies down. It is also possible that the slight metabolic changes which take place when the individual is standing or walking about may contribute to the production of albuminuria in kidneys of low resisting power. The investigations of Zuntz and Schumburg, Albu, Henschen,[1] and others show that during *violent muscular exertion*, as in certain athletic pursuits, cardiac insufficiency with extreme congestion, going on to cyanosis and dyspnea, may develop and lead to albuminuria with urinary casts, even when the kidneys are healthy. In this case it is possible that the metabolic products which are formed in excessive quantities and accumulate in the blood are associate causes by virtue of the irritation they exert on the kidneys.

P. Edel[2] attributes the favorable influence of the horizontal position to the "physiologic truth that the blood-pressure is then much greater than in the erect posture." A number of observations taken by Dr. E. Ekgren in the writer's clinic with Gärtner's tonometer do not confirm this "truth." The results were extremely variable, but on the whole rather indicated a diminution of pressure in the horizontal position. Edel also observed a diminution of the albumin after meals in some cases, and attributed the diminution to the increased velocity in the circulation of the kidneys, causing augmentation of the quantity of urine and diminution of the quantity of albumin. As the writer has already said elsewhere, he has not infrequently seen the albuminuria increase after the midday meal, or even appear for the first time at that period of the day. Blood-pressure falls during digestion, as is shown by the investigations of Colombo, H. Weiss and Ekgren,[3] although the fall is preceded by a short period during which, probably owing to the act of mastication, there is a temporary rise.

[1] Zuntz and Schumburg, *Deutsch. militärärztl. Zeits.*, 195; Albu, *Berlin. klin. Woch.*, 1897, p. 202; Henschen, "Skidlauf und Skidwettlauf.," Jena, 1899.

[2] *Münch. med. Woch.*, 1901, Nos. 46 and 47.

[3] S. Ekgren, *Zeits. f. physikalische u. diatetische Therapie*, 1901, v., p. 191.

The writer's own experience suggests a warning against regarding in every case and without exception these intermittent or "cyclic" forms of albuminuria as mere functional disturbances without significance, even in the absence of other pronounced signs of diseases. Such an albuminuria in the majority of, although not in all, cases is in his opinion a sign of a very insidious nephritis. The condition is observed in young people, especially in growing girls; the nephritis to which it points is usually secondary to some infectious disease, as scarlet fever, diphtheria, infectious angina, or the like, and remains latent for a long time, until the intermittent, or in some cases remittent, albuminuria is discovered by accident. The fact that children and young adults are most exposed to such infections at once affords a ready explanation of the occurrence of this form of albuminuria ("*albuminuria adolescentium*"—Gull). With proper management the morbid process may be arrested or the disease entirely cured; but in some cases, after the condition has lasted for years, unequivocal symptoms develop, especially in the vascular apparatus. (See Nephritis, Acute and Indurative, Symptoms, Etiology, Diagnosis, etc.) In every case of "cyclic" albuminuria, therefore, a minute search should be made for one of the known exciting causes of the cycle—that is, the appearance of albuminuria at certain periods only—and if any such cause is found, it should be removed if possible.

A number of different theories have been advanced in regard to the place where the excretion of albumin takes place in the kidneys, in harmony with the diversity of opinion in regard to renal excretion itself, and especially the function of the glomeruli. Most of these theories are based on the assumption that the albumin in these, as in most other pathologic cases, makes its way from the blood into the urine through the glomerular vessels, and while this assumption has a good deal in its favor, it cannot be regarded as applicable in every instance. It is not at all inconceivable that albumin might make its way into the uriniferous tubules from the interstitial blood- and lymph-vessels if the epithelial covering becomes damaged and the normal function is interfered with; moreover, if the epithelium is destroyed, it is possible that not only nucleo-albumin, as was formerly thought, but perhaps also true albumin, may be liberated and escape in the urine. Finally, albuminuria may be produced by disease of the epithelium covering the uriniferous tubules, which under normal conditions possibly absorbs a part of the albuminous fluids that escape from the glomeruli, so that, if the epithelium becomes diseased, this absorption is interfered with.

In the cases now under discussion, in which albumin occurs in *normal* urine, and in cases of *physiologic* albuminuria, the assumption of grave injury to the uriniferous tubules is hardly admissible; if this were so, not only albumin, but also nucleo-albumin, would appear in the urine; but this is not the case, as has been explained. The writer is therefore inclined to accept the current theory, that the source of the albumin found in normal urine and in "physiologic albuminuria" is to be sought in the glomeruli.

The writer may refer to the well-known theory of Heidenhain, that the glomeruli represent a true glandular apparatus, the epithelium of which possesses the faculty of separating water and its soluble salts from the blood and at the same time arresting the albumin. On this theory every form of albuminuria must be regarded as pathologic. The occurrence of albumin in normal urine and physiologic albuminuria would have to be regarded as the result of a very mild disease or functional disturbance, a defective condition of the renal epithelium depending on individual predisposition. Not to enter upon the general objections that have been urged against Heidenhain's theory of renal secretion, it may be remarked that if the hypothesis of such a functional disturbance or "weakness" of the epithelium were to be admitted, other deviations from the normal function, besides the escape of albumin, would be expected to take place in this epithelium, such as, for example, rapid diminution in the percentage of water and soluble constituents. But such an assumption is contrary to the fundamental conception of normal urine; not to dwell on the fact that in physiologic albuminuria the urine is by no means deficient in water and salts, although it is not infrequently somewhat more concentrated than usual as the result of certain conditions, such as muscular exertion, for example.

According to the other theory of renal secretion, first particularly promulgated by C. Ludwig, the glomeruli produce not a true glandular secretion, but a transudate from the blood-plasma; and as the occurrence of albumin in normal urine was formerly unknown, and even the slightest albuminuria was regarded as pathologic, investigators spent their time in casting about for an explanation why both this transudate and normal urine should be free from albumin. Passing over some of the earlier explanations which are quite untenable, it was first believed that the escape of albumin required a *very high pressure*, such as does not normally obtain in the glomeruli; while later the opposite view, that albuminuria was associated with diminution in the blood-pressure, for a time prevailed (Runeberg [1]). Others again sought the cause for the absence of albumin in the peculiar structure of the glomerular vessels (Ribbert [2]), or in their epithelial covering (Cohnheim [3]). But now that it has been demonstrated that albumin is a normal constituent of urine, these explanations all become superfluous and are, besides, quite incorrect, since every transudate contains albumin without regard to the blood-pressure and the structure of the blood-vessel walls. These two factors, it is true, have a certain influence on the *quantity* of the albumin in the transudate, and may be responsible for the fact that the transudate from the glomerular vessels contains only a very little albumin; less, perhaps, than any other transudate. As this transudate in its subsequent progress becomes mingled with the secretion from the epithelial lining of the uriniferous tubules, which is generally admitted to be free from albumin, it is evident that the urine resulting from the

[1] *Deutsch. Arch. f. klin. Med.*, xxiii., 1879, p. 41.
[2] "Nephritis and Albuminurie," Bonn, 1881.
[3] *Allg. Path.*, 1st and 2d ed., vol. ii.

mixture of these two fluids must contain even less albumin. It is also possible, as the writer has just remarked, that during the passage of the transudate from the glomerular vessels through the uriniferous tubules the epithelial elements of the latter may absorb all or part of the albumin from the fluid as it passes through. In short, from the standpoint of the transudation or "filtration" theory, the explanation of the appearance of albumin in normal urine and of the occurrence of physiologic albuminuria presents no difficulties whatever, and it is quite easy to understand its ultimate disappearance or reduction to a mere trace.[1] The fact that physiologic albuminuria does not occur in everyone under the conditions referred to is not without numerous analogues in physiology; for normal individuals do not react in the same way to identical influences. For example, one individual can assimilate more sugar than another—that is, the latter is more apt to present glycosuria than the former, although both may be perfectly healthy. One man sweats on the slightest provocation, while another's skin remains dry; and so examples might be multiplied.

These differences may depend on different constitutional properties in the organ, on differences in predisposition, or differences in power of performance and of resistance; and the existence of such differences does not justify the assumption that every deviation from the *usual* course of events is pathologic; at most, it may be said that such a deviation occupies the boundary line of the physiologic.

Albuminuria of the Newborn.—Another form of physiologic albuminuria is that which occurs in the newborn, and which was first observed by Virchow[2] and later confirmed by numerous other observers. According to Martin and Ruge, Cruse and Hofmeier,[3] albuminuria of the newborn is practically constant during the first eight to ten days of life, the degree being quite variable; the condition disappears gradually or quite suddenly after that period. In addition to albumin, the urine contains hyaline casts, epithelial cells, and urates.

The cause of this albuminuria was formerly thought to be the increase in the blood-supply to the kidneys and the change in metabolic conditions incident to birth, and the uric acid infarct of the newborn was also thought to bear a causal relation to it. This explanation not only rests on a confused conception of the existing condition of things, but it is absolutely refuted by Ribbert's[4] discovery of albumin in the urine of stillborn infants. Ribbert demonstrated that the albumin is excreted from the vascular glomeruli within Bowman's capsule, and the process is accompanied by desquamation of the epithelial cells covering the vessels. According to Ribbert, this same process takes place in the embryo, and he believes that the excretion of albumin is to be attributed to the fact that the glomeruli are not fully developed, and therefore allow albumin to transude at this early period of their existence. The desquamation of epithelium he explains as a kind of molting,

[1] Cf. H. Senator, *Die Albuminurie*, 2d ed., p. 44.
[2] *Virchow's Verhandl. der Ges. f. Geburtshilfe*, 1846, p. 70.
[3] *Virchow's Archiv.*, lxxxix., 1882. [4] *Virchow's Archiv.*, xcviii., 1884, No. 9.

similar to the desquamative process in the skin (see p. 21). On this theory nucleo-albumin ought to be found in the urine of the newborn, and, as a matter of fact, "nucleo-albuminuria" was observed in the newborn by C. Flensburg,[1] being probably produced by the irritation of the high percentage of urates in the kidneys. (See section on Uric Acid Infarct of the Newborn.)

Albuminuria of Parturition.—Lastly, the albuminuria of the woman in labor, which is the result of the excessive exertion incident to childbirth, is to be regarded as falling within the limits of the physiologic. According to Aufrecht and W. Friedeberg,[2] this form of albuminuria, which was known to some of the earlier observers, occurs immediately after labor in 39.2 per cent. of women who have been healthy up to that time, favoring factors being excessive duration and unusual severity of the labor pains. The albuminuria disappears within twenty-four to forty-eight hours after labor. In a few cases hyaline casts were found in the urine, and they also disappeared in a short time. This form of albuminuria, in all probability, is due to congestion of the kidneys, brought about by the unusual muscular effort accompanied by bearing down with closed glottis which is incident to parturition. This albuminuria accordingly occupies the boundary between physiologic albuminuria and that form of pathologic albuminuria which is produced by stasis; but in view of its frequency and the physiologic nature of its exciting cause, it cannot be classed as absolutely pathologic.

Pathologic Albuminuria.—The cause of pathologic albuminuria in the great majority of cases is undoubtedly to be sought in alterations in the kidneys, either simple circulatory disturbance or disease of the renal parenchyma, such as inflammation or degeneration. These conditions will be discussed in their appropriate places. There remains a small number of cases in which pathologic albuminuria is found without any of the renal changes referred to being demonstrably present. In such cases the cause of the excretion of albumin is thought to be *some change in the constitution of the blood*, and the term *dyscrasic* or *hematogenous albuminuria* is therefore employed.

Strictly speaking, the latter class should include every case of albuminuria caused by any defective condition of the blood, particularly the presence of *poisons*, whether organic or inorganic. However, these toxic forms are placed in a separate group, under the name of "toxic or infectious" nephritis, since in most, although not in all, cases the process in the kidneys is of an inflammatory nature. The term dyscrasic albuminuria is applied more particularly to the forms which are supposed to depend on some abnormality in the albuminous bodies of the blood, by virtue of which these bodies, unlike the normal albumin of the blood, are enabled to make their way into the urine even when the kidneys themselves are intact.

It is an indisputable fact that when heterogeneous albuminous bodies foreign to normal blood for any reason make their way into the blood, they ultimately appear in the urine either wholly or in part. This has been

[1] *Nordisk med. Archiv.*, 1894, No. 9. [2] *Berlin. klin. Woch.*, 1894, No. 4, p. 81.

positively proved in the case not only of albumoses and "peptones," which have already been discussed on page 22, but also in the case of egg-albumin, casein, gelatin, hemoglobin, and a number of other albuminous bodies.[1] With this fact as a basis a number of attempts have been made recently, especially by Semmola, to explain by means of various ingenious hypotheses certain clinical forms of albuminuria, particularly so-called Bright's disease, as caused by such a dyscrasia.

Unfortunately, however, in cases of albuminuria in the true sense of the word, none of these or any other foreign albuminous body is found, the albumin consisting always of the normal albumins of the blood—namely, serum-albumin and globulin; at least, the numerous attempts that have been made up to the present time to demonstrate any material difference have resulted in failure; and so far as our present knowledge goes a dyscrasic or hematogenous albuminuria in this sense still lacks a solid foundation.

In addition to these *qualitative changes in the albuminous bodies* contained in the blood there are other alterations of a *quantitative nature*, as well as *similar deviations relating to other* constituents of the blood, such as the urea, the salts, etc. As changes of this character in the constitution of albumin-containing fluids cannot fail to have their effect on the escape of albumin from such fluids, it must be admitted from the standpoint of the transudate or "filtration" theory (see p. 36) that *quantitative* changes in the proportions of the normal constituents of the blood, the albuminous bodies, the salts, the urea, and others may cause the escape of considerable quantities of albumin and thus lead to the production of albuminuria.

A positive decision of this question is exceedingly difficult, because the renal tissue, and particularly the renal epithelium, react at once to any abnormal condition in the blood and are very easily injured in their nutrition and function. Hence, an albuminuria developing after such changes have been brought about by the injection of certain heterogeneous bodies, for example, or the abstraction of certain normal constituents of the blood, such as sodium chlorid, may be also due to these renal changes, and therefore actually renal in origin and only indirectly due to a dyscrasia.

As with the aid of improved methods of examination more minute structural changes have been found in the kidneys in an ever-increasing number of such cases of albuminuria, which were formerly regarded not as renal but as dyscrasic in nature, the number of the latter has become more and more limited. Another consideration is that all, or at least many, of these alterations in the condition of the blood exert a disturbing influence on the *general circulation* as well as on that of the kidneys in particular, and may thus indirectly lead to albuminuria. In short, the question is complicated by so many interrelated factors and the conditions are so confused that it cannot be said to have been positively demonstrated that a simple "*dyscrasic, hematogenous albuminuria*"

[1] S. Senator, *Albuminurie*, p. 117; and J. Munk and Lewandowsky, *Arch. f. Physiol.*, 1899, Sup. vol., p. 73.

ever occurs as a clinical manifestation in the hitherto accepted sense of the term. All that we know positively is that there are certain forms of albuminuria in which the condition of the blood is either probably or undoubtedly altered, and yet the changes observed either clinically or anatomically in the kidneys in albuminuria of undoubted renal origin are not demonstrable. It must not be inferred, however, that no change of any kind is found in the kidneys; for, as a matter of fact, changes in the epithelium of the uriniferous tubules can quite often be demonstrated in the cases of albuminuria at present under consideration, but these changes have only recently been recognized, and they were formerly not thought to have any connection with the albuminuria, because it was customary to assume that the glomeruli were the source from which the albumin was derived in every case of albuminuria—an assumption which, as the writer has already explained on page 35, does not appear to be justifiable.

In this category belong the following forms of albuminuria:

1. *Febrile albuminuria.* This term has been applied since Gerhardt's[1] time to the excretion of albumin which occurs in the acute infectious diseases, typhoid fever, pneumonia, rheumatism, the acute exanthemata, diphtheria, influenza, and erysipelas *during the fever and disappears with it.* In addition to albumin, the urine often contains hyaline casts and albumoses (propeptone), sometimes these latter without albumin, but never any other (morphologic) constituents indicative of true inflammatory renal disease. It is in these very cases that the above-mentioned parenchymatous—that is, epithelial—changes have been found in very recent times, and were by many regarded as the first beginnings of an acute inflammatory process, caused by infection and intoxication. (See Acute Nephritis.) Febrile albuminuria may therefore be regarded as the expression of a very mild grade of infectious nephritis (Leyden[2]); but it is somewhat remarkable that the nephritis as well as its product albuminuria should disappear with the fall in the temperature. The febrile process, however, is attended by a number of other factors capable in themselves, and *à fortiori* when they act together, of producing albuminuria. These factors are changes in the constitution of the blood; such, for example, as an increase in the proportion of urea, and possibly also in that of the salts and the albumin, the presence of microbic toxins, or perhaps of albuminous bodies altered in such a way as to be more readily dialysable (albumoses, see reference to Krehl and Matthes on p. 24); changes in the blood-pressure, especially ischemia in the kidneys; the elevated temperature; and finally the concentration of the urine.

2. *Albuminuria occurring in non-febrile general diseases with special involvement of the blood and without demonstrable changes in the kidneys.* This category includes the cases of albuminuria which occur quite frequently in the various forms of benign and malignant *anemia*, in leukemia and pseudoleukemia, *scorbutus*, and in many cases of *icterus*,

[1] *Deutsch. Arch. f. klin. Med.*, v., 1868, p. 212.
[2] *Zeitsc. f. klin. Med.*, iii., 1881, p. 161.

diabetes, and so on. In these conditions also, parenchymatous—that is, epithelial—changes have sometimes been found; but it has never been satisfactorily determined whether they are to be regarded as a sufficient cause for the albuminuria, as the pathologic condition of the blood and the circulatory disturbance which are so frequent may in themselves explain the albuminuria; and finally the influence of the nervous system, especially in diabetes, since Cl. Bernard produced albuminuria by trephining, must also be taken into account. As regards *diabetes mellitus* in particular, it is stated by R. Schmitz[1] that albuminuria frequently occurs in this disease after the inordinate indulgence in raw or boiled eggs, and disappears again when the excessive ingestion of eggs ceases. According to the writer's own observations, which extend over a number of years, albuminuria occurring in the course of diabetes mellitus is not infrequently due to an insidious nephritis or to sclerosis of the kidneys. (See Chronic Indurative Nephritis, pp. 259–300.)

3. *Albuminuria occurring in non-febrile diseases of the nervous system.* In various pathologic conditions of the nervous system, such as *epilepsy*, *delirium tremens*, various *psychoses*, *cerebral apoplexy*, *nervous exhaustion*, *migraine*, and *Basedow's disease*, transient albuminuria (or albumosuria), with or without hyaline casts, and sometimes the latter alone, have been noted by a large number of observers, M. Huppert, de Witt, v. Rabenau, Kleudgen, Fürstner, Köppen, Vassale and Chiozzi,[2] Voisin and Péron. This category does not, of course, include chronic renal diseases, which may coexist with the above-mentioned conditions or may be attended by similar manifestations (uremia), nor does it include dyspnea or passive congestion occurring as the result of convulsions. The cases outside of this category are explained by assuming a special influence on the part of the nervous system, either a direct influence on the part of the medulla oblongata, as suggested by Cl. Bernard's albuminuria after puncture, or an indirect influence through changes in the circulatory conditions. The transient albuminuria that sometimes occurs in normal individuals after *psychic emotion* (p. 32) possibly represents a transitional form between the physiologic albuminuria and the form here under discussion. Such an albuminuria has a certain diagnostic influence when there is a suspicion of simulated convulsions or mania.

4. *Albuminuria in affections of the intestinal tract*, without demonstrable primary disease of the kidneys. Englisch[3] and Frank[4] find albumin in the urine in about two-thirds of a series of cases of intestinal obstruction from kinking of the bowel, the quantity being, generally speaking, proportionate to the severity of the disease. As the intestine becomes permeable, either by the removal of the obstruction or by the development of gangrene, the albuminuria diminishes. The urine is scanty, and contains in addition to albumin, hyaline or granular casts.

[1] *Berlin. klin. Woch.*, 1891, No. 15.

[2] Chiozzi, *La Riforma med.*, 1891, No. 249. The rest of the literature is given by Goldstein, *loc. cit.*, p. 393.

[3] *Oesterr. med. Jahrb.*, 1884, Nos. 2 and 3.

[4] *Berlin. klin. Woch.*, 1887, No. 38.

The albuminuria cannot be attributed to the absorption of toxic substances, such as phenol or indol, from the intestine, nor to the collapse, since both these conditions are present in acute peritonitis, in which albuminuria is rare unless there is fever to cause it. It is impossible to say positively whether the cause is to be sought in a peculiar condition of the blood or in reflex processes interfering with the circulation in the kidneys.

Transitory albuminuria has also been observed by J. Fischl,[1] B. Stiller,[2] and others in cases of severe *acute diarrhea*, in which the causal conditions are probably the same as in the case of intestinal obstruction; inspissation of the blood is probably also a contributory factor. On the other hand, Kobler and Wallerstein[3] reported the occurrence of albuminuria and casts in certain forms of impaction with colic, the urinary findings in this case being due probably to circulatory disturbances and the absorption of toxic substances from the intestine. The albuminuria observed in *diseases of the liver*, when not due to coexistent disease of the kidneys, is perhaps attributable to a disturbance of the circulation or to morbid alterations in the constitution of the blood.

[It will be noted that in most of these forms of pathologic yet non-renal albuminurias there is, or may be assumed to be, an altered condition of the blood, and one cannot help feeling that probably this is the explanation of the phenomenon in most instances. Just how the albuminuria results, whether from minimal altered condition of the cells of the glomeruli or of the tubules, through some hemic, chemical irritant, or through some change in the chemical and physical composition of the blood inducing osmotic pressure changes, must be largely a matter of conjecture. As has been said, the more closely the kidneys are examined in these cases, the oftener are structural changes found. In the febrile albuminurias, for example, acute parenchymatous degeneration (cloudy swelling) will perhaps serve to explain the escape of albumin from the blood.—Ed.]

The **effects** of albuminuria on the organism are in most cases insignificant. The loss of albumin was at one time overestimated, as the methods of determining the quantity of albumin evacuated with the urine were not then known. It is now well known that the daily loss of albumin in ordinary cases of albuminuria rarely exceeds a few grams, a quantity that is not worth considering and is easily made up. In very rare cases, it is true, the loss of albumin may be much more considerable and may have a weakening effect on the organism.

The **treatment** of albuminuria in every instance consists in the removal of the underlying causes and the correction of any existing morbid conditions. The loss of albumin in disease may be disregarded except in the very rare cases just referred to, in which the loss may have to be made up by the exhibition of albuminous foods.

[1] *Prager Vierteljahrsschr.*, 1878, cxxxix., p. 27.
[2] *Wien. med. Woch.*, 1880, Nos. 18 and 19.
[3] Wallerstein, *Wien. klin. Woch.*, 1901, No. 21.

MUCINURIA AND FIBRINURIA.

Mucus, according to the older views, occurs in very small quantities in normal urine, being the product of the mucous membrane of the urinary passages, and is increased by irritation of this mucous membrane, especially in acute and chronic cystitis and pyelitis. It appears from the investigations of recent times, however, that this so-called mucus does not contain true "mucin," but *nucleo-albumin*, or, according to Mörner, a combination of albumin with substances capable of precipitating the albumin in the urine, which has been fully discussed on page 21.

R. v. Jaksch[1] discovered in the case of a woman, forty-five years of age, who presented the symptoms of renal colic, that the urine, which was neutral or faintly alkaline, contained ribbon-like masses of spiral shape, resembling the spirals found in sputum or the structures evacuated in mucomembranous enteritis, which were composed of "mucin" and fibrin. As these masses appeared to come from the ureter, R. v. Jaksch regards them as the product of a *membranous ureteritis*. A similar case had been described by Baumüller[2]; it was that of a woman, thirty-eight years of age, presenting symptoms of renal colic, who passed whitish "mucoid" masses, which on closer inspection turned out to be casts of the calices and pelvis of the kidney, and of the ureters. Chemically, they were found to consist of a mixture of mucin and a coagulated albuminous body. In a similar case reported by Frank,[3] the coagula were composed of inspissated mucus and pus corpuscles.

Fibrin is not of common occurrence in the urine. Urinary casts were formerly regarded as fibrin coagula, and fibrin was accordingly believed to be a common constituent of the urine; but if we exclude blood-clots, the substance is extremely rare. It is relatively most common in chyluria, which will be discussed presently, and in the isolated cases in which firm and gelatinous coagula are formed in the urine immediately after it has been evacuated, or are passed during the act of micturition, in which case the coagulation takes place within the body—that is, within the pelvis of the kidney, the ureter, or the bladder. The term true fibrinuria should be limited to the latter class of cases; it is always a sign of intense inflammation of the urinary passages, the pelvis of the kidney, the ureters, or the bladder. It is not known what special conditions are necessary to produce in these rare cases, which differ from most inflammatory conditions, this so-called "spontaneous" coagulability of the urine. Except for this coagulability, the symptoms are therefore the same as those of inflammation of the parts referred to; when the coagulation takes place within the body, however, the act of micturition may be accompanied by colicky pain, or there may be difficult micturition.

Such cases are mentioned by Prout.[4] J. Vogel,[5] in a case of a woman suffering from "Bright's disease," repeatedly observed the pre-

[1] *Zeits. f. klin. Med.*, xxii., 1893, p. 551.
[2] *Virchow's Archiv*, lxxxii., 1880, p. 261.
[3] *Zeits. f. klin. Med.*, xxxviii., p. 479.
[4] *Urinary Diseases*, 3d ed., p. 112.
[5] Neubauer and Vogel, *Anleitung zur Harnanalyse*, 6th ed., 1872, p. 269.

cipitation on the bottom of the vessel after the urine had been evacuated of a pale-red coagulum which contained numerous pus corpuscles and a few red blood-cells. The observation extended over a considerable time. The writer[1] has seen spontaneous coagulation of the urine in two instances, in both of which it appeared to be caused by extensive use of cantharides plaster in acute rheumatic polyarthritis. In one of these cases the coagula were carefully examined and gave the same reactions as fibrin. The urine, in addition, contained serum-albumin and globulin, numerous red cells, and a few leukocytes, but no casts. Similar observations were made by Bozzolo[2] in a case of a man suffering from calculous pyelitis; by Klein,[3] in a man, fifty-two years of age, with atrophy and amyloid degeneration of the kidneys; and by Tritschitta,[4] in a woman, twenty-nine years of age, who was thought to have had a hemorrhage into the pelvis of the kidney. Finally, v. Jaksch,[5] in a case of renal abscess of unknown origin, in which the urine was deeply blood-stained and gave forth an ammoniacal odor, observed a mass of arborescent, interlacing coagula, consisting of fibrin and covered with epithelium from the uriniferous tubules.

In decomposed alkaline urine, such as is evacuated in catarrh of the pelvis of the kidney and of the lower urinary passages, flakes and shreds consisting of a dense conglomeration of pus corpuscles, mucus, batceria, and triple phosphates are sometimes found, and may, by occluding the ureters, give rise to marked discomfort. Lastly, pieces of tumor that have entered the pelvis of the kidney or the ureter from the kidneys or other parts of the body may possess the appearance of coagula (A. Rothschild).[6]

URINARY TUBE CASTS.

The structures known as casts were unquestionably first seen in the urine by J. Fr. Simon[7] and H. Nasse,[8] and later by Henle,[9] who also found them in dissecting the kidneys. As they were universally regarded as the product of an inflammatory exudation, they were called "exudation" or "fibrin casts or cylinders." But this view was later attacked both from clinical and experimental quarters when many forms and several different modes of origin were discovered.[10]

Urinary casts owe their shape to their passage through the uriniferous tubules; they are therefore always derived from the kidneys, and are always a sign of disease of those organs, even though the disturbance be insignificant. Although casts have been found in rare cases in apparently normal urine, and particularly in urine that was free from albumin (S. Rosenstein, A. Key, Nothnagel, and others), nevertheless, in view of the origin of casts, the writer refuses to accept the conclu-

[1] *Virchow's Archiv*, lx., 1874, p. 490.
[2] *Clin. Med.*, Torino, 1877.
[3] *Wien. klin. Woch.*, 1896.
[4] *Wien. klin. Woch.*, 1896.
[5] *La Clin. Med.*, 1900, No. 9.
[6] *Deutsch. med. Woch.*, 1901, No. 50.
[7] *Müller's Archiv*, 1843, p. 26.
[8] *Med. Corresp. Bl. rhein. u. westphal. Aerzte*, 1843, No. 8.
[9] *Zeits. f. rationelle Med.*, 1., 1844, p. 60.
[10] The older literature will be found in *Die Harncylinder*, Berlin, 1874, by A. Burkart.

sion that the kidneys in such cases were entirely normal and that there was no alteration in their function.

[It must be remembered, however, that with the use of the centrifuge, and particularly when the lower portion of urine that has stood for twelve or twenty-four hours in a conical sediment glass is centrifuged—*i. e.*, with a refinement of centrifuging and of sedimentation—an occasional cast may be found in the urine of nearly every individual, even of young adults and those in seemingly good health.[1] And in those past the middle period of life too harsh an interpretation ought not to be put upon the detection of an occasional cast. This fact is of great importance in examinations for life insurance. It is doubtful if in many of these cases the stray cast means much more as regards health than the appearance of wrinkles on the face or a few gray hairs on the head as one advances in years.—ED.]

The number of casts in the urine is subject to great variation. They are found in greatest abundance in acute inflammation of the kidney and in chronic, so-called "parenchymatous nephritis"; they are less numerous in the contracted kidney and in amyloid degeneration and congestion of the kidneys, in which cases they are at times only found after a long search in the sediment obtained by centrifugation. They vary also as to length and, in a lesser degree, as to thickness. Not infrequently we find very short fragments which cannot be identified as casts except by comparison with other larger ones; in other cases casts may attain an unusual length, 1 mm. and more, the amorphous hyaline casts being the ones which almost exclusively attain such an unusual length. Their thickness corresponds approximately to the lumen of the uriniferous tubules at different points or to the lumen of abnormally distended sections of these tubes. Individual casts are often spiral in form, either throughout their entire extent or only at one extremity; but this spiral shape is not a proof that the casts are derived from the tortuous portions of the uriniferous tubules; it may be due simply to the progress of the tough, elastic mass of which the cast is composed through a narrow canal (P. K. Pel[2]), or to its being forced from a narrow canal into one with a larger caliber (H. Senator[3]). Casts with forked or bifid extremities are extremely rare.

Casts are divided, according to their outward appearance, into (1) such as are composed wholly or chiefly of *cells;* (2) *granular casts;* and (3) *amorphous casts* presenting a more or less uniform, homogeneous appearance without any distinct structure, or at most a striated surface. In addition to these three varieties there are all kinds of transitional forms, including those in which one part of a cast belongs to one variety, and the remainder to one of the other two varieties. The casts are also very frequently covered with all kinds of urinary constituents, such as cells, crystals, microparasites, and the like. Sehrwald[4] has dem-

[1] Cf. Haines and Skinner, "An Improved Method of Detecting Casts in the Urine," *Jour. Am. Med. Assoc.*, xxx., No. 5.

[2] *Zeits. f. klin. Med.*, ix., pp. 36 and 37.

[3] *Deutsch. Arch. f. klin. Med.*, li., pp. 413 and 621. [4] *Deutsch. med. Woch.*, 1890, No. 24.

onstrated that the casts may disappear from the urine after it has been voided, and attributes the phenomenon to digestion by the pepsin contained in the acid urine. [The urine to be examined for casts should be as fresh as possible. In alkaline, and particularly in decomposed, urine, casts readily disintegrate. It is often, therefore, advisable to put into the urine that is to be kept some time before examination a few grains of chloral or boric acid, a few drops of formalin or of chloroform, etc., remembering, of course, that some of these substances, while not interfering with the examination for these organized sediments, may disturb certain chemical reactions—*e. g.*, for sugar.—ED.]

1. **Cellular Casts.**—The cells are chiefly epithelial cells from the uriniferous tubules, and red blood-cells. Casts rarely consist exclusively of leukocytes, but these elements are quite frequently found adherent to other kinds of casts. The formation of these cellular casts is not difficult to understand. *Epithelial casts* are due to the separation in a continuous piece of the epithelial lining of the uriniferous tubules (epithelial tubes), or to the amalgamation of the individual cells during their passage through the tubes, particularly the narrow portions, into a compact, cylindric mass. The cells may be intact or nearly so, or they may appear in various stages of granular or fatty degeneration; they may be swollen, they may still possess distinct nuclei, or the nuclei may have disappeared.

So-called *blood-casts* are formed in a similar manner from red blood-corpuscles, the process of cohesion being probably assisted by the presence of coagulated fibrin.

2. **Granular casts** are subdivided into the coarse granular and fine granular; the latter often present an appearance as if they had been sprinkled with a fine dust. The granules often consist of minute fat-droplets (*fatty granular casts*), as is shown by their refractive power and chemical reaction (osmic acid turns them black and saffranin red). Other forms appear to consist of an albuminous substance that has undergone granular degeneration. There can be no doubt that all these various forms of granular casts are in many instances derived from epithelium or epithelial casts, the cells of which have undergone granular or fatty metamorphosis either prior to their desquamation or subsequently while in the uriniferous tubules. Lastly, it would appear that amorphous casts, when they are retained in the kidney for any length of time, may undergo granular and fatty degeneration similar to that which frequently overtakes albumin that has been cast off and become coagulated within the animal body.

3. **Amorphous** or **structureless casts** are again subdivided according to their appearance into (*a*) *hyaline casts*, also called colloid, vitreous, and fibrin casts; and (*b*) *waxy casts*.

(*a*) *Hyaline casts* are pale and translucent; their surface is uniformly homogeneous or striated or fibrillar in appearance. Owing to their extreme pallor and to their transparency they are often detected with great difficulty, and sometimes can be recognized only by the presence of substances, such as crystals, salts, and the like, deposited on the

PLATE II.

Hyaline casts, thick and slender, straight and convoluted. Finely and coarsely granular casts; epithelial casts; epithelial cells from the kidneys and urinary passages; isolated leukocytes and amorphous granules. Chronic interstitial nephritis (arterio-sclerotic contracted kidney) (Rieder).

surface. They may be rendered more readily visible by being stained with weak iodin solution or some other stain. Hyaline casts take the same stains as coagulated albumin; thus, for example, they are stained violet by Ehrlich's triacid mixture; and in other respects they also give the reactions of albumin.

[It is often better to begin the search for casts with a drop of urine on the slide without a cover-glass and using a low power. In this way a much larger and thicker field can be seen, a great advantage where the casts are scattered. Care is necessary, also, not to use too strong a light, as the delicate, transparent hyaline casts may otherwise readily escape detection.—ED.]

There has been much dispute about the nature and origin of these casts. The oldest view, to which reference has been made on page 44, is that they consist of coagulated fibrin derived from an exudate, such as is found in inflammation elsewhere in the body. Not to mention other objections, this view is refuted by the fact that *hyaline casts unquestionably occur in conditions in which there is not the faintest sign of inflammation*, as in congestion of the kidneys, in simple amyloid degeneration, in the above-mentioned cases of so-called dyscrasic albuminuria in which no abnormality of any kind can be demonstrated in the kidneys (p. 38), and finally in the albuminuria of the newborn (see p. 37).

Then again, as Rovida[1] demonstrated long ago, these casts do not give the same chemical reactions as true fibrin. It is true that, in spite of this discovery of Rovida's, it was argued later, from the fact that many of these casts present a striated or fibrillar appearance like that of true fibrin, and that many of them take the so-called Weigert's fibrin stain (a blue color when treated with anilin water, gentian-violet, and iodin), that they in fact consist of exuded and coagulated fibrin. But in the first place the stain referred to is not by any means specific for fibrin, for O. Lubarsch[2] has shown that the stain is equally characteristic of other fibrillar and hyaline substances that have nothing to do with fibrin; and, conversely, hyaline casts behave differently in the presence of other fibrin stains, such as those of Altman and Russell; and finally it has been discovered by Th. Burmeister[3] that the true products of exudation and transudation, which are found coagulated in the capsules of the glomeruli and in the uriniferous tubule after temporary compression of the renal veins, do not stain by Weigert's method.

This leaves only two possible sources for the albuminous substance of hyaline casts—namely, the albumin of the blood-serum and the epithelial cells of the uriniferous tubules.

As regards the former, the widespread impression that the albumin which escapes from the vascular system at once undergoes coagulation in the capsules of the glomeruli or in the uriniferous tubules, and so leads to the production of casts, is absolutely mistaken, as the writer

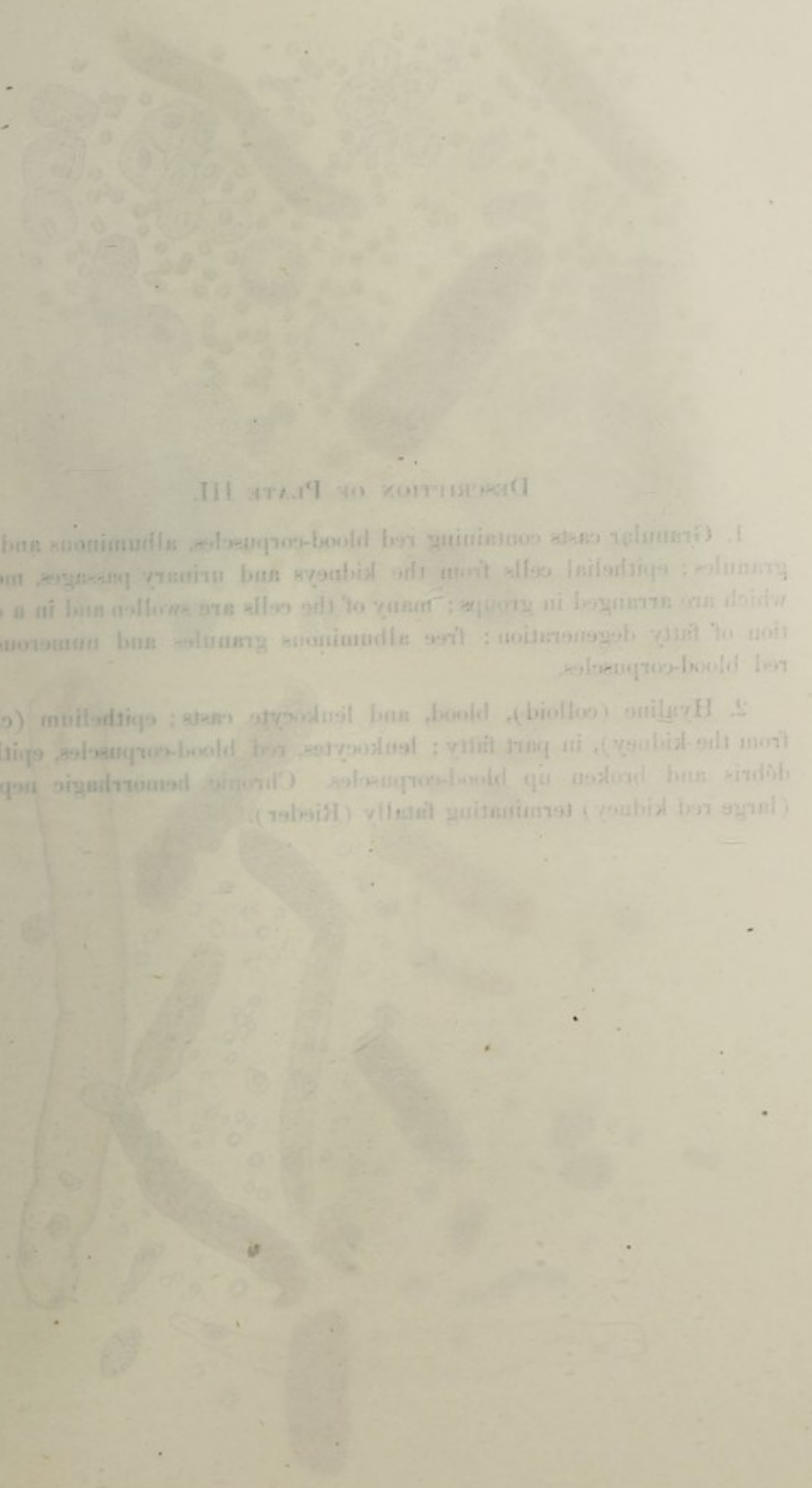
[1] Rovida in *Moleschott's Untersuchungen zur Naturlehre*, etc., 1872, xi., p. 1.
[2] *Centralbl. f. allg. Pathologie and path. Anat.*, 1893, iv.
[3] *Virchow's Archiv*, cxxxvii., 1894, p. 442.

explained some time ago.[1] In order that coagulation be effected some additional factor is required, for the urine itself rather tends to retard than to favor the process of coagulation, as has been shown beyond the possibility of a doubt, both experimentally by J. C. H. Lehmann[2] and by clinical observations. For example, in chyluria, in which the urine contains albumin in a very coagulable condition, and therefore coagulates very readily on exposure to the air, casts are almost never found. The writer, in a case of fibrinuria in which the urine was peculiarly coagulable, was unable to find any casts (see p. 43). It is also to be observed that there is no definite relation between albuminuria and the number of casts contained in the urine. Albumin may be quite abundant in a urine containing very few or no casts at all (amyloid kidney, contracted kidney); and, inversely, even hyaline casts are not infrequently found unassociated with albuminuria, as has been mentioned on page 45, particularly in various forms of poisoning—in sulphuric acid poisoning (O. Wyss,[3] Litten,[4] E. Fränkel and Reiche[5]) and alcoholic poisoning (K. Glaser[6]); in beginning stasis of the kidney (Radomyski[7]); in cholera; in jaundice; and after protracted constipation (Kobler, Wallerstein (see p. 42)).

These last observations suggest that casts, at least in many cases, have nothing to do with the albumin in the blood-serum, unless it be assumed that all of the escaping albumin coagulates to form casts without leaving any albumin in solution to make it possible for an albuminuria to make its appearance. But the occurrence of casts without albuminuria in those forms of infection and intoxication in which degeneration and disintegration of the epithelial lining of the uriniferous tubules have been proved to take place is strong evidence that the casts are formed from these epithelial elements. When the actual findings of Wallerstein,[8] in a case of cylindruria produced by constipation, are analyzed, it is found that there were no appreciable alterations in the glomeruli and their capsules; while on the other hand the epithelium of the convoluted tubules, and to a lesser degree that of Henle's loops, was in all stages of degeneration and presented every kind of transitional forms from these degenerated cells to hyaline casts. Lastly, the finding of very broad casts in the collecting tubules, which could not well have passed through the narrow Henle's loops, is difficult to square with the view that casts are formed from albumin that has escaped from the glomeruli (Aufrecht[9]).

For all these reasons it is impossible to regard coagulation of the albuminous bodies in the blood-serum as the cause of hyaline casts, at all events, not for the greater portion of them; and it is more plausible to assume that the principal part in their formation is taken by the

[1] *Virchow's Archiv*, lx., p. 476, and *Die Albuminurie*, etc., p. 22.
[2] *Ibid.*, xxxvi., p. 127.
[3] *Wien. med. Presse*, 1868, p. 212.
[4] *Berlin. klin. Woch.*, 1881, No. 42.
[5] *Virchow's Archiv*, cxxxi., p. 130.
[6] *Deutsch. med. Woch.*, 1891, No. 43.
[7] Radomyski in *Unverricht's Ges. Abhandl. aus d. med. Klinik in Dorpat*, Wiesbaden, 1893, p. 423.
[8] *Loc. cit.*
[9] *Centralbl. f. inn. Med.*, 1894, No. 19.



Description of Plate III.

1. Granular casts containing red blood-corpuscles, albuminous and fatty granules; epithelial cells from the kidneys and urinary passages, most of which are arranged in groups; many of the cells are swollen and in a condition of fatty degeneration; free albuminous granules and numerous free red blood-corpuscles.

2. Hyaline (colloid), blood, and leukocyte casts; epithelium (chiefly from the kidney), in part fatty; leukocytes, red blood-corpuscles, epithelial débris and broken up blood-corpuscles. Chronic hemorrhagic nephritis (large red kidney) terminating fatally (Rieder).

PLATE III.

1

2.

epithelial cells of the uriniferous tubules. The mechanism of their formation is susceptible of various interpretations. It is possible that the epithelial cells die, and after being converted into the hyaline substance fuse into the form of casts, a process which appears to be practically established by the microscopic picture, as the same cast frequently shows the various stages of gradual conversion of the epithelial elements into hyaline substance. Another possibility is that the death of the epithelial cells removes the barrier between themselves and the surrounding albuminous fluid (lymph), which then becomes mingled with the necrotic cellular material and forms a coagulum (Weigert[1]). Lastly, the view is upheld that the epithelial cells, by a kind of secretion, provide a coagulating material from which the casts are formed.

(*b*) *Waxy casts*, so called on account of their faintly glistening appearance suggesting yellowish wax, are usually broader and of a firmer consistence than hyaline casts, and, as a rule, present small clefts or fissures. Nothing definite is known in regard to their formation. It seems probable that they represent the results of transformation of other casts which have been retained a long time within the uriniferous tubules and have thus gradually acquired a firmer consistence. In some cases waxy casts can be stained with Lugol's iodin solution and sulphuric acid in a manner resembling the amyloid reaction; but they are not by any means characteristic of amyloid degeneration of the kidneys.

From the foregoing, the great *diagnostic significance* of urinary tube casts is at once apparent. They are always indicative of a *pathologic process* in the kidneys, more particularly in the epithelial elements, ranging from a mere nutritional or functional disturbance to complete destruction of the parenchyma. It goes without saying that epithelial casts indicate pronounced desquamation of the epithelium; fatty granular casts or hyaline casts covered with fatty epithelium, a degenerative process; casts covered with leukocytes—which are almost always uninuclear—an inflammatory condition; and casts characterized by deposits of red blood-cells or true blood-casts, hemorrhages within the renal parenchyma.

The name *cylindroid* has been given by Thomas[2] to a variety of coagula which, while resembling casts, are not circular or cylindric in shape, but rather more like ribbons with longitudinal striations; they are generally excessively long and often bent or folded over; sometimes they are divided longitudinally or dichotomously. As a rule, they are very narrow, and very rarely attain the width of ordinary casts. A variety of transitional forms between casts and true cylindroids also occurs. There are structures which present the characteristic of cylindroids at each extremity, while the central portion in no wise differs from a cast. For these reasons, and because they give the same chemical reactions as casts, Thomas is inclined to believe that they have the

[1] *Volkmann's Sammlung klin. Vorträge*, Nos. 162 and 163.

[2] *Arch. der Heilk.*, xi., 1870, p. 148; and *Gerhardt's Handb. d. Kinderheilk.*, iv., 3, 1878, p. 294.

same origin and significance as urinary casts. According to the writer's experience, distinct cylindroids occur in cases of catarrh of the urinary passages, extending into the pelvis and possibly somewhat further into the papillæ, and in themselves, therefore, in nowise indicate disease of the renal parenchyma.

A certain resemblance to urinary casts is possessed by the so-called "mucous" coagula and collections of micrococci arranged in the form of cylinders; but with a little practice the confusion is readily avoided, and another point of differentiation is that these structures are insoluble in acetic acid. [Some of the salts of the urine—*e. g.*, urates—may be arranged in the form of casts, and may, indeed, really be molded into that shape in the tubules of the kidney.—Ed.]

HEMATURIA.

The term hematuria is used to designate the admixture of blood or red blood-cells with the urine, or the evacuation of pure blood from the urinary passages. In the latter case the nature of the evacuated fluid can hardly remain in doubt; in the former case the color will differ more or less from that of pure blood according to the quantity mixed with the urine, and may be a brownish red or the color of more or less diluted meat juice. If the admixture of blood is so slight that it does not affect the macroscopic appearance of the urine, it is not customary to employ the term hematuria. When the urine contains a very large percentage of blood-fibrin, clots are usually present at the same time.

Hematuria may be simulated in various ways. Blood not derived from the urinary apparatus may become mixed with the urine, as often happens, for example, during menstruation, and not infrequently in cases of hemorrhage from structures contiguous to the orifice of the urethra, such as the anus or vagina; or the blood may be intentionally mixed with the urine for purposes of deception. It may also be simulated by the presence of other pigments, giving the urine an appearance more or less similar to that of bloody urine.

The former group of fallacies is not difficult to avoid with a little care, and, if necessary, the urine may be withdrawn with the catheter. To distinguish blood from other pigments, various methods are available:

1. The most important of these is **microscopic examination** for the presence of red blood-cells of the fluid or of the sediment obtained by allowing the urine to stand or by centrifugation. In acid urine the cells are preserved intact for a considerable period of time; when the urine is highly concentrated they assume the shape of a mulberry; while in urine of a very low specific gravity they become paler by the washing out of the hemoglobin, but may still be recognized by their biconcave shape and reddish-yellow color. In certain cases they present the alteration known as *fragmentation*. In addition to red blood-cells, leukocytes are also present in numbers corresponding to the proportions of the two structures in the blood; they are, therefore, usually less numerous than the red cells. As the urine undergoes decomposition, the red blood-cells are broken up into reddish-brown or

yellowish-brown granular masses. These at first retain approximately the shape of the original cells; gradually, however, they fall apart or form irregular heaps. (Compare Hemoglobinuria.) The finding of red blood-cells is in itself quite sufficient to establish the presence of blood in the urine. In doubtful cases and as confirmatory tests the examination should be supplemented by testing for *hemoglobin* either with the *spectroscope* or by *chemical means.*

2. By means of the **spectroscope,** hemoglobin or hematochromogen can be demonstrated. The urine must be clear, or at least not excessively turbid; it should be filtered, and if it is very dark, diluted with water.

Freshly passed urine containing blood presents in the spectrum the two lines of *oxyhemoglobin* between Frauenhofer's lines D and E in the yellow and in the green. The line in the yellow is the narrower. If the urine and blood have already undergone decomposition, the specimen will contain *methemoglobin* instead of, or in addition to, hemoglobin; that substance presents in the spectroscope three lines, of which the one in the red, between the lines C and D and nearer the line C, is the most characteristic.

Hematochromogen may be demonstrated after Donogany[1] with pyridin by adding to 10 c.c. of urine 1 c.c. each of ammonium sulphate and pyridin. A reduction takes place at once and the color of the fluid becomes an *orange red.* In the presence of very small quantities the spectroscope may still show two lines, a dark line at the boundary between D and E, and a broader, paler band between E and C in the green.

3. The **chemical tests** for blood are as follow:

(*a*) *Heller's Test.*—The urine is rendered strongly alkaline by the addition of caustic potassium or sodium and boiled. The earthy salts separate and, as they cool, precipitate the blood-pigment, which collects at the bottom as a distinct bright-red or rust-colored sediment. Vegetable pigments, such as those of rhus, senna, and the like, also appear as reddish flocculi, but with a more violet tint; besides, when the urine contains vegetable pigments, its color becomes darker on the addition of alkalies and lighter on the addition of acids.

(*b*) *Almén's Guaiac Test.*—Equal parts of old oil of turpentine and fresh tincture of guaiac are added to acid urine and the whole thoroughly shaken. If blood or blood-pigment is present, the mixture takes on a more or less distinctly bluish color. A similar coloration, however, is produced by pus.

[In place of the tincture of guaiac a solution of aloin in alcohol may be employed, a rose-red color indicating blood.

Minute quantities of blood can be detected by the method of Müller and Weber that is employed for the detection of blood in the feces or stomach contents. To about 3 c.c. of urine 1 c.c. of glacial acetic acid is added, and then ether, the mixture being gently shaken. The decanted ether can then be tested for blood by the guaiac or aloin method.—Ed.]

(*c*) *Teichmann's Test For Hemin Crystals.*—A small quantity of the sediment remaining on the filter paper is spread out with a knife point on a slide and carefully allowed to dry by evaporation; a crystal of

[1] *Virchow's Archiv,* cxlviii., p. 234.

sodium chlorid is then mixed with the smear, a drop of glacial acetic acid is added, and the cover-slip applied. A few drops of glacial acetic acid are then slowly introduced between the slide and the cover-slip until the latter begins to float. The slide is now heated until bubbles begin to form, the heat is then taken away, and as much glacial acetic acid added drop by drop as will evaporate on the still warm slide. If blood-pigment is present the microscope will show, after the specimen has cooled, scattered through the colorless remains of the sodium chlorid reddish-brown rhombic plates and columns which are insoluble in water, ether, and alcohol, but readily dissolve in caustic potash.

Spectroscopic and chemical demonstration of the presence of blood-pigment does not take the place of microscopic examination, for blood-pigment may be present in the urine unassociated with blood-corpuscles, a condition which is known as hemoglobinuria, and which will be discussed separately on page 55.

After the existence of true hematuria has been demonstrated, the source of the hemorrhage must be determined, as it is most important to decide whether the blood is derived from the *renal parenchyma* itself or from the *urinary passages*—the pelvis of the kidney, the ureters, bladder, or the urethra. The decision may under certain circumstances present considerable difficulty and cannot always be based solely on the examination of the urine; other factors in the diagnosis are the mode of evacuation and other signs pointing to one or the other portion of the uropoietic system. Diseases of the urinary passages will be discussed in their appropriate places; for the present we are concerned with *hemorrhage from the kidney itself*, or *renal hematuria*.

The blood and urine are usually intimately mingled, and the specimen does not, as a rule, contain many blood-clots. In the very rare cases of hemorrhage from a large vessel within the kidney, as a result of traumatism, the rupture of an aneurism or of a dilated varicose vein, large macroscopic blood-clots may be found. But in the great majority of cases, owing to the mixture of the two fluids, the color is uniform, either more or less bloody, or resembling meat juice, or dichroistic, and there is no difference in color between the first and the last urine evacuated. *Fragmentation of the red blood-cells* is a very important sign of renal hematuria (Gumprecht[1]). It does not occur in hemorrhage derived from a point below the kidneys, and is therefore believed by the author mentioned to be caused by the action of the urea contained in the renal epithelium on the blood-cells. According to D. Gerhardt,[2] the red blood-cells in renal hemorrhage are spheroid, and leather-colored or decolorized, and the same brownish-yellow color is observed in all the morphologic elements derived from the kidneys.

This color is due to the conversion of hemoglobin into hematin by the continued action of the urine. B. Goldberg[3] mentions the following points as diagnostic of renal hematuria: If the urine contains less

[1] *Deutsch. Arch. f. klin. Med.*, liii., 1894, p. 45.
[2] *Mittheilungen aus den Grenzgebieten der Med. u. Chir.*, 1897, ii., p. 739.
[3] *Berlin. klin. Woch.*, 1895, No. 49.

than 1000 to 3000 red blood-cells, as counted by the Thoma-Zeiss apparatus, a distinct flocculent precipitate of albumin in the filtrate indicates renal albuminuria. And further, if the fraction obtained by dividing the parts of albumin contained in 1000 parts of the filtrate, which is free from hemoglobin (?), by the number of red blood-cells contained in 1 c.mm. is greater than $\frac{1}{3000}$, it indicates the existence of false as well as true (renal) albuminuria. If the fraction is smaller, there is little or no renal albuminuria. (See p. 19.)

In cases of renal hemorrhage the urine usually contains casts, both cellular blood-casts and other varieties (see p. 46), as well as renal epithelium and other signs indicating a renal affection. The urine, after being clarified by sedimentation and filtration, as a rule contains more or less albumin; while if the hemorrhage is derived from the urinary passages, the blood can usually be more readily separated from the urine, and the latter contains little or no albumin unless the disease of the renal passages, which is the cause of the hemorrhage, is associated with some renal affection.

The **causes** of renal hematuria, in rare cases, are of a *traumatic nature*, as a severe blow or a shaking up on horseback, affecting particularly the region of the kidneys. Other traumatic forms are the hematuria due to compression of the kidney, as in palpating a movable kidney (see Special Portion, p. 140), or to *concretions* or the ulceration they produce. Although the seat of the injury is the pelvis of the kidney, similar traumatisms sometimes occur in the papillæ of the kidney. Another cause that is not very infrequent is *embolism* (*hemorrhagic infarct* and *malignant new growths*, especially tuberculosis, sarcoma, carcinoma, and cystic kidney). The various forms of *acute*, *subacute*, and *chronic diffuse nephritis* may be attended by hemorrhages, particularly the acute forms, and among the chronic a few of the so-called "hemorrhagic" forms. In *circumscribed* (purulent) nephritis traces of blood are found mixed with the pus, while in cases of traumatism the blood occurs in more considerable quantities. In amyloid disease and in the ordinary forms of *renal congestion* associated with diminished cardiac activity hemorrhage is not a feature; at most a few traces of blood may be found microscopically. But in the congestion due to *thrombosis of the renal veins*, especially in the newborn, hematuria is a common symptom, unless there is suppression of the urine. Lastly, *aneurisms* and *varicosities* of the renal veins may give rise to more or less abundant hemorrhage.

Renal hemorrhage is not uncommon in the various forms of the *hemorrhagic diathesis*, such as hemophilia, scorbutus, morbus maculosus Werlhofii, and purpura, in which the manifestations may be entirely confined to the kidneys ("*renal hemophilia*"—Senator, Grosglik, E. Hahn, and others).[1]

Renal hemorrhages are sometimes due to the presence of *parasites*, which usually reside in the urinary passages (*q. v.*) and in exceptional

[1] Senator, *Berlin. klin. Woch.*, 1891, No. 1; Grosglik, in *Sammlung klin. Vorträge*, N. F., 1898, No. 203; E. Hahn, *Münch. med. Woch.*, 1900, No. 42.

cases invade the kidneys themselves. These parasites, for the most part, are those which occur in the tropics (*Distoma hæmatobium* and *Filaria sanguinis—hæmaturia intertropica*—see p. 438); an ameba (*Sporydium polyphagum*) discovered by Bonome[1] in sheep affected with hematuria; and an acarus found by Myake and Scriba[2] in a case of renal hemorrhage, and designated by them *Nephrophages sanguinarius*. (See Hemoglobinuria, p. 61.)

Hereditary renal hemophilia was observed by H. W. Attlee[3] and even more extensively by L. G. Guthrie,[4] who observed the condition altogether in 12 children of 2 sisters, who were themselves sufferers from periodic hematuria without any other demonstrable cause. Other signs of hemophilia were not present in these patients.

There still remains a group of cases in which nothing can be found in the kidneys or outside of the kidneys to account for the hemorrhage and the accompanying continuous or paroxysmal pain; these have accordingly been called cases of "*essential renal hemorrhage.*"[5]

In a few of them careful examination revealed the presence of certain changes which are to be regarded as the cause of the hemorrhages; thus, for example, angiomatous proliferation was reported by E. H. Fenwick[6] in the papillæ, and after the removal of the latter by papillectomy the hemorrhage ceased.

[Cases of renal hematuria without demonstrable lesion at operation have been described also by M. L. Harris.[7]

The editor has seen a case of painless hematuria in a man of about forty-five, the bleeding having lasted for ten months. Cystoscopic examination showed that it came from the right ureter. The examination of the kidney at the operation revealed nothing pathologic in the pelvis or kidney proper. A section of the kidney showed normal structure. The hemorrhage ceased ten days after the operation, and at the time of writing, twenty weeks after the patient has left his bed, has not recurred, and the man is apparently well and is at work.—Ed.]

In other cases more or less extensive inflammatory processes have been found in the kidneys, and the hemorrhages have therefore been ascribed to a hemorrhagic nephritis. But the inflammatory changes in some of these cases were very slight and the process had evidently subsided long before, so it is not probable that these changes had any causal connection with the hemorrhages. Such cases and a few others in which no changes, and certainly no nephritic processes, could be detected even with the aid of the microscope, suggest that these essential hemorrhages depend on a nervous disturbance, and are either angio-

[1] *Virchow's Archiv*, 1895, cxxxix., p. 1.
[2] *Berlin. klin. Woch.*, 1893, No. 16.
[3] *St. Bartholomew's Hosp. Jour.*, December, 1901.
[4] *Lancet*, May 3, 1902, xviii.
[5] As a great deal of literature has appeared on this subject within the last few years, the writer will refer the reader to the following: Grosglik, in *Sammlung klin. Vorträge*, N. F., 1898, No. 203; Albarran, *Ann. des maladies des organs génitaux-urinaires*, 1898 and 1899; R. Robinson, "Pathogénie et traitement des hématuries renales dites essentielles," Paris, 1899; Guyon, *Assoc. française d'urologie*, IV. Session, 1899, and the discussion; J. Israel, *Chirurg. Klinik der Nierenkrankheiten*, Berlin, 1901, p. 403; H. Senator, *Deutsch. med. Woch.*, 1902, No. 8.
[6] *British Med. Jour.*, 1900, No. 3.
[7] *Philada. Med. Jour.*, 1898.

neurotic or neuropathic in nature (Botkin-Sokoloff,[1] G. Klemperer,[2] Lancereaux,[3] Poljakoff[4]). (Compare also Nephralgia, p. 145.) [Schuller[5] has recently reviewed this subject, and questioned the non-existence of demonstrable changes.—Ed.]

Sometimes these hemorrhages cease of their own accord; in other cases they yield to remedies and therapeutic measures calculated to combat the nervous disposition, such as quinin and hydrotherapy; in a third group of cases recovery has been brought about by exposing the kidney, dividing it lengthwise, and sewing it together again, or sometimes merely by exposing it without splitting the viscus. It is difficult to understand how these last measures in particular should bring about the cure of a nephritis; on the contrary, they would appear to be more calculated to produce an inflammation or aggravate an already existing one. The nephritis should therefore not be regarded as the cause of these hemorrhages, which for the present must be interpreted as having a vasomotor basis, or as being of an entirely unknown nature.

In the **treatment** of renal hematuria the causes which produce it must be removed; for this the reader is referred to the sections devoted to the respective subjects. In the *renal hemophilia* extirpation of the bleeding kidney, and in other cases, as the writer has said, simple enucleation (Ausschälung) of the viscus, whether it was split or not, and replacing the same brought about a cure; in one case the renal hemorrhage ceased when the bladder was opened (Passet)![6]

HEMOGLOBINURIA.

The term *hemoglobinuria* (hematinuria) is used to designate the excretion of blood-pigment in the urine with total absence of red blood-cells, or with only a relatively small number that cannot be considered sufficient to explain the altered, bloody, or dark, blood-like appearance of the urine. The pigment found is not always unchanged hemoglobin; quite frequently it consists of methemoglobin; in fact, Hoppe-Seyler[7] asserts that free hemoglobin—that is, hemoglobin not combined with red blood-cells—never occurs in solution in fresh urine that has not undergone decomposition, or at most occurs in the very rarest cases, and that the substance under these circumstances is methemoglobin, so that it would be more correct to describe the process under consideration as *methemoglobinuria*.

The phenomenon is observed:

(1) When hemoglobin in sufficient quantity is *injected into the blood.*

(2) After various experimental procedures resulting in *solution of the red blood-cells;* as, for example, the transfusion of blood or even serum from another animal, the injection of pure water, oil, glycerin, gallic-acid salts, and other like substances into the blood.

[1] *Berlin. klin. Woch.*, 1874, No. 20.
[2] *Deutsch. med. Woch.*, 1897, Nos. 9 and 10.
[3] *Bull. de l'Acad. de Méd.*, 1900, No. 34.
[4] *Deutsch. med. Woch.*, 1899, No. 44.
[5] *Wien. klin. Woch.*, 1904, p. 477.
[6] *Centralbl. f. die Krankh. der Harn- and Sexualorgane*, 1896, ix.
[7] *Physiol. Chemie*, 1881, p. 822.

(3) It may be produced by a number of organic and inorganic *poisons* if they make their way into the blood in sufficient quantities, whether from the intestinal tract, the skin and mucous membranes, by injection, or by inunction. The list of poisons includes a number of substances that are used for therapeutic purposes, and the employment of which calls for special care; they are chlorates, pyrogallic acid, phenol, naphtol, glycerin, tincture of iodin, arseniuretted hydrogen, hydrogen stibiate, hydrogen sulphid, sulphuric acid, hydrochloric acid, toluylendiamin, phenylhydrazin, quinin, and a poison contained in morils (*Helvella esculenta*).

(4) After extensive *burns* and in consequence of *severe infectious diseases*, such as scarlet fever, erysipelas, typhoid fever, pernicious malarial and tropical fever, pernicious forms of jaundice, and Winckel's epidemic hemoglobinuria of the newborn, and in many cases of severe acute and chronic so-called hemorrhagic nephritis. In these cases the red blood-cells are probably dissolved or hemolyzed by the action of the causal micro-organisms or other toxins.

[In fact, hemoglobinemia, that is in some cases, at least, the basis of hemoglobinuria, reminds one forcibly of the phenomena of hemolysis, laking of the blood, etc., as seen in the test tube, and which have been so thoroughly investigated by Ehrlich and his followers. The drugs and chemicals above mentioned, and the toxins of many of the infectious diseases, would seem, in certain strengths and under certain conditions not clearly understood, to act as hemocytotoxic or hemolytic agents freeing the hemoglobin, which escapes through the kidney. Michaelis[1] observed hemoglobinuria during the absorption of the blood that escaped from the rupture of an ectopic pregnancy. Usually, such blood-absorption causes urobilinuria. Michaelis is inclined to regard the hemoglobinuria in this case as due to the hemolytic, really autolytic, action of the escaped blood. Ensor and Barratt[2] observed hemoglobin in the urine of a man after extensive bruising of the forehead by pounding. Here, also, the explanation offered was that some hemolytic (autolytic?) process due to the extravasated blood was the cause of the hemoglobinemia, and, therefore, of hemoglobinuria. The experimental work of Todd[3] is suggestive along the same lines. Using a toxin derived from Bacillus megatherium, he produced hemoglobinuria by injecting it into guineapigs. By using an antiserum, huge doses of the megatherium toxin could be injected without producing hemoglobinuria.—Ed.]

(5) Lastly, there is the so-called *periodic* or *paroxysmal* (*intermittent*) *hemoglobinuria*, a peculiar chronic affection in which hemoglobin appears in the urine at intervals, accompanied by characteristic clinical symptoms. Because of the practical importance of this disease, as well as the theoretic interest attaching thereto, it merits detailed description.

Although it is probable that the disease had been observed before his time, its true nature was first recognized by Dressler,[4] who, in the year 1854, demonstrated hemoglobin in the urine in the absence of red

[1] *Deutsch. med. Woch.*, No. 4, 1901.
[2] *Med.-Chi. Trans.*, vol. lxxxvi., p. 165.
[3] *Lancet*, Dec. 14, 1901.
[4] *Virchow's Archiv*, 1854, vi., p. 264.

blood-cells. His discovery was followed by a series of communications, chiefly by English physicians (G. Harley,[1] Dickinson,[2] W. Gull,[3] Hassal,[4] Pavy,[5] and others), under the caption of "intermittent or winter hematuria or hematinuria," and later by Lichtheim,[6] Kobert, Küssner,[7] and many others in Germany, so that we now have a fairly extensive literature on this disease.

The attacks are frequently ushered in by a *chill* which is followed by *fever*, the temperature at times rising to 40° C. (104° F.) and over. [At the time of the chill the temperature may be low. Saundby[8] cites a case in which the axillary temperature was at first only 96.1° F. —Ed.] The fever is accompanied by dragging pains in the back, running down into the thigh, pallor of the skin, and later cyanotic discoloration of the finger-tips, toes, and ears. [In a case reported by Rohrer[9] bluish or violet discoloration of the ear was followed by superficial gangrene. Somewhat similar gangrenous effects have been seen by Hilton Fagge and Pye-Smith. In some instances Raynaud's disease has been associated with paroxysmal hemoglobinuria.—Ed.] Lassitude, a tendency to yawning, oppression, nausea, pains in the hypochondriac regions, and occasionally neuralgic pains in the extremities, have also been observed. In some cases there is a slight *icteroid* discoloration of the skin and mucous membranes or a macular hyperemia with *urticarial wheals*. [Circumscribed edema is sometimes seen, and rarely purpuric lesions.—Ed.] Parques[10] had a patient in whom urticaria could be produced by cooling the hands; the wheals were of a peculiar red color and lasted from one to two hours. The fever is followed by sweat and subsidence of all the subjective symptoms.

The *urine* evacuated during the attack appears bloody or dark reddish-brown. On spectroscopic examination it shows the presence of methemoglobin, either alone or in association with hemoglobin (see Hematuria, p. 51); and on microscopic examination amorphous blood-pigment in granules or irregular masses or in the form of casts or, occasionally, in crystalline form is usually found, but no red blood-cells or very few. In addition the sediment often contains hyaline and granular casts, renal epithelial cells whose nuclei are also stained red, and not infrequently calcium oxalate in unusual abundance. The urine always contains albumin and often bile pigment; but, according to Leube,[11] bile acids are absent. In one instance the latter found a diastatic ferment in the urine. As the attack subsides the color of the urine becomes paler and paler, until finally it is impossible to demonstrate any blood-pigment; the albumin, however, does not disappear until after a few

[1] *Med.-Chi. Trans.*, 1865, xlviii., p. 161. [2] *Med.-Chi. Trans.*, 1865, xlviii., p. 175.
[3] *Guy's Hosp. Reports*, 1866, xii. [4] *Lancet*, 1865, i., p. 368.
[5] *Guy's Hosp. Reports*, xviii., and *Lancet*, 1868, ii., p. 33.
[6] *Volkmann's Sammlung klin. Vorträge*, 1878, No. 134.
[7] *Berlin. klin. Woch.*, 1878, No. 43, and *Deutsche. med. Woch.*, 1879, No. 37.
[8] *Renal and Urinary Diseases*, p. 418, Philada., 1897.
[9] "Ueber ein Symptom der Hämoglobinurie: Cyanose und Gangrän am Ausseren Ohre," *Zeitschr. f. Ohrenheilk.*, xxxix., 2.
[10] *Semaine med.*, May, 1898. [11] *Würzburger physikal.-med. Sitzungsber.*, 1886.

hours or days. According to O. Rosenbach[1] and O. Silbermann's[2] observations, the appearance of blood-pigment at the beginning of the attack also is preceded by the excretion of albumin in the urine. [Traces of hematoporphyrin are at times found in the urine along with the hemoglobin or after the hemoglobin has disappeared. An unusual, if not unique, case has been described by J. Pal,[3] in which, in an old luetic of sixty-six years, several attacks simulating paroxysmal hemoglobinuria had occurred, following exposure to cold. Pal found, however, on examining the urine during one of these attacks, that the dark color was due to a large amount of hematoporphyrin. Blood and hemoglobin were absent, albumin and casts present. The next day the urine was normal. He describes the case, therefore, under the caption Paroxysmal Hematoporphyrinuria.—ED.]

The *internal* organs do not present any sign of abnormality that could be connected with the disease except possibly enlargement of the spleen and liver, which however is not constant, and a faint systolic (hemic) murmur in the heart. During the intervals between the attacks no marked symptoms are observed, at most a variable degree of anemia and weakness. Occasionally, it appears that the disease may leave a chronically enlarged spleen (Bettmann[4]).

During the attack the blood, according to Hayem[5] and F. Chvostek,[6] exhibits an unusual tendency to coagulation, but the coagula are readily dissolved. The red blood-cells are considerably diminished in number and show little tendency to rouleaux formation; some of them are quite decolorized, Ponfick's so-called "shadows" or "shadow cells." The number of leukocytes is usually somewhat increased, and the cells sometimes contain in their interior red blood-corpuscles or the products of their disintegration. According to Chvostek, masses of pigment and an unusual number of blood-plaques are also found. Hemoglobin is frequently, but not by any means constantly, found dissolved in the blood-serum, lending to the latter a reddish or ruby-like tint (hemoglobinemia).

Other blood-changes have also been reported; thus, for example, it is said that the isotonicity of the blood is altered, but neither Viola[7] nor the writer[8] was able to confirm this observation. On the other hand, the writer found that when blood was withdrawn *during the attack* the red cells took on a very deep stain with methylene-blue or methyl-violet, a phenomenon which occurs much more rarely in the intervals of freedom. Vaquez and Marcano[9] found a much greater reduction in the hemoglobin than in the number of red blood-cells during the attack. Finally, A. v. Koranyi[10] found that during the attack the molecular

[1] *Berlin. klin. Woch.*, 1880, Nos. 10 and 11.
[2] *Ibid.*, 1886, Nos. 29 and 30.
[3] *Centralbl. f. innere Med.*, xxiv., No. 25, 1903.
[4] *Münch. med. Woch.*, 1900, No. 23.
[5] *Gaz. hebdom.*, 1889, No. 11.
[6] *Ueber das Wesen der paroxysmalen Hamoglobinuri*, Leipzig and Wien, 1894.
[7] *Il. Policlinico*, 1895, ii.
[8] S. Berditschewsky, "Ueber zwei Falle paroxysmaler Hamoglobinurie," *Diss.*, Berlin, 1896.
[9] *Archives de Méd. exp.*, 1896, viii.
[10] *Zeits. f. klin. Med.*. 1898, xxxiv., p. 38.

concentration of the blood was heightened as in renal insufficiency, and that the serum had a solvent action on the red blood-cells. [This is practically confirmed by Ardein-Delteil.[1]—Ed.]

For all these reasons it appears that the red blood-cells in this affection have a lessened power of resistance to chemical as well as to physical influences. Their sensitiveness to physical impressions is demonstrated by Chvostek's[2] discovery that when the blood of a person suffering from periodic hemoglobinuria is shaken up, the red blood-cells become partially dissolved. Mannaberg and Donath[3] also found that the resistance of the cells to shaking and to carbon dioxid was diminished.

The attacks vary in *duration* from half an hour to several hours. The *frequency* is also extremely variable, and it is impossible to describe a regular type in this respect. Usually they are less frequent or altogether absent during the warm season and become more common at the approach of winter, cold being the most important exciting cause of the attacks. An attack can often be induced in such patients by the influence of *cold;* in some of them the mere immersion of the hands or feet in cold water is enough (O. Rosenbach, Ehrlich,[4] Boas,[5] and others). Chvostek believes, however, that the cold in itself has nothing to do with it, and that constriction of the finger, which causes a disturbance of the circulation similar to that produced by cold, suffices to bring about the same changes in the blood. This was observed some time ago by Dapper.[6] The next most important exciting cause is *walking,* while other muscular exercises fail to have the same effect. (Fleischer,[7] Kast,[8] Chvostek.) [Possibly some light is thrown on the occurrence of hemoglobinuria after muscular exertion by the experimental work of Camus and Pagniez.[9] They found that by the intravenous injection of hemoglobin containing muscle juice, even though it contained no red blood-corpuscle hemoglobin, hemoglobinuria was produced. They accordingly make three groups of hemoglobinuria: 1. Muscle hemoglobinuria —*i. e.*, through a lesion of the muscles. 2. Blood-corpuscle hemoglobinuria, through destruction of red blood-corpuscles in the vessels. 3. Urine hemoglobinuria, through the hemolytic power of the urine.—Ed.]

Periodic hemoglobinuria occasionally occurs during *pregnancy.* Brauer[10] observed its occurrence in a woman during each of her pregnancies. [Meinhold[11] also has seen hemoglobinuria during the latter months of pregnancy in a woman of twenty-four. A week after the birth of the child the hemoglobin had disappeared from the urine. —Ed.]

According to J. Wolff,[12] *menstruation* may bring on an attack; in rare instances psychic emotion or excesses appear to be the immediate

[1] *Montpelier Médic.*, No. 18, 1903.
[2] *Montpelier Médic.*, No. 18, 1903.
[3] *Deutsch. Arch. f. klin. Med.*, lxv.
[4] *Zeitschr. f. klin. Med.*, 1881, iii., p. 383; *Charite-Ann.*, 1885, x., p. 142.
[5] "Diss. inaug.," Halle, 1881.
[6] Diss., Bonn, 1887.
[7] *Deutsch. med. Woch.*, 1884, No. 52.
[8] *Breslauer ärztl. Zeitschr.*, 1883, No. 12.
[9] *Compt. rend.*, vol. cxxxv., Nos. 6 and 22.
[10] *Münch. med. Woch.*, 1902, No. 20.
[11] *Münch. med. Woch.*, 1903, No. 4.
[12] *Berlin. klin. Woch.*, 1881, No. 47.

cause of an attack. v. Koranyi[1] observed in one of his patients that the attacks occurred oftenest after the eating of salad, and he succeeded in bringing on an attack by the administration of 0.2 gm. of oxalic acid or 0.2 to 0.3 gm. of rhubarb.

Among the **predisposing causes** of the disease, the most important appear to be *malaria* and *syphilis*, including the hereditary form of the latter disease (Copeman, Courtois-Suffet).[2] A case of Saundby's[3] suggests that *heredity* may also play a part as a predisposing factor. Trumpp[4] observed the disease in 2 members of the same family, who were probably sufferers from hereditary syphilis.

[Gilman Thompson,[5] in a review of the subject, including a report of 2 cases, inclines to the view that paroxysmal hemoglobinuria is a profound neurosis chiefly affecting the vasomotor system, and called into activity by exposure to moderate degrees of cold, by muscular fatigue or mental emotion. Syphilis is, he believes, often the groundwork on which the disease is built.—Ed.]

The disease is more frequent in the *male* than in the female sex, and in *middle age* than during the other periods of life; it has, however, been observed in children during the first years of life, and after fifty years of age.

The **course** of the disease is chronic, the duration, as a rule, being counted by years, and but little is known at present in regard to the **prognosis.** Some cases ultimately ended in recovery; in others the outcome was never ascertained, as the patient usually disappeared from observation. A lethal termination as the direct result of periodic hemoglobinuria appears not to have been observed up to the present time.

The *postmortem reports* are accordingly very scanty; most of them concern patients who died of other affections. These showed no characteristic findings. In a case observed by Murri,[6] in which the patient had been free from attacks of hemoglobinuria for six months before death, the kidneys presented infiltration of the epithelial cells of the cortex ranging in color from a yellowish red to black; but in a case observed by Prior[7] the organs were quite normal. F. Widal[8] reports that in a case observed by himself and Dieulafoy, in which death occurred during the attack, he found a deposition of pigment in the kidneys, such as Kelsch and Kiener described in malarial cachexia, and a "sclerosis" of the kidneys, which they regarded as the result of repeated escape of hemoglobin into the kidney substance.

Hemoglobinuria similar to the form in human beings has also been observed in *animals*, especially in horses, in which the disease is known as "black strangury" and "Winddrehe," and represents a much graver affection than in man. In these animals the attacks of hemoglobinuria are accompanied by paresis of the posterior extremities and

[1] *Berlin. klin. Woch.*, 1881, No. 47.
[2] Copeman, *Schmidt's Jahrb.*, 1891, i., p. 50; Courtois-Suffet, *Med. mod.*, March 2, 1895.
[3] *Med. Times*, 1880, May 1.
[4] *Münch. med. Woch.*, 1897, No. 18.
[5] *Med. News*, Oct. 3, 1903.
[6] *Della Emoglobinuria dal Freddo*, Bologna, 1880.
[7] *Münch. med. Woch.*, 1888, No. 30.
[8] *Traité de Medicine par Charcot, Bouchard, Brissaud*, 1891, i., p. 861.

by disturbance of the digestive, respiratory, and circulatory apparatus; death often supervenes in a few days. At the autopsy the paralyzed muscles are found to be edematous and present granular clouding, with fragmentation and hyaline degeneration of the muscle fibers, and the blood contains free hemoglobin of a laky color. The disease has been especially observed in horses that had stood in the stable for several days and had then been used for heavy work, especially in cold weather; hence, cold and excessive exertion of the legs appear to play a part in the etiology of the disease in animals also.

Neat cattle and sheep are subject to a form of endemic hemoglobinuria which, according to the observations of Babes[1] and of Krogius and Heller,[2] is caused by *blood-parasites*. These investigators found a hematococcus, which is contained in the red blood-cells, which stains with Löffler's methylene-blue solution, and occupies an intermediate position between bacteria and protozoa. Babes[3] believes it is the same as that found by Bonome in sheep affected with hematuria (see p. 54).

[Lately several reports have been made of hemoglobinuria in cattle, as well as in horses, dogs, and other animals, in which cases the blood has shown the Piroplasma bigeminum; and ticks have been found as the probable conveyers of the parasite, as shown by Smith and Kilbourne in the case of Texas fever. Hemoglobinuria in these lower animals is thus regarded as piroplasmosis. It is so classed by Ellenberger and Schütz,[4] who give several references to this subject.—Ed.]

As for the **pathogenesis** of (met-)hemoglobinuria, it presents no difficulties in those cases in which free hemoglobin is introduced into the blood in sufficient quantities either directly or by subcutaneous injection, and in those cases in which relatively large quantities of hemoglobin are liberated by wholesale destruction of red blood-cells. The latter series includes cases of intoxication with "cythemolytic" substances and other similar conditions enumerated above under 1 to 3. The *hemoglobinemia* produced by these toxic influences is the chief cause of the hemoglobinuria, the pathogenesis of which has been considerably elucidated by the investigations of Ponfick,[5] who suggests the two following explanations for the liberation of hemoglobin: First, the individual cells break up into a number of small fragments and finally into granular débris, as in burns; the granular remnants of the cells remain in the blood-stream for some time, and finally disappear either as fragments of cells or after they have parted with their hemoglobin. Second, the hemoglobin separates as a whole from the red blood-cells, leaving the latter behind as so-called "shadows."

In both cases the organism may get rid of the liberated hemoglobin without the development of hemoglobinuria, the fragments of red blood-cells being taken up by the spleen; that organ enlarges—the so-called "spodogenous" *splenic tumor* of Ponfick (*σποδός*, ashes)—

[1] *Compt. rend. de l'acad. des sciences*, 1888, cvii., No. 18.
[2] *Arch. de méd. expér.*, 1894, vi., No. 3.
[3] *Virchow's Archiv*, cxxxix., p. 382.
[4] *Virchow u. Hirsch's Jahresbericht*, 1902.
[5] *Virchow's Archiv*, lxii, 1874, p. 273, and *Berlin. klin. Woch.*, 1883, No. 26.

until the remains of the blood-cells have been disposed of. The hemoglobin thus liberated, or in the second variety dissolved in the blood, is utilized by the *liver* in the production of bile or bile pigment, and a temporary hypercholia (polycholia) may develop. Hemoglobinuria does not begin to develop until the powers of the spleen and liver to dispose of the hemoglobin liberated in the blood have become inadequate, and this, according to Ponfick, is the case whenever the mass of liberated hemoglobin exceeds one-sixth of the quantity contained in the entire mass of the blood.[1] The excretion of hemoglobin in the kidney is wholly or chiefly confined to the glomeruli, it being doubtful whether any hemoglobin is excreted by the cells of the tubules. The ferruginous blood-pigment which is often found in these cells can be explained as the result of the absorption of water and inspissation of the fluid that has entered the tubules from the glomeruli (Ribbert).[2]

The occurrence of hypercholia explains the occasional presence of bile pigment in the urine in hemoglobinuria, and the fact that jaundice is sometimes present before hemoglobinuria has developed.

The *albuminuria* which precedes the hemoglobinuria and persists some time after the latter has ceased (see above) is probably to be explained by the wholesale destruction of red blood-cells as well as of hemoglobin, a certain portion of which can be disposed of by the liver, and the resulting escape of an excessive quantity of albumin into the blood and its subsequent excretion through the urine ("hematogenous albuminuria"). This form of albuminuria has also been explained as a sequel of congestion of the kidneys, said to occur when the body is cooled, as a result of the contraction of the cutaneous blood-vessels. But the mere fact that much more abrupt changes in temperature as well as actual chills do not produce congestion of the kidneys nor the characteristic urine of the condition, but, on the contrary, a rather abundant urine of low specific gravity, is against this assumption. Mere contraction of the cutaneous arteries does not produce *venous* congestion in the internal organs, but rather an increase of pressure in the *aorta* and in the *arteries* of the internal organs, including, therefore, those of the kidneys. According to other authorities, albuminuria results from the irritation of the kidney by the hemoglobin; but while this view might explain the albuminuria which *follows* the hemoglobinuria, it fails to explain that which precedes the condition.

The destruction of numbers of red blood-cells and the overloading of the blood with free hemoglobin is followed by a congeries of grave disturbances. In the first place the *absorption of oxygen is diminished*, and the nutrition and efficiency of the organs as well as the entire process of metabolism are thus impaired. In the second place, as the investigations of Al. Schmidt and his disciples as well as those of O. Silbermann[3] have shown, the hemoglobin which circulates freely in

[1] In rabbits hemoglobinuria develops when a quantity of hemoglobin, in the proportion of 1 gm. to each kilogram of the animal's weight, is injected under the skin for more than five or six consecutive days (Schurig in *Arch. f. exp. Path.*, etc., xli.).

[2] *Bibliotheca medica C.*, 1896, pp. 2 and 3. [3] *Virchow's Archiv*, cxix., 1890, p. 488.

the plasma destroys some of the leukocytes, the *fibrin ferment thus becomes greatly increased in quantity*, and this is followed by the usual results—extensive clot formation, obstruction of the circulation of the blood, embolism, and febrile temperature. In the third place the broken-down red blood-cells discharge *other constituents besides hemoglobin into the serum*, substances that are normally not present at all or only in minute traces, such as potassium, iron, and nuclein bodies, and this leads to further disturbances. These pathologic changes furnish a sufficient explanation of the symptoms observed in hemoglobinemia, especially the sense of oppression and dyspnea, the fever, the circulatory disturbances, hemorrhagic infarcts and the like, as well as the changes in the kidneys, such as congestion, degeneration of the epithelium, inflammatory processes, attributable not to the escape of the hemoglobin itself, but to the sequential changes already described, and that are to be observed in the later stages of the disease (O. Silbermann).

As the writer has already said, there can be no doubt that in the conditions noted under 1 to 3 the mechanism of the process is such as has been described, and especially that hemoglobinuria must be regarded as the immediate consequence of *hemoglobinemia*. Under the conditions described in paragraph 4 the same causal connection may be assumed, if not with absolute certainty, at least with great probability; and similarly in cases of burns, in which the blood-changes described can be demonstrated (O. Silbermann), and probably in *severe forms of malarial and tropical pernicious fever*, in which the blood undergoes the same or similar alterations (Kelsch and Kiener[1]). The hemoglobinuria which occurs in *other severe infectious diseases* is also explained by the same mechanism, the destruction or dissolution of the red blood-cells being ascribed to the causes of the infection, the *microbes*, or their metabolic products, the toxins. There is no doubt that this destruction of red blood-cells takes place; but it is questionable whether the destruction is severe enough to cause a hemoglobinemia of sufficient gravity to allow unchanged hemoglobin to make its way into the kidneys. So far as the writer knows, hemoglobinemia has never been demonstrated in these cases any more than in hemoglobinuria, which occasionally occurs in the course of acute or chronic nephritis. Berthier[2] even failed to discover hemoglobinemia in 2 cases of malarial hemoglobinuria.

Finally, as regards the fifth variety—*periodic (paroxysmal) hemoglobinuria*—it is much more frequently attended by hemoglobinemia than the other forms, although in some cases hemoglobinemia is absent; but in the majority of typical cases one is justified in regarding hemoglobinemia as the cause of the hemoglobinuria.

How the dissolution of red blood-cells and the liberation of hemoglobin are effected in this disease, and particularly how the effect is brought about by *lowering of the temperature* and by *walking*, the two exciting causes of an attack, are questions that cannot be answered

[1] *Traité des maladies des pays chauds*, 1889.
[2] *Arch. de méd. expér.*, etc., 1896, viii., p. 628.

with any degree of certainty. One thing seems to be certain, however—that the power of resistance of the red blood-cells to various influences is reduced. It is possible that the albuminuria which in otherwise healthy individuals occurs after a cold bath (see p. 32) represents the transitional stage from hemoglobinemia to hemoglobinuria, being due to diminished power of resistance on the part of the red blood-cells, part of which are destroyed, thus allowing the hemoglobin to be completely converted into bile pigment in the liver, while the albumin is excreted by the kidneys.

Ehrlich believed that the injury to the red blood-cells was due to some agent (ferment?) produced by the vessels under the influence of cold. While this may be plausible, it is impossible to assume that walking, to the exclusion of other muscular exertion, should have the same effect, and Ehrlich's explanation cannot, therefore, be regarded as *generally* applicable. Chvostek, on the ground of his above-mentioned observations, assumes that a mechanical action similar to agitation which destroys the blood-cells may be brought about by abnormal circulatory conditions, especially contraction of the cutaneous vessels and its consequences. Such circulatory disturbances, he believes, are brought about by reduction of the temperature and by the position of the body during walking, and these disturbances and their baneful effects on the red blood-cells might be confined to individual regions or organs, particularly the *kidneys*. This theory of Chvostek's, of the destructive process being confined to the kidneys, serves to explain the cases of hemoglobinuria in which no changes are found in the blood. But the mechanical effect of a circulatory disturbance is hardly comparable to that of agitation; it is more likely that the effect produced is to be attributed to an accumulation of carbon dioxid.

The theory that the separation of hemoglobin from the red blood-cells takes place not in the general blood-stream, but in the *kidneys* and in the *urine*, has been advanced by a number of authors. It was first mentioned by van Rossem,[1] who attributed the process to an abnormal quantity of sodium oxalate in the urine. It is true that, judging by the above-mentioned observations of A. v. Koranyi (see p. 60), the internal administration of oxalic acid may cause hemoglobinuria, and van Rossem's explanation is therefore applicable in some cases. On the other hand, an excess of oxalic acid is not by any means regularly found in hemoglobinuria, nor is the destructive power of the substance in the urine admitted to the extent asserted by van Rossem (Murri). Other authors (O. Rosenbach,[2] Lépine,[3] Silvestrini,[4] Mackenzie,[5] A. Robin,[6] Berthier, and others) regard the kidneys as the scene of the process, in part explained by circulatory disturbances in these organs. Later this view was crowded into the background by another, according to which a general hemoglobinemia was regarded as a necessary pre-

[1] Diss., Amsterdam, 1877. [2] *Berlin. klin. Woch.*, 1880, Nos. 10 and 11.
[3] *Revue mensuelle de méd.*, etc., 1880, No. 9.
[4] *Collezione italiana di letture sulla medicina*, Ser. 2, 1882, cited by Chvostek, *loc. cit.*, p. 24. [5] *Lancet*, 1879, ii., p. 116.
[6] *Gaz. méd. de Paris*, 1884, Nos. 14, 21, and 22.

liminary condition in every case of hemoglobinuria; nevertheless, it receives fresh support from the above-mentioned investigations of Chvostek. The theory that a *hemoglobinuria of renal origin* is possible is, at least, worthy of consideration, not only in the explanation of many cases of typical periodic hemoglobinuria, but, as the writer believes, to a still greater degree in cases belonging to other categories, especially the variety of hemoglobinuria which, as mentioned above (p. 63), is occasionally observed during the course of severe infectious or acute or chronic nephritis in which hemoglobinemia is unknown.

A. Baginsky's[1] discovery of numerous specimens of a form of nematode (Rhabditis) in a case of hemoglobinuria occurring in a child should be mentioned; it is doubtful, however, whether there is any causal relation between the nematodes and the hemoglobinuria.

The **treatment,** or rather the *prophylaxis,* of hemoglobinuria in all the conditions enumerated above under 1 to 4 coincides with the treatment of the basal causes or diseases; poisonous and other injurious agents known to produce hemoglobinuria must, of course, be avoided or used only with the requisite caution.

In severe cases it might be advisable to make an attempt, by the transfusion of human blood or the importation of blood (or hemoglobin solution?) by some other means, such as subcutaneous or intraperitoneal injection, to combat the disturbances resulting from the wholesale destruction of red blood-cells.

Periodic (met-)hemoglobinuria, when due to an antecedent or still-existing syphilis, often yields wholly or, at least, in part to the use of mercury, and Murri recommends the remedy even in cases in which there is no suspicion of syphilis. If there is a suspicion of malaria, the use of quinin is justifiable, although the drug itself is by many regarded as the cause of hemoglobinuria (blackwater fever); but recovery has been brought about by the judicious use of quinin in suitable doses, which must not be too large. *Arsenic* may also be tried; and the symptomatic indications are to be fulfilled in accordance with the conditions of each individual case; anemia and weakness particularly must be combated by suitable means.

The attacks may be *prevented,* and when they occur, *shortened,* with tolerable certainty by avoiding the exciting causes, especially cold and walking. In appropriate cases a sojourn in a milder climate is to be advised during the winter. In order to prevent the contraction of the cutaneous vessels, which, according to his opinion mentioned above, is responsible for the hemoglobinemia, whether the contraction be general or circumscribed, Chvostek recommends the inhalation of *amyl nitrite,* for he found that in his own patients he could nip the attack in the bud by the use of this drug. Berthier, on the contrary, who, as has been explained above, finds the cause of malarial hemoglobinuria not in the blood, but in congestion of the kidneys, gives injections of *ergotin.* Personally, the writer has not seen any benefit result from amyl nitrite.

[1] *Berlin. klin. Woch.,* 1887, No. 30.

To guard against the evil effects of cold, a cautious use of hydrotherapeutic procedures calculated to harden the body has been recommended (Klemperer[1]) and certainly deserves a trial, although the writer himself in one case failed to obtain any good result in this way.

[The writer has seen 2 cases of recurrent or paroxysmal hematuria that in some respects resemble very closely paroxysmal hemoglobinuria, although the urine always contains blood-corpuscles in large numbers, but not the free hemoglobin. Both patients are young men, about thirty years old, leading rather quiet, sedentary lives, of good habits and with no luetic taint. The urine of the one in the intervals is normal and the patient appears to be in perfect health. But upon four occasions and without ascertainable cause there have come on chilliness, pain in the back and legs, slight temperature for a few days, with bloody urine containing considerable albumin and a few casts. In about a week the trouble disappears. The second young man has at all times the signs of a chronic interstitial nephritis—moderate albuminuria, a few casts, cardiac hypertrophy with increased vascular tension. Subjectively he feels well. Yet every winter for nine years he has been taken, generally after exposure to cold, with chill, severe pain in the back, followed by marked hematuria lasting for three or four days, though blood shows microscopically for a longer time. So similar is one attack to another that he has learned the significance of the chill and pain in the back and at once goes to bed, sends for a physician, and calls attention to the certain appearance of blood in the urine.—Ed.]

FAT IN THE URINE; LIPURIA AND CHYLURIA.[2]

Fat is excreted in the urine under a great variety of conditions. When the fat is finely divided and suspended by albumin in the form of an emulsion, giving the urine a milky or chylous appearance, the condition is spoken of as *chyluria* or *galacturia;* under other conditions the presence of fat in the urine is designated *lipuria* or *adiposuria*, providing there is an appreciable quantity of fat present. In cases belonging to the latter group, which are comparatively rare, the fat can be seen with the naked eye in the form of drops, or, after the urine cools, as solid suet-like particles floating on the surface of the urine. The occurrence of fat in the urine in minute traces not recognizable with the naked eye is much more common.

In every case of lipuria, and particularly when the fat can be recognized with the naked eye, the possibility of the urine having been *polluted after its evacuation, either intentionally or unintentionally*, as by the introduction into the bladder of a lubricated catheter, the use of an improperly washed receptacle, or the admixture of fat-containing fluids,

[1] *Charité-Ann.*, N. F. xx., and *Berlin. klin. Woch.*, 1895, No. 36.

[2] For the literature see Aug. Rassman, "Ueber Fettharn," *Diss.*, Halle, 1880; R. Kobert, "Ueber Fettharn," *Schmidt's Jahrb. d. ges. Med.*, 1881, vol. clxxxix., p. 1; F. Monvenoux, *Les matières grasses dans l'urine*, Paris, 1884, 2 vols.; Senator, article, "Chylurie," in *Eulenburg's Realencyklop. der ges. Heilk.*, 3d ed., 1894, vol. iv., and "Lipurie," vol. xiii.; Schrwald in *Klin. Handb. der Harn- u. Sexualorgane* by Zülzer-Oberländer, vol. i., 1894, p. 431.

suppositories, or other similar substances derived from the vagina or the intestine, must be excluded before any judgment in regard to the specimen is formed. *Fat may also be simulated by phosphates* which produce a glistening fatty appearance when, as not infrequently happens, they form in combination with bacteria an iridescent, glistening pellicle on the surface of the urine.

The **demonstration** of macroscopic masses of fat, which float on the surface of the urine, presents no difficulties whatever, the nature of the material being proved by the fact of its floating, its appearance, and the grease spots which it leaves on paper; if desired, the chemical tests, such as insolubility in water and acids, and solubility in ether, benzol, chloroform, carbon bisulphid, xylol, and the like, may be applied for purposes of confirmation. If any doubt still remains, the suspected substance, after it has been extracted and purified as perfectly as possible, may be tested for the acrid odor of acrolein during combustion, and its power of forming a soap with alkalies, and an emulsion with albumin and other colloidal substances. For the methods employed in making these tests and those used in the quantitative determination of fat, the reader is referred to text-books on chemistry.

Minute traces of fat, which are of more frequent occurrence and are not described as lipuria, are recognized under the microscope as strongly refractive droplets of variable size, either floating free on the fluid or seated upon morphologic elements, such as cells or casts. They are stained black by osmic acid in 0.5 to 1 per cent. solution, and red by tincture of alcanna or sudan. In addition to fat-droplets, *cholesterin* in variable quantities has also been found, as well as other abnormal constituents—albumin, sugar, blood, and the like—depending on the causal condition.

Normal human urine usually contains no fat or only exceedingly minute and doubtful traces, while in the case of animals (dog, cat), urine which is apparently normal shows an appreciable percentage of fat.

The **sources** from which fat in the urine may be derived are: (*a*) the *blood*—hematogenous lipuria, and (*b*) the *urinary organs*—renal or vesical lipuria.

(*a*) *Hematogenous* lipuria occurs when there is lipemia—that is, an abnormally high percentage of fat in the blood—which may be due to:

1. Abundant ingestion of fat with the food or as a medicament; for example, cod-liver oil (*alimentary lipuria*).

2. Intravenous or subcutaneous injection, or inunction of large quantities of oil.

3. The escape of fat from fat-containing organs and tissues into the blood. Such an accident occurs especially in cases of *fracture with extensive destruction of the marrow*, the fat from which enters the circulation; and more rarely after other diseases of the bone-marrow caused by inflammation and other morbid processes; in puerperal *eclampsia*, in which the lipuria, according to Virchow's view, is due to the contusion and laceration of the fatty tissue in the pelvis; and, finally, after laceration and disintegration of the subcutaneous adipose tissue or other tissue

containing a large percentage of fat, such as liver or the tissue of tumors; as, for example, in cases of maniacal insanity.

4. Various diseases, particularly *diabetes mellitus, alcoholic dyscrasia, phthisis, obesity,* and *nephritis.* Insanity, diseases of the pancreas and of the heart, and some forms of poisoning—for example, phosphorus-poisoning—are said to be associated with an abnormal percentage of fat in the blood; but the assertion lacks confirmation.

Of all these morbid conditions said to be associated with lipemia, fracture, contusion of the skin, and a few cases of diabetes mellitus are the only ones in which *lipuria* has been demonstrated beyond the possibility of a doubt; the mechanism by which the body frees itself of any excess of fat in the blood in other diseases is not known. In some of these cases fat-emboli have been observed in the glomerular capillaries of the kidneys in addition to emboli elsewhere in the body; but the presence of these emboli does not prove that the fat necessarily enters the urine, for, unless it is in very great excess, it can undoubtedly disappear from the glomeruli by some other channel.

(*b*) The passage of fat from the *urinary organs* into the urine occurs as the result of *fatty degeneration* of the tissue, particularly of the renal epithelium, as in the fatty degeneration of chronic nephritis, in infections, intoxications, anemia, and blood-dyscrasia; or of extensive fatty degeneration of pus cells and tumor masses which are situated somewhere in the urinary passages from the pelvis to the urethra, or have ruptured into the kidneys or urinary passages from the neighboring tissue. In a remarkable case of this kind reported by Ebstein[1] the urine contained large drops of fat, which hardened on exposure to the air; the fat was derived from a tumor in process of fatty degeneration.

In addition to fat, *cholesterin* may get into the urine in large quantities from the urinary organs—*cholesterinuria*—being derived from the fatty metamorphosis of old purulent foci or degenerated tissue; as, for example, in hydronephrosis and pyonephrosis (Schetelig,[2] Murchison,[3] Hirschlaff[4]).

(*c*) There are many instances in which a *combination of lipemia with fatty degeneration of the urinary organs* takes place, and the presence of fat in the urine might therefore be ascribed to both of these sources. This class includes, for example, poisoning by phosphorus and carbon dioxid, grave *phthisical* states, chronic alcoholism, and the like.

The **diagnosis** of lipuria, as appears from what has been said about it in regard to the findings in the urine, presents no difficulties whatever; as for its distinction from *chyluria*, that subject will be discussed presently in connection with the latter condition.

The *prognosis* and *treatment* depend altogether on the causes of the lipuria.

Chyluria is readily distinguished from lipuria by the microscopic appearance of the urine, which usually resembles chyle or thin milk.

[1] *Deutsch. Arch. f. klin. Med.*, 1879, xxiii., p. 115. [2] *Arch. f. Gyräcol.*, i.
[3] *Trans. Path. Soc.*, xix. [4] *Deutsch. Arch. f. klin. Med.*, 1899, lxii.

Occasionally the urine has a pale-reddish color or a turbid curd-like appearance from the admixture of blood.

The freshly voided urine is faintly acid or neutral and one misses the normal urinary odor. On standing, loose fibrin clots frequently separate and the surface is sometimes covered with a layer of fat resembling cream. *In addition to the fat, the urine always contains albumin.* The presence of the latter can be demonstrated by the usual tests for albumin, either at once or after the fat has been removed by shaking up the specimen with ether, with or without the previous addition of caustic potassium or sodium. Cholesterin and lecithin have also been found in addition to fat (Eggel,[1] Brieger,[2] Götze,[3] H. Wolff[4]).

The albuminous bodies that have been demonstrated in chyluric urine include, in addition to the ordinary serum-albumin and globulin, a fibrinogenous substance (Eggel, Brieger), hemialbumose or propeptone (Senator,[5] Götze) and so-called "peptones" (Brieger). The percentage of albumin varies from 0.2 to 2 and over; that of the fat, from a mere trace to more than 3 per cent. The relation of one to the other may vary greatly in the same patient. Sugar is not found in chylous urine.

Microscopic examination reveals the presence of minute fat-droplets, an occasional leukocyte, and a few red blood-cells. In the variety known as *parasitic chyluria* (see p. 70) the characteristic Filaria sanguinis is found, usually enclosed in fibrin coagula. Casts and other morphologic constituents are never found unless there is some complication to account for their presence.

These findings in the urine in many cases appear only periodically, the urine being normal in the intervals; thus, it often happens that the night urine is chylous, while that voided during the day is clear, or *vice versâ*. In a number of instances the evacuation of chylous urine appeared to be influenced by the attitude of the patient—the horizontal position (Huber[6]), or the erect position (Francotte[7])—or by digestion; in other cases bodily exertion or mental excitement appeared to play a part in its production.

As regards any other symptoms of chyluria, either there are none or they are extremely variable or not at all characteristic, so that it is not necessary to enumerate them. It may be worth mentioning, however, that the act of micturition, according to Scheube,[8] is sometimes painful on account of the urine having deposited coagula in the bladder.

In a few cases the blood also was found to contain an unusual number of fat-droplets.

The *course* and *duration* of chyluria are extremely variable. The disease may last a few months or many years. In the latter group of

[1] *Deutsch. Arch. f. klin. Med.*, vi., p. 421.
[2] *Charité-Ann.*, 1882, vii., p. 257.
[3] *Die Chylurie und ihre Ursachen*, Jena, 1887.
[4] "Zur Lehre von der Chylurie," *Diss.*, Berlin, 1891.
[5] *Charité-Ann.*, 1885, x., p. 207.
[6] *Virchow's Archiv.*, 1886, cvi., p. 126.
[7] *Ann. de la soc. méd. chi.*, Liège, 1886.
[8] *Volkmann's Sammlung klin. Vorträge*, No. 232, and *Beiträge zur path. Anat. u. klin. Med.*, E. Wagner, gewidmet, Leipzig, 1887.

cases long intervals often elapse between the successive appearances of chylous urine. Ultimately the chylous character of the urine disappears for no demonstrable reason, so that the disease, as a rule, *ends in recovery*. In extremely debilitated individuals death may occur from exhaustion.

Chyluria is *endemic* in certain tropic and subtropic regions. It has its widest distribution in certain districts of Brazil, both on the coast and inland; and it also prevails in the Antilles, in India, on the coast of Zanzibar, on the Islands of Mauritius and Reunion, in Egypt, in the Colony of Queensland, Australia, in certain regions of North America, as Florida and Charleston (Guitéras [1]), and in Japan.

In Europe the disease formerly was observed only in persons who had been in one of these tropic regions; but recently a few isolated cases have been reported in persons who had never left Europe (Golding Bird,[2] L. Beale,[3] W. Roberts,[4] Boissard,[5] Glasier,[6] Oehme,[7] Brieger,[8] Siegmund,[9] A. Huber, Götze). The disease has never been observed in *infancy* or *old age*. The influence of *sex* is uncertain. According to Lewis, chyluria is a little more frequent in women than in men.

As regards the actual *cause* and *essential nature* of *tropic chyluria*, its parasitic character was first demonstrated by Wucherer [10] and later by Lewis [11]; the former discovered in the urine, and the latter in the blood as well as in the urine, in individuals suffering from chyluria, a parasite belonging to the class of nematodes, which Lewis named *Filaria sanguinis hominis*. This microscopic worm is the embryo of a parasite the adult form of which was first found by Bancroft, and then by Lewis, S. Aranjo, and Jos. Santos, in lymph abscesses, lymphatic glandular tumors, and in elephantiasis of the scrotum. As described by Lewis, the embryo is 0.34 mm. long and 0.014 mm. broad; while Scheube gives its dimensions as 0.216 and 0.004 mm. respectively. The different dimensions given for the mature parasite appear to depend on the fact that they are found in different localities. For an account of the remaining properties and developmental conditions and life history of this parasite, the reader is referred to special books on animal parasites. It may be mentioned, however, before leaving the subject, that the embryo is usually taken into the body with the water, either when drinking or bathing, having been deposited there by the female mosquito (Manson [12]).

[The embryo of the filaria is sucked up with the blood when the female mosquito bites an individual whose blood contains these organisms. Within the body of the mosquito it undergoes a metamorphosis, the whole cycle of change lasting about sixteen days, at the end of which time the filaria is found coiled up at the base of the proboscis of the

[1] *Amer. Med. News*, 1886.
[2] *London Med. Gaz.*, 1843.
[3] *Kidney Diseases*, etc., 1869.
[4] *A Practical Treatise on Urinary and Renal Diseases*, London, 1872.
[5] *La France méd.*, 1882, p. 410.
[6] *Lancet*, June, 1877.
[7] *Deutsch. Arch. f. klin. Med.*, xiv., p. 262.
[8] *Deutsch. Arch. f. klin. Med.*, xiv., p. 262.
[9] *Berlin. klin. Woch.*, 1884, No. 10.
[10] *Zeits. f. Parasitenk.*, 1869, i., p. 376.
[11] *Monthly Micros. Jour.*, May, 1875; *Brit. Med. Jour.*, June, 1878.
[12] *Med. Times and Gaz.*, November, 1875; *Lancet*, February, 1882.

mosquito. "Thence from the sixteenth to the twentieth day it passes into the proboscis, by means of which it is doubtless inserted into the tissues of a human host when the mosquito next feeds on human blood. It is possible, though not likely, that a few of the metamorphosed filariæ escape into water, and in this medium reach man" (Manson).—Ed.]

A curious observation made by Manson and then confirmed by others is that the embryos can only be found in the peripheral blood during the night and when the patient is asleep, being absent during the day. Mackenzie,[1] by completely changing the mode of life of a chyluric individual and having him stay in bed during the daytime and walk about during the night, succeeded in reversing the conditions, so that the embryos were found in the blood during the day and not during the night. [An independent species, the *Filaria diurna*, common on the lower Niger, is said to be found in the blood during the day only, while another species, the *Filaria perstans*, is found both day and night.—Ed.]

On the strength of these facts, the theory at present entertained is that *parasitic tropic chyluria* results from obstruction of the lymph vessels by the embryos themselves, or more probably, according to Manson, by mature filariæ; this obstruction is followed by laceration of the vessels and the escape of lymph, which becomes mingled with the urine either in the kidney or in the bladder.

This theory appears to be supported by some of the postmortem findings. In a case of chyluria in which filariæ had been demonstrated in the lymphatic apparatus and embryos in the blood, Mackenzie found a marked dilatation of the *thoracic duct* and of the *iliac*, *lumbar*, and *renal* lymphatics, especially of the left side, with numerous calculi in the lymph vessels of the left kidney. A similar dilatation of the lymph vessels, especially on the posterior wall of the abdomen, was found by Kentaro Murata,[2] who observed at the same time the destruction of numerous glomeruli in the kidneys in the case of a woman who, during her lifetime, had been found to harbor parasites in the urine and in the blood. Havelburg[3] found in the left hypogastric region a large sac filled with chylous material and extending to the left kidney, with a whole series of hazelnut- and walnut-sized lymph glands, and on the mesentery thick white cords. On the other hand, Ponfick,[4] when he performed the necropsy on a patient who had acquired chyluria in Brazil eighteen years before, also found marked dilatation of all the lymph vessels in the abdomen and of the thoracic duct, but no filariæ; but this case may nevertheless have been originally one of parasitic chyluria, as it is quite conceivable that the parasites gradually disappeared from the body, and the dilatation of the lymph-channels remained as the only sign of the disease.

That there exists a *non-parasitic form* of chyluria is proved beyond

[1] *Trans. Path. Soc.*, 1882, xviii.

[2] "Mittheilungen aus der med. Facultät in Tokio," *Virchow-Hirsch's Jahresb.*, 1887, i., p. 373.

[3] *Virchow's Archiv*, 1882, xci., p. 365.

[4] *Deutsch. med. Woch.*, 1881, p. 624.

a doubt by the above-mentioned cases, which occurred in persons who had never lived where *Filaria sanguinis* is indigenous and in whom no parasites were found. In the only one of these cases of which there is a postmortem report (W. Roberts) *no dilatation of the thoracic duct or lymph vessels* was found; the kidney and bladder were normal; there was also tuberculosis of the intestines and other organs. Nevertheless, it is usually believed that in these cases also the chyluria depends on an effusion of lymph into the kidneys or urinary passages, which in its turn is the result of some form of obstruction with secondary dilatation of the lymph vessels. This assumption, however, is without foundation in actual fact, and a number of reasons might be cited against it, which likewise throw some doubt on the theory that *parasitic chyluria* is due to an admixture of lymph with the urine.

One of these reasons is the *absence of sugar* from chylous urine, whereas lymph almost always contains sugar; another is that the *percentage of fat* contained in chylous urine was found by various observers to be considerably *higher* than that of lymph, whereas it ought to be lower in a fluid consisting of a mixture of urine and lymph; and, finally, the percentage of *specific urinary constituents* in chylous urine is not lower than in normal urine, as we should expect it to be on the same assumption.

On the other hand, Grimm and Huber noted in their cases a distinct increase in the fat percentage of the urine when they increased the quantity of fat in the food, and special kinds of fat also found their way into the urine as they did into chyle and lymph.

Another theory, put forward by Cl. Bernard, Engel, Littré and Robin, and Primavera, is that chyluria is caused by an abnormal quantity of fat in the blood, due to deficient combustion or assimilation; but no such abnormal quantity of fat is found in the blood and in exudates —as, for instance, in medicinal blisters—except in the very rarest cases; nor would it explain the occurrence of albumin, since the latter is not usually observed in lipemia unless there is a renal complication (see p. 67). Götze believes that the fundamental cause lies in the liver, and that the fat in the urine is derived from the alimentary albumin, which, as a result of the liver disease, fails to be assimilated. In support of his view he refers to the circumstance that both in his and the writer's case there was a diminution in the size of the liver, and that after injecting pulverized sputum into the peritoneal cavity in rabbits he found small-cell foci in the liver and fat in the urine.

The most definite statement that our present knowledge will permit us to make is that chyluria is not dependent upon any deep-seated kidney disease.

As regards the **prognosis,** it follows from what has been said that it is on the whole not unfavorable.

Prophylaxis.—The way to prevent parasitic chyluria is to avoid bathing in water which contains the parasites, and not to drink the water unless it has been boiled and filtered. For the *treatment* of the disease, antiparasitic remedies have been recommended; Scheube, in

1 case, found picronitrite of potassium, in the dose of 0.05 gm., three times a day, useful.

[Accepting Manson's views concerning the transmission through the bite of the mosquito, prophylaxis demands, as for malaria, the screening of houses, staying indoors at night, the destruction of the larvæ of the mosquito, and the draining or filling up of the pools of water that serve as their breeding-places. Manson advises, in the absence of any known specific, that active treatment should consist of rest in bed with the pelvis elevated, low diet with a minimum amount of fats, chyle-forming foods and fluid; gentle saline purges are indicated. The subjects of chyluria and of the various other forms of filarial varix should avoid all violent efforts, such as are likely to lead to rupture of the engorged and thinned vessels. In a filarial woman pregnancy is dangerous, as chyluria is apt to be induced thereby.—ED.]

No effective treatment is known for the non-parasitic form of chyluria. Götze, on the basis of his above-mentioned theory of the pathogenesis of chyluria, recommends that the albuminous foods be limited and the fat and carbohydrates be increased.

OXALURIA.

Strictly speaking, this term should be applied to the excretion of an abnormally large quantity of oxalic acid in the urine, but the word is frequently used to designate an unusually abundant excretion of calcium oxalate which appears in the sediment.

Oxalic acid is a normal constituent of urine; the average daily quantity when the individual is taking ordinary mixed diet amounts to several milligrams. The utmost physiologic limit is about 35 mgm.[1]

Notwithstanding a number of contrary opinions, the proposition may now be stated with certainty that the oxalic acid in the urine is derived from the oxalic acid ingested with the food and that formed during the process of metabolism.

Of the acid introduced with the food a small portion is excreted in the urine and feces, to follow Stradomsky and G. Klemperer and Tritschler,[2] while another portion is decomposed in the intestine by putrefaction and fermentation. Whether oxidation of the oxalic acid in the body takes place after its absorption from the intestinal canal has never been determined with certainty in the case of man.

A number of investigations by Pierallini, Lüthje, Lommel, Mohr and Salomon, G. Klemperer and Tritschler,[3] not to mention certain older investigators, prove conclusively that oxalic acid is found in the urine as a product of metabolism, even when it is entirely excluded from the diet, and, in fact, even in a state of absolute starvation. This metabolic

[1] Older statements which give a lower number are based on defective methods of analysis.

[2] Stradomsky, *Virchow's Archiv*, vol. clxiii.; see also Pierallini, *Ibid.*, vol. clx.; Klemperer and Tritschler, *Zeits. f. klin. Med.*, vol. xliv.

[3] Pierallini, *loc. cit.*; Lüthje, *Zeits. f. klin. Med.*, vol. xxxv.; Lommel, *Deutsch. Arch. f. klin. Med.*, vol. lxiii.; Mohr and Solomon, *Ibid.*, vol. lxx.; Klemperer and Tritschler, *loc. cit.*

oxalic acid was formerly thought to be connected with the formation of *uric acid*, and the theory seemed to find support in the observation, first made by Lommel, that the quantity of uric acid and of oxalic acid in the urine could be increased by feeding the animal with gelatin. Other substances, however, which increase the excretion of uric acid—the nuclein bodies—do not produce any increase in the quantity of oxalic acid, or, at least, not with any regularity. In fact, it appears from the investigations of Klemperer and Tritschler that during a diet of gelatin the oxalic acid is derived from the *glycocoll* which comes from the gelatin, and probably also from the *creatin* which can be made synthetically from glycocoll and cyanamid, as well as from the glycocholic acid in the bile.

Under *pathologic* conditions the quantity of oxalic acid in the urine may undergo considerable increase, and a number of morbid conditions are mentioned in which such an increase is said to take place with a fair degree of regularity. But in this connection it is to be remarked in the first place that the excessive secretion of acid (oxaluria) is frequently only inferred from the occurrence of a *sediment* of oxalates (calcium oxalate); and, in the second place, that until quite recently none of the methods used for the quantitative determination of oxalic acid was quite trustworthy (E. Salkowski [1]).

As regards the formation of the oxalate sediment, it is influenced by the percentage of calcium oxalate in the urine, and, in addition, by the quantity of *acid phosphates*, especially *magnesium phosphates* (L. Scott,[2] Klemperer and Tritschler), as the quantity of calcium oxalate that can remain in solution in the urine depends on the quantity of magnesium present.

For the reasons here indicated, the occurrence of an increased excretion of oxalic acid (oxaluria) in the following morbid conditions is to be accepted with caution:

Oxaluria, then, was observed by Schultzen [3] in *jaundice*, and by the writer, Fürbringer, Neidert, Kausch, and particularly Czapek,[4] in *diabetes mellitus*. Cantani,[5] more than anyone else, emphasizes the close relation existing between oxaluria and diabetes. According to the statements of some of the older authorities, oxaluria is frequently present in *obesity*, but Kisch [6] was not able to confirm the observation. Oxaluria has also been observed in *gout*, in emphysema, and other *disturbances of the respiratory apparatus*, in *digestive disturbances*, and, finally, more than in any other conditions, in *neurasthenia* and *spermatorrhea*.

[1] *Centralbl. f. die med. Wissenschaften*, 1899, No. 16.

[2] *Brit. Med. Jour.*, Oct. 12, 1900.

[3] Schultzen, Reichert and du Bois-Reymond, *Arch. f. Anat. u. Physiol.*, 1868, pp. 179 and 720.

[4] H. Senator in *v. Ziemssen's Handb. d. Path.*, xiii., 2d ed., p. 444; Fürbringer, *Deutsch. Arch. f. klin. Med.*, xviii.; Neidert, *Münch. med. Woch.*, 1890, No. 34; Kausch and Naunyn, "Diabetes mellitus" in *Nothnagel's Spec. Path.*, etc., vii., 6, p. 175; Czapek, *Prager. Zeits. f. Heilk*, 1881, ii., p. 348.

[5] *Stoffwechselkrankh.*, translated by Hahn, 1880, ii.

[6] *Berlin. klin. Woch.*, 1892, and *Centralbl. f. die Krank. der Harn- u. Sexual-organe*, 1896, vii., 4.

Dunlop[1] asserts that the excretion of oxalic acid in the urine increases with the increase of acidity of the gastric juice, a phenomenon which may be explained on the ground that the calcium oxalates ingested with the food are more perfectly dissolved by the hydrochloric acid of the gastric juice.

It is a very noteworthy fact that not a single one of the diseases herein enumerated presents oxaluria or the appearance of calcium oxalate in the urinary sediment as a constant symptom.

Why the phenomenon should occur only at intervals is not positively known. The appearance of oxalates in the sediment is in part due to the presence of certain other substances in the urine, being especially dependent on the amount of magnesium, and in part to other factors, especially nervous influences.

The remaining symptoms that accompany oxaluria are quite numerous and very variable. Cantani, it is true, like certain others before him, erected a special clinical entity which he called "oxaluria," and which is said to be characterized by nervous excitement or depression, weakness, lumbar pain, digestive disturbances, a tendency to sweating, and even the formation of abscesses. But, unfortunately for this assumption, the same symptom-complex, on the one hand, is found quite frequently without "oxaluria," and, on the other hand, is frequently absent when there is "oxaluria" or a sediment of calcium oxalate in the urine. It is evident, therefore, that oxaluria does not stand for a clearly defined clinical picture. The presence of a heavy sediment of oxalates in the urine may cause burning and pain during urination, and the oxalates may form the nucleus for the formation of an oxalate of calcium calculus (see p. 407).

The theories which attempt to explain "oxaluria," barring the oxaluria due to the nature of the ingested food, are also quite untenable. They are all based on the assumption that oxaluria depends on a retardation of the process of metabolism, causing the deposition of oxalic acid as an incomplete combustion product of the carbohydrates (sugar) or of albumin. In support of this theory, it is mentioned by Reale and Boen,[2] as well as by v. Terray,[3] that in animals the artificial production of severe dyspnea is followed by excessive secretion of oxalic acid in the urine. But these experiments are quite unsupported. In other numerous investigations in regard to the effects of lack of oxygen and dyspnea no such conspicuous "oxaluria" was ever observed, and if it occurs in such cases at all, it ought to suggest some changes in the urine favoring the precipitation of a sediment of oxalates.

It is not impossible, however, that either in the intestine or in later stages of metabolism some pathologic process might lead to the abnormal formation of oxalic acid, and hence to oxaluria. In this connection it may be mentioned that, according to de Dominicis,[4] thyroidectomy in dogs is followed by "oxaluria."

[1] *Edinburgh Med. Jour.*, 1896, p. 634.
[2] *Wien. med. Woch.*, 1893, No. 38.
[3] *Pflüger's Archiv.*, vol. lxv.
[4] *Wien. med. Woch.*, 1896, No. 18.

The indications in the **treatment** of oxaluria are, in the first place, to remove if possible the morbid conditions of which the oxaluria is a concomitant, and, in the second place, to prevent the precipitation of oxalic acid in the urine. To effect the latter result there are two available methods, which follow from the explanation that has just been given: (1) limitation of the oxalic acid in the food, and (2) treatment of the urine so that it shall be acid in reaction and contain as much water and magnesium as possible with a minimum quantity of calcium.

Accordingly, all such articles of diet as contain a great deal of oxalic acid are to be prohibited; they are spinach, sorrel, rhubarb, artichokes, beans, and beets; among animal foods, spleen and thymus, and among beverages, tea and cocoa. In view of the feeding experiments above referred to, gelatin and any food which contains a large percentage of gelatin are also to be avoided.

On the other hand, meat, fish, bread, and farinaceous foods and apples are to be recommended on account of their small percentage of calcium (and oxalic acid) with a fairly high percentage of magnesium. In a case which he observed very carefully, E. Haas[1] succeeded, by maintaining a strictly animal diet, in bringing about a considerable reduction in the excretion of oxalic acid, which before the experiment had been quite high. Eggs, milk, and vegetables of the cabbage family are to be avoided on account of the large percentage of calcium which they contain. For the purpose of diluting the urine, the drinking of large quantities of water and of carbonated waters, particularly such as contain a considerable percentage of alkaline salts, the so-called simple carbonated waters like Apollinaris, Harzer, Grauhof-Sauerbrunnen, Giesshübler, Rohitscher, Tempelbrunnen, and the like, is recommended; and in view of the above-mentioned investigations by L. Scott,[2] Klemperer, and Tritschler, the use of magnesium or, preferably, bitter waters containing magnesium salts (Kissingen, Friedrichshall, Hunyadi, Saidschetz, etc.).

PHOSPHATURIA.

Phosphaturia is not an independent, sharply defined nosologic entity; it is merely a symptom that may occur in various diseases, and even in them without any degree of regularity. As in the case of oxaluria, the condition is often assumed to be present not when there is an actual increase of phosphoric acid, but whenever the so-called "phosphates" are unusually numerous in the urinary sediment. This, as is well known, occurs when the urine is neutral or alkaline instead of acid, be it from decomposition within or without the body with the presence of ammonia, or from an excess of vegetable diet, or an abundance of alkalies in the food, or certain alterations in the constitution of the urine.

The sediment under these conditions contains, in addition to phosphoric acid in combination with calcium and magnesium, calcium in combination with carbon dioxid, oxalic acid or sulphuric acid; and the

[1] *Ueber Oxalurie*, Bonn, 1894. [2] *Brit. Med. Jour.*, Oct. 12, 1900.

urine does not necessarily contain an abnormal quantity of phosphoric acid.[1]

Ralfe[2] distinguishes under the name of phosphaturia the condition characterized by the presence of phosphates in the urinary sediment from an actual increase in phosphoric acid excretion, which latter condition he calls *phosphatic diabetes*, in agreement with Teissier[3] (see p. 78). A pathologic increase in the excretion of phosphoric acid in the urine may be assumed to be present only when, in an adult who is taking a sufficient daily quantity of ordinary mixed food, the phosphoric acid exceeds 3.5 to 4 gm. daily, or the proportion of phosphoric acid to urinary nitrogen, which, according to Zülzer,[4] should normally be 17–20 : 100, becomes considerably augmented in favor of the former—that is to say, when there is relatively, if not absolutely, more phosphoric acid than normal in the urine. A relative excess of phosphoric acid occurs in a state of starvation or insufficient feeding, and is accordingly observed frequently in diseases associated with inanition, unless it is offset by a concomitant increase in the excretion of nitrogen; as, for example, in febrile states and in carcinoma.[5]

Numerous other conditions have been mentioned in which "phosphaturia" is said to occur at intervals for a variable length of time, sometimes only at certain times of the day. But most of these statements relate to the occurrence of so-called phosphatic sediments—Ralfe's "phosphaturia"—which is no criterion whatever for the quantity of phosphoric acid excreted, as the sediment contains only the phosphoric acid which is combined with earthy salts and not that which has entered into combination with the alkalies; indeed, a phosphatic sediment may be precipitated even when the phosphoric acid in combination with earthy salts is not increased, providing only the urine be not acid.

The causes for a diminution in the acidity in the urine are, besides the decomposition of the urine, an abundant supply of carbonic acid and vegetable acid salts in the food and in the drink (alkaline waters) or in medicines, the abstraction of a large quantity of hydrochloric acid from the stomach by vomiting, or from the metabolism by hyperacidity with motor insufficiency of the stomach (F. Klemperer, A. Robin[6]).

[1] Thus, in a case of "phosphaturia" under the writer's own observation, in which the daily quantity of urine was 1200 to 1600 Cc., the total quantity of phosphoric acid in 1000 parts was 0.9, and that of nitrogen 6.945, of which 6.10 was contained in the urea, 0.68 in ammonium, and 0.18 in uric acid. Later, after a diet rich in albumin and when the urine was weakly acid but still contained a sediment, the phosphoric acid was 1.24 (earthy phosphates 1.12 and calcium 0.472).

[2] *Lancet*, Feb. 26 and March 5, 1887.

[3] *Lyon méd.*, 1875, No. 26, and Thèse, Paris, 1876.

[4] *Semiologie des Harns*, Berlin, 1884.

[5] Further information on this subject will be found in *v. Noorden's Lehrb. der Path. des Stoffwechsels*, Berlin, 1893.

In the case of a girl, six years old, suffering from catarrhal colitis and "phosphaturia," Soetbeer also failed to find an abnormally large quantity of phosphoric acid, although the percentage of calcium was increased over that obtained from a control individual. The excess of calcium is explained by a diminution in the quantity excreted into the large intestine (Soetbeer and Krieger in *Deutsch. Arch. f. klin. Med.*, lxxii., and Soetbeer, *Jahrb. f. Kinderheilk.*, liv., 1902).

[6] F. Klemperer, *Therapie der Gegenwart.*, 1899, No. 8., A. Robin, *Bull. de l'Acad. de méd.*, vol. xliv., 1900.

Phosphatic clouds and sediments—Ralfe's "phosphaturia"—are, however, also observed when there is no change in the reaction due to causes from without; sometimes they occur unaccompanied by any other recognizable disturbance, in which cases they are usually ephemeral. They occur most frequently in *neurasthenia*, especially after sexual excesses, masturbation and pollution, or sustained psychic emotion followed by depression, and much more frequently in the male than in the female sex.

It is not known what causes the alterations in the urine; but, in view of the causes and the rapid changes in the constitution of the urine, it seems probable that nervous influences, the exact nature of which it is impossible to describe, are the chief factors in its production. Gonzalez and Tanago[1] were of the opinion that some irritation in the genito-urinary apparatus, especially in the urethra (urethritis), lies at the bottom of the trouble. A. Peyer[2] applies the term "lumbar enlargement symptoms" to some of the symptoms, as pollution, strangury, and the like, which are observed more frequently in some patients than in others.

According to L. J. Teissier,[3] an actual increase of phosphoric acid in the urine occurs in many cases which in other respects present a similarity to *diabetes mellitus*, in some of which sugar is at the same time excreted in the urine, while others are free from glycosuria. This author has collected these cases and used them as the basis for the erection of a special disease under the name of "phosphatic diabetes," which he subdivides into four different forms.

1. Cases with polyuria and pronounced disturbances of the nervous system, with or without organic changes in the latter.

2. Cases characterized by the development, at their inception or during their subsequent course, of a pulmonary affection that eventually terminates in death.

3. Cases in which phosphaturia goes hand-in-hand or alternates with glycosuria.

4. Cases that cannot be classified under the three preceding heads, and which present at the same time frequent attacks of oxaluria and increased excretion of uric acid as well as a slight albuminuria, and bear a certain relation to gout.

In all these cases the chief symptom after phosphaturia is polyuria, which Teissier explains by the high endosmotic equivalent of phosphates producing a certain degree of hydremia and consequent increased diuresis, to which is superadded the irritation of the kidneys by the abnormal urine exciting them to abnormal activity. In some of the cases belonging to the second and third groups he finds a cause for the phosphaturia in the presence of *lactic acid* in the blood, which is said to be produced from the sugar and to dissolve the phosphates contained in the tissues, particularly in the bones.

[1] Tanago, Casper and Lohnstein, *Monats. über die Gesammtl.*, etc., 1900, p. 705.
[2] "Die Phosphaturie," *Volkmann's Sammlung klin. Vorträge*, 1889, No. 336.
[3] "Du diabète phosphatique," *Thèse*, Paris, 1877, and Laveran and Teissier, *Nouveaux éléments de pathologie médicale*, 1889.

Teissier's views have not obtained a wide acceptance, partly because they are based more on theoretic speculation than on facts, and partly because most of the cases which he describes can readily be classified under some well-known clinical head, and the more or less pronounced phosphaturia, whether we mean by that term an actual increase of the phosphoric acid or merely the occurrence of phosphates in the sediment, may be due to some special causes inherent in the individual case. The diseases to which reference is here made are *diabetes mellitus* and *insipidus*, *tuberculosis*, and perhaps also a few *bone affections*. In *diabetes mellitus* an increase in the elimination of phosphates—in other words, phosphaturia in the true sense of the word—is not uncommon, being dependent in part and most frequently on excessive ingestion of food, particularly of meat, and partly on incipient phthisis. In both cases the excretion of nitrogen is also increased; only it cannot be expected that the two should be parallel in a *temporal* sense, as the two substances are not eliminated at the same rate. In *diabetes insipidus* similar conditions probably obtain, but so far the number of trustworthy observations in regard to the excretion of phosphates in this disease with reference to the food and nutritional conditions is still very small, and the same is true of *pulmonary tuberculosis*. Finally, as regards diseases of the *bones*, the assertion by the older authorities that *rachitis* is accompanied by increased excretion of phosphates in the urine has been shown to be erroneous, and similar statements in regard to *osteomalacia* also appear to be untenable. On the other hand, Verchère[1] has published a series of cases of polyuria and phosphaturia associated with *abnormal fragility of the bones* or with *protracted osteitis* and *osteomyelitis*.

Finally cases appear to occur, although with extreme rarity, in which an increase in the excretion of phosphates is the only prominent symptom, with the exception of general lassitude and emaciation, and a long list of other indefinite complaints, to which, later, other symptoms, as polyuria or glycosuria, are sometimes superadded.[2] It is not unlikely that many cases of *diabetes insipidus*, in which the urine is high in specific gravity, contrary to what is usual in this disease, belong to this class; if they were associated with actual phosphaturia, such cases would represent "*phosphatic diabetes*" in the truest sense of the term.

Treatment.—The indications are first to prevent the decomposition of the urine in the urinary passages, as in inflammation and bacteriuria, by appropriate remedies, which are discussed in connection with Pyelitis (p. 348) and under Diseases of the Bladder, and if possible to remove the causes. If the alkaline or neutral reaction of the urine is due to diet and to the ingestion of alkalies, these errors are to be corrected by ordering a diet more abundant in animal (albuminous)

[1] "De la phosphaturie et de la polyurie dans les lésions osseuses," *Gaz. méd de Paris*, 1885, Nos. 39 and 40.

[2] The writer once observed an increased excretion of phosphates in the case of a lady who later had sugar in her urine; both conditions disappeared in the course of time. Compare *v. Ziemssen's Handb. der Path. u. Therapie*, xiii., 1, 2d ed., 1879, p. 439.

food, and replacing the alkalies by inorganic acids, particularly hydrochloric acid, since the organic acids are converted in the organism to water and carbon dioxid, and the latter forms carbonates.

If the urine contains an excess of earthy salts, a diet poor in calcium and magnesium, such as one consisting of meat, fish, bread, potatoes, and apples, would be appropriate.

Hyperacidity and other disturbances of the gastric function, which may be the cause of a "phosphaturia," should be treated by appropriate remedies, and any disturbances in the genito-urinary apparatus, and especially neurasthenia, must also receive appropriate treatment.

If the cause cannot be removed by therapeutic methods, or if no cause can be found, an attempt may be made with drugs to render the urine acid or reinforce its acidity. Drugs of this class are urotropin, camphoric acid, potassium chlorate, and the balsamics. (See Pyelitis, p. 348, and Lithiasis, p. 425.)

In the treatment of phosphatic diabetes Teissier recommends especially phosphorus, and after that nux vomica, coffee, alcohol, and possibly arsenic, supplemented by cod-liver oil and a diet suited to the patient's needs.

In latent diabetes mellitus (Teissier's third variety and some cases belonging to his second variety) an antidiabetic diet with alkalies and with nux vomica should be ordered.

DROPSY.

While dropsy is not a symptom of all diseases of the kidney, it is so prominent in the most common forms of the disease that even the older physicians, whose knowledge of kidney disease was very imperfect, could not fail to note the connection between the two conditions. (See Historic Introduction, p. 17.) Dropsy is characteristic only of those diseases of the kidney which were first described by Bright, and therefore grouped for a long time in the same class under the name "Bright's Disease." The list embraces certain cases of *acute nephritis*, so-called *chronic parenchymatous nephritis* (subchronic, large white kidney and many-colored kidneys), and *amyloid degeneration*. Other diseases of the kidney may under certain conditions be associated with more or less extensive dropsy, but in such cases the pathogenesis is different, depending as it does on defective cardiac action which results in venous stasis and the transudation of a serous fluid. This kind of dropsy is in every respect analogous to that which is observed in cardiac valvular disease with ruptured compensation, and occurs in the various forms of contracted kidney, along with other signs of venous congestion, whenever the heart permanently or temporarily is incapable of doing its work, a condition which therefore usually develops in the advanced stage or toward the end of the disease.

Another variety of dropsy, which is not characteristic, occurs toward the end of life, as the result of advanced anemia and cachexia, in diseases of the kidney with exhausting hemorrhages or suppuration, and

in the presence of cancer or other grave diseases of the kidneys associated with profound prostration. This form is usually less extensive than the other and belongs to the category of "hydrops cachecticus."

The typical renal dropsy differs from the last two varieties by its early appearance; it is often the first symptom to attract the patient's attention. There is not a trace of cyanosis; on the contrary, the skin and mucous membranes are unusually pale.

The skin usually first appears bloated around the eyes and over the ankles and the bone of the leg; the pallor and swelling of the eyelids and face on waking in the morning is a conspicuous symptom in these patients; the swelling of the feet and legs increases as the patient remains longer on his feet. The scrotum and prepuce as well as the vulva often become dropsical early in the disease. Sooner or later the dropsy spreads from these situations until it involves the entire subcutaneous tissue (anasarca). The development of the *dropsy* in the skin is accompanied or, to judge by clinical investigation, shortly followed by the *effusion of serum into the serous cavities*, first into the peritoneum, producing the condition known as ascites, and then into the pleural sacs, where the transudation is termed hydrothorax; later and more rarely into the pericardium, and rarest of all, at least to any appreciable extent, into the arachnoidean space. In rare cases a few of the *mucous membranes* in the body become edematous, of which, judging from the symptoms, the intestinal mucous membrane, and of those portions which are accessible to examination during life, the mucous membrane covering the uvula and soft palate, and after that the laryngeal mucous membrane, are most frequently involved. Toward the end of life *edema of the lungs* is a still more frequent symptom.

Sometimes the serous cavities are the seat of transudation for a variable length of time without the presence of dropsy of the skin; or the latter may remain circumscribed to certain regions; such, for example, as the scrotum.

These peculiarities of renal dropsy, such as the writer has just described, may become obscured in the advanced stages of the disease, when, owing to failing power of the heart muscle or any other cause, *congestion in the venous system* is superadded.

And in this connection it is worth noting that chronic nephritis is sometimes accompanied by an ascites of milky or chylous nature, due not to fat-granules, but to the admixture of extremely minute particles of albumin and lecithin.

In the great majority of cases, although there are some exceptions, and especially in cases characterized by an acute course, the excretion of urine diminishes as the dropsy develops, and continues below normal during its progress; sometimes the excretion is so slight that there is complete anuria for an entire day or even for several days. Quite frequently, and again more commonly in acute than in chronic cases, the degree of dropsy varies proportionately with the excretion of urine, and the disappearance of the former is usually accompanied by a copious flow of urine. On the other hand, the albuminuria exhibits no con-

stant relation to the dropsy, although in a general way the effusion is more copious when the urine contains a large amount of albumin than when only a little albumin is present. Sometimes the dropsy precedes by a short period the appearance of albumin in the urine, and in a few very rare cases of renal dropsy no albuminuria has been observed, although the signs of renal inflammation were found after death.

The **pathogenesis** of this form of dropsy, which is peculiar to diseases of the kidneys, has been explained in various ways; but none of these attempts at explanation has so far been able to satisfy all the conditions of the problem, probably because several causes are at work at the same time.

1. According to the oldest theory, which was first promulgated by Bright, the loss of albumin produces *hypalbuminosis* and *hydremia*, which permit watery constituents of the blood to escape more readily from the blood-vessels. While it has been demonstrated that hydremia may be present in diseases of the kidney, it has never, so far as the writer knows, been found before the occurrence of dropsy, which is a necessary condition for its being regarded as the cause of the dropsy. And although the hydremia may be conceded to be present in chronic cases before the development of dropsy, it is certainly not true for the majority of the acute cases, such, for example, as the dropsy of scarlet fever, especially as the dropsy very often develops at the same time as the albuminuria or but little later, at a time when there has as yet been no appreciable loss of albumin. Thus, although W. Brunner[1] found the percentage of water in the blood somewhat increased in acute nephritis, he failed to find any uniform relation between dropsy and hydremia.

On the other hand, there is no lack of morbid conditions in which a much greater loss of albumin takes place from some other cause and persists for some time without the development of dropsy; while hydremia may continue for weeks and months—as, for example, in cancer patients—and yet the dropsy, if any develops, is quite unimportant and not at all of the characteristic kind, but rather of the type described (page 81) as "hydrops cachecticus." And, conversely, very considerable and very excessive loss of albumin may be present in diseases of the kidney, especially in toxic nephritis, and yet no dropsy appear. (See Acute and Chronic Parenchymatous Nephritis.)

Simple hydremia, therefore, does not adequately explain the phenomenon. It is possible in chronic cases, when the patient is in a very depraved state of health—as, for example, in amyloid degeneration—that it may be a subordinate factor among several others in hastening the development of dropsy by injuring the nutrition of the vessel walls and increasing their permeability.

2. The explanation proposed by Grainger Stewart,[2] and especially by Bartels,[3] appears to be much better supported. According to the theory

[1] *Centralbl. f. inn. Med.*, 1898, No. 18.
[2] *A Practical Treatise on Bright's Disease of the Kidneys*, 2d ed., Edinburgh, 1871, p. 82.
[3] *v. Ziemssen's Handb. der spec. Path.*, ix., 1, 1875, p. 87.

of these authors, dropsy is produced by hydremia in combination with an increase of the total mass of the blood—that is to say, by *hydremic* or *serous plethora*. In regard to the origin of the hydremia, Bartels entertains the same view as Bright and others—namely, that it is due to the loss of albumin; while he attributes the plethora to the lessened excretion of water by the diseased kidneys, adducing in support of his argument the well-known fact, which he himself confirmed by numerous and long-continued observations, that increase and diminution of the dropsy is frequently inversely proportionate to the quantity of urine. But even this explanation is not altogether without flaws. The fault is not that hydremic plethora, as Cohnheim [1] insists on the strength of his experiments performed in association with Lichtheim, is not adapted to the production of dropsy. For, in the first place, those dogs which received large intravenous injections of physiologic salt solution in a short space of time, while they developed dropsy of all the glands of the abdomen, of the peritoneum, of the gastro-intestinal canal, and of the salivary glands, failed to develop dropsy of the skin, which is the variety that Cohnheim was particularly concerned with; and, in the second place, Gärtner [2] and R. Magnus [3] have shown that the latter form can also be produced by administering the injections more slowly and continuing them for a greater length of time, especially when the kidneys are diseased (Albu [4]). But unfortunately there is no proof that hydremic plethora really exists in sufferers from kidney disease, especially *before* the appearance of dropsy; for the arguments brought forward by Bartels to support his theory are not convincing. And especially it cannot be admitted that a diminution of the quantity of urine *in itself* effects an increase in the total quantity of the blood, as it has been shown by experimental ligation of the ureters as well as by clinical observations in cases of occlusion of the ureters by calculi, tumors, and the like, that the secretion of urine is not only considerably diminished, but even may be entirely suppressed for days and weeks without leading to the production of dropsy. This is partly because the organism has at its disposal other means of excreting water, which it presses into service in renal insufficiency, especially in the case of sufferers from renal disease, whether they have dropsy or not, and particularly because the organism has the power to limit the ingestion and formation of water. It is therefore evident that some other factor must be superadded to the diminished excretion of urine in order to produce hydremic plethora.

Nor is it always the case that the onset or progress of dropsy is preceded by a diminution in the quantity of urine secreted. On the contrary, dropsy has often been observed to appear and to increase, especially in chronic cases, when there was no diminution in the urine and even when there was copious diuresis.

The proposition that in the case of renal disease the hydremic plethora exists *before* the appearance of dropsy has therefore never been

[1] *Allg. Path.*, 2d ed., 1, p. 437 *ff.*, and 2, p. 446 *ff.*
[2] *Wien. med. Presse*, 1883, Nos. 20 and 21.
[3] *Arch. f. exp. Path.*, etc., xliv.
[4] *Virchow's Archiv*, vol. clxvi.

proved; or, at least, it may be said that the plethora is not produced in the manner assumed by Bartels. Nevertheless, hydremic plethora may possibly be present from other causes and may be enhanced by deficient kidney action. On this assumption hydremic or serous plethora may be regarded as a contributory cause of dropsy at least in chronic cases; for in acute nephritis hydremic plethora as a cause of the disease is quite as inadmissible as simple hydremia.

3. Cohnheim, who, as has been said, denies that hydremic plethora is the cause of dropsy, advanced the theory that in certain forms of acute inflammation of the kidney, especially after scarlet fever and exposure to cold, and in a number of chronic or subchronic forms, an inflammatory or other alteration of the cutaneous and subcutaneous blood-vessels with abnormal permeability of the same is the cause of the dropsy, at least of the skin. To support this theory he invokes the before-mentioned experiments performed by himself and Lichtheim, in which hydremia and hydremic plethora were followed by cutaneous dropsy only when the vessels of the skin were previously put into a state of inflammation, and appeals more particularly to the inflammatory condition of the skin and of the cutaneous vessels in scarlet fever. He starts out with the assumption that the dropsy of scarlet fever is limited to the subcutaneous cellular tissue, and takes no account of dropsy in the various cavities of the body, which, as S. Rosenstein[1] quite properly contends, is very frequently found in scarlet fever. The latter objection, however, is not difficult to overcome, for, as the writer showed many years ago,[2] there is nothing to prevent the assumption that the same conditions exist in other vascular regions, especially in the blood- and lymph vessels of the serous membranes, as in the cutaneous blood-vessels. No one to-day doubts that scarlet fever is not only a disease of the skin and possibly of the pharynx, but that all the organs of the body become more or less involved on account of the poison circulating in the fluids of the body; and it is a well-known fact that the serous membranes are often attacked not only by inflammatory hyperemia, but also by true exudative inflammation. It is not too bold to assume that just as a true inflammation develops in these cases under the influence of the poison, so in other cases the same irritant produces a somewhat less-marked alteration in the blood-vessels, similar to that which occurs in the skin, increasing their permeability and thereby producing so-called "irritative dropsy" (*hydrops irritativus*).

The influence that the condition of the vessels after they have been injured by the disease poison has on the production of dropsy is best shown by a comparison between the forms of nephritis with dropsy and those in which no dropsy occurs, especially the acute forms. It is at present well known that acute nephritis is an exceedingly common affection, and is in fact one of the most frequent concomitants or sequelæ of most if not all of the acute infections and of very many intoxications. In addition there are two other forms of nephritis, that which

[1] *Die Path. u. Therap. der Nierenkrankh.*, 4th ed., 1894, p. 226.
[2] *Albuminurie*, 2d ed., 1890, p. 143.

occurs after exposure to cold, the explanation of which is far from being clear, and *perhaps* the so-called "kidney of pregnancy," the inflammatory nature of which is, as everyone knows, open to question. Of all these numerous forms of nephritis, these are only a few that are followed by dropsy. They are, first of all, *scarlatinal nephritis*, which greatly surpasses in frequency all the others; the nephritis produced by *cold* and by *malaria;* and, if it is desired to include it in this class, the "*nephritis of pregnancy.*"

From the anatomic standpoint, the latter forms have in common *early involvement of the vascular tufts of the kidneys*, which is constant; or, in a word, "*glomerulonephritis*" exists, the most frequent form of nephritis in scarlet fever and practically typical of the disease; it is the form that has been studied more than any other. On the other hand, in the numerous other forms of acute infectious or toxic nephritis in which dropsy is not a feature, but occurs only exceptionally and late in the disease, the epithelium of the urinary tubules is first attacked, while the vascular tufts either escape altogether or become involved late in the disease, and with less constancy and to a lesser extent than in the first-mentioned forms of nephritis.

Now, the dropsy which occurs in the cases accompanied by glomerulonephritis might be explained, as has actually been done, by a cessation or reduction in the function of the inflamed glomerular vessels, which function is to excrete water, and a consequent retention of water with resulting dropsy. But it has already been noted that diminished excretion of water in the urine does not in itself suffice to produce dropsy, a proposition which is strikingly illustrated in that other group of "parenchymatous" nephritis without dropsy; for in the latter the obstruction of the urinary tubules by the swollen epithelium, urinary casts, and other morphologic elements usually offers an equally great obstacle to the excretion of urine and the function of the glomeruli, and yet these forms of nephritis do not lead to dropsy.

Between the latter variety of nephritis and glomerulonephritis there must therefore be some other relation. The writer believes it is justifiable to assume that under the influence of certain injurious substances, such as a poison circulating in the blood, the capillaries of the glomeruli are the first to become diseased; later, if the injury reaches a certain degree of severity or persists for a certain length of time, the interstitial vessels and other vascular areas outside of the kidney, such as those of the skin and of the serous cavities, also become involved. Obviously, the glomerular vessels are more easily affected by any change in the constitution of the blood than are other capillaries, including the interstitial vessels of the kidney, because the blood is under very high pressure and flows very slowly through the tufts, and there is thus a better opportunity afforded for the closest interchange between the blood and the vessel walls. If the injury is great enough to affect, in addition to the glomerular vessels, the blood- or lymph vessels of the skin and serous membrane, cutaneous dropsy and serous effusions result, but not otherwise. On this assumption, then, the presence of dropsy

would lead one to expect to find an affection of the glomeruli, but the converse of this is not true. The actual findings tally with this assumption.

According to this explanation, it is also intelligible that edema sometimes occurs in the absence of any kidney affection, simply from irritation of the vessels of the skin by any cause whatsoever. This has been observed in scarlet fever and other exanthemata. (See Acute Nephritis, p. 181.)[1]

That the cutaneous vessels in kidney patients are in fact damaged in some way, and on that account probably allow fluid to pass out through their walls more readily than in the opposite direction for purposes of absorption, is shown by certain experiments of O. Reichel,[2] who found that physiologic salt solution injected into the subcutaneous cellular tissue is less rapidly absorbed than by healthy individuals or those affected only with cardiac dropsy.

The clinical and anatomic characters of dropsy occurring in so-called chronic parenchymatous nephritis ("subchronic nephritis," "second stage of Bright's disease") indicate that they have the same origin. This form of nephritis is diffuse and involves the glomeruli; it closely resembles the acute inflammatory conditions, and also predisposes to other kinds of inflammations. Hence the origin of dropsy in this form may be explained in the same way, *hydremia* and *hydremic plethora* favoring its development whenever the action of the kidney is insufficient and other organs fail to excrete the water vicariously. In course of time the abnormal constitution of the blood exerts an unfavorable influence on the structure of the vessel walls.

When the gradual contraction of the organ takes place in very chronic cases, the acute inflammatory process in the kidney subsiding and the corresponding urinary changes disappearing (secondary contraction, transition from the so-called second stage to the third stage), or when from the first there has developed the so-called primary contracted kidney, the irritation being less severe and more insidious, the view here presented enables one to understand that therefore the irritation in the vascular areas outside of the kidney also gradually subsides or is slight from the outset, and that an existing dropsy gradually disappears, or in the latter case is only very slight or even absent from the beginning. With every recrudescence of the inflammatory process, which at once registers itself in the urine, a tendency to a return of the dropsy at once becomes manifest.

The dropsy which occurs in simple *amyloid degeneration* uncomplicated by inflammatory processes is, according to the present state of our knowledge, chiefly due to a defective condition of the blood and possibly also to abnormal permeability of the vessels. Its severity and extent are practically the same in these cases as in other conditions of hydremia and cachexia. Whenever the extensive form of dropsy characteristic of renal disease is present, the kidneys exhibit a combination

[1] *Cf.* the so-called idiopathic edema of children.—Ed.]
[2] *Centralbl. f. inn. Med.*, 1898, No. 14.

of amyloid degeneration and inflammation, and the same conditions of the cutaneous and other vessels that have just been described may be assumed to exist.[1]

[There should be mentioned in connection with the theories of edema, the fact that alterations in the osmotic pressure due to change in the chemical composition of the blood or of the cells and tissues outside the vessel may, perhaps, account for transudation. Cells, for instance, in which, as the result of catabolism, there are accumulated smaller molecules due to the breaking down of larger molecules, would have a greater water-attracting power than when they contained the larger molecules.

Meltzer,[2] who gives a comprehensive summary of the theories of edema, assumes that certain cells may have the power—perhaps through ultramicroscopic pseudopods—of drinking or imbibing solutions. To this power he applies the name potocytosis (*πίνω*, to drink; *κύτος*, a hollow cell). The endothelial cells of the capillary wall also possess a certain tonicity. Alteration in this may lead to change in the size or shape of the pores of the vessel wall and permit of the escape of fluid. Such alterations might easily be brought about by substances circulating in the blood—*e. g.*, in chronic parenchymatous nephritis—while in the chronic interstitial nephritis the toxic substance might increase the tonus and tend to prevent edema, but lead to increased peripheral resistance and cardiac hypertrophy.—Ed.]

When moderate in extent, dropsy gives rise to few *symptoms;* but when it is great enough to afford a mechanical hindrance to the organs, it gives rise to a variety of disturbances, and is not without danger. Even edema confined to the prepuce or vulva may interfere more or less with the evacuation of urine. High grades of cutaneous edema not only disfigure the face and the limbs, but interfere with the movement of the body, and by compressing the vessels impair the nutrition of the skin. This, aided by the great tension, gives rise to fissures and slight wounds that are apt to become the seat of erysipelatous inflammation with a tendency to ulceration and gangrene, and may thus in themselves be sufficient to cause death. Pleural and pericardial effusions are a menace to respiration and circulation; ascites brings about congestion in the abdominal organs and in the lower extremities, and if it is very great forces the diaphragm high into the thoracic cavity, and thus interferes with the action of the heart and lungs. Edema of the gastro-intestinal mucous membranes produces digestive disturbances; edema of the laryngeal mucous membrane, and especially of the vocal cords, is fraught with the danger of asphyxia; the same is true of pulmonary edema; and, finally, the collection of serum in the cavities of the brain, and consequent edema of the cerebral substance, leads to all kinds of nervous disturbances—headache and vertigo, insomnia, clouding of the consciousness, and convulsions.

If the edema persists for a long time, either in the lower extremities or in the face, a thickening of the skin resembling *scleroderma* develops,

[1] See Cohnheim, *Allg. Path.*, 2d Ed., ii., p. 456.
[2] *Amer. Med.*, viii., Nos. 1, 2, 4, and 5, 1904.

being apparently favored by compression and constriction of the corresponding parts; as, for example, by tight bandaging.

Dropsy is always a grave symptom, and its appearance at once complicates the *prognosis*. Nevertheless, it often disappears entirely, not only when the causal kidney disease is cured, but also even when the latter persists, if the morbid process diminishes in intensity and finally assumes a chronic character.

The most unfavorable cases and those which are most refractory to treatment are those in which the morbid process in the kidneys is associated with venous stasis from insufficiency of the heart muscle or some other cause, such as the pressure of ascites on the abdominal vessels, leading to the development of the above-mentioned mixed variety of renal and cardiac dropsy.

In the **treatment** of dropsy due regard must be had, in the first place, to the different varieties of the condition and the different causes that may give rise to it, as appears in the preceding discussion. It is not often, however, that special indications exist in this respect, and when they do exist, it is not always possible to fulfil them; in fact, the rules for the treatment of moderate grades of dropsy are practically the same, whatever causes may lie at the bottom of the trouble. But if in an individual case the dropsy is dependent upon or favored by a definite and known cause, an attempt must, of course, be made to combat that cause.

Whenever there is distinct *hydremia*, as in many cases of nephritis, suppuration, tuberculosis, and in amyloid degeneration, an attempt must be made to improve the constitution of the blood by placing the patient under the most favorable hygienic surroundings possible, regulating the diet, stimulating the digestion with suitable remedies, such as bitter tonics, orexin, quinin preparations, and condurango, by giving him easily digestible iron preparations, and under certain circumstances by means of an intravenous infusion of blood after the method of v. Ziemssen.

In those cases of disease of the kidney in which the dropsy depends on *stasis in the venous system*, in its turn due to insufficient heart action (see p. 80), the same general treatment is indicated as for cardiac lesions with ruptured compensation: absolute rest, easily digestible but nourishing food, and digitalis or one of the numerous remedies that are regarded as substitutes for digitalis. The latter class of drugs also finds a place in the treatment of the form of dropsy peculiar to renal disease now to be discussed.

The *first and universal rule* is that patients with dropsy amounting to more than the most insignificant effusions are not to indulge in any form of bodily exercise; hence they are not to stand or walk about, but are to maintain the horizontal position, preferably in bed; or if the horizontal position cannot be borne on account of oppression or dyspnea or on account of the presence of hydrothorax or diffuse bronchial catarrh, the patient must maintain the semi-recumbent or sitting posture.

In *acute nephritis* the dropsy in the majority of cases requires no

special treatment, as it usually disappears of its own accord when suitable hygienic and dietetic treatment, such as will be described later, is instituted for the basal trouble. It is only when the anasarca attains an alarming degree or is protracted that the same remedies and procedures are indicated as are used in cases which are *chronic* from the beginning. Among these therapeutic procedures the most important are those which are designed to abstract water from the body without the agency of the kidneys—purgatives producing thin, watery evacuations, and diaphoretic drugs and procedures. Certain diuretic measures may, however, also find a useful application.

When *purging* is to be brought about, drastics which irritate the kidneys are not to be employed, especially in recent cases; instead, vegetable and saline laxatives may be recommended, such as pulpa tamarindorum depurata, in tablespoonful doses or as a confection, essence, or the like, or a senna preparation (infusum sennæ compositum), cascara sagrada, or one of the numerous bitter waters, and, if desired, potassium-sodium tartrate and similar salts—*e. g.*, sodium sulphate or phosphate.

The best *diaphoretic procedures* are warm or hot tub baths, warm packs, warm-air baths, and the like. The choice of the procedure will depend on circumstances in the individual case, the available number of assistants, and the facilities at hand. One of the simplest methods and one that can be used with a minimum of assistants and facilities is *hot air;* for instance, by an apparatus like the *phénix à air chaud.* In this method the patient is well wrapped up in blankets which are brought up over the chin, and a lamp is placed on the floor alongside of the bed. Above the lamp is the opening of a pipe which is provided with an elbow. The other end of this pipe is inserted under the blanket, near the patient's legs. The latter are protected from immediate contact with the air by a "cradle," a foot-stool, or the like, which separates the legs from the hot-air pipe. When the patient is unable to lie down at all or for any length of time, the same result may be achieved by placing the lamp—after guarding the flame with a wire screen—under a cane-seated chair, on which the patient sits completely wrapped up in blankets. It is needless to say that even greater care is necessary than in the former procedure to guard against the danger of fire.

The employment of *dry hot air* is even more to be recommended, because it abstracts more water, and owing to the active evaporation that goes on higher temperatures can be used. With the above-mentioned *phénix à air chaud* the hot air may be deprived of some of its moisture by the simple plan that the writer has followed of introducing into the hot-air pipe metal dishes containing calcium chlorid, which absorbs a part of the water from the air as it passes through the pipe.

The same object is accomplished more successfully in the *hot-air apparatus,* such as that of Tallermann, which have recently come into vogue, and by the *electric incandescent-light baths, sun baths,* and *hot-sand baths;* these methods are, of course, more expensive than simple hot-air baths.

If hot-air baths are used, it has been the writer's experience that all other kinds of baths, especially *tub baths*, may be dispensed with. If desired, however, they may be employed after the method prescribed by Liebermeister,[1] which is a very convenient one, the temperature of the water at first being 37° to 38° C. (98.6°–100.4° F.), and by the gradual addition of hot water raised to 41° or 42° C. (105.8°–107.6° F.). After the patient has been in the tub for half an hour or longer, during which time the head is to be covered with cold compresses to prevent congestion, he is wrapped in a blanket which has been previously warmed, put back into bed, and well covered up with additional blankets or feather beds. After he has perspired from one to three hours he is well rubbed down and changed to another, previously warmed, bed. The abstraction of water by perspiration during this procedure may be quite considerable, but the method is heroic and not well borne by patients with weak hearts who are suffering from dyspnea. For cases of the latter class, if hot-air baths are not available, the *hot wet pack* advised by v. Ziemssen,[2] and consisting in wrapping the patient in sheets wrung out of hot water and covering him with woollen blankets, is to be recommended.

Partial baths and *partial packs*, while much less exhausting and therefore applicable without hesitation in every case, are also less effective. A half-bath consists in subjecting the abdomen or the lower extremities to the same treatment as in the full bath after Liebermeister. A half-pack is administered by treating the entire lower half of the body or the trunk, or even the lower extremities alone, after the method prescribed by v. Ziemssen. *Hot sand* can also be used conveniently for the purpose of administering partial baths, especially to the extremities; and finally there are various kinds of apparatus for *hot-air baths* to individual portions of the body as well as for the entire body which can be readily used on bedfast patients.

[Another excellent way of giving a sweat to a bed patient is to place over and beneath him blankets or, better still, blankets and rubber sheets and then surround him by hot bricks placed under the blankets, care, of course, being taken not to burn the patient by bringing them directly against the unprotected body. Alcohol can also be poured over the bricks. The body is soon bathed in perspiration, and after twenty minutes to an hour the bricks are removed, the patient rubbed dry, and dry bedclothing substituted for the wet. Leube's advice to give the patient who is to take a sweat a liberal drink of water is, we believe, good. Pilocarpin can be given hypodermically just before a sweat, though, as stated by the author, it is a heart depressant, and we prefer to give it only in obstinate cases, where sweating is induced with difficulty by the ordinary measures, and then only in doses of $\frac{1}{12}$ gr. or less. Increased bronchial secretion with weak heart makes the danger from edema of the lung a dreaded reality when too large does are given.—Ed.]

On the other hand, the internal diaphoretics which were freely used

[1] *Prager Vierteljahrs.*, lxxii., p. 1. [2] *Deutsch. Arch. f. klin. Med.*, ii., 1867, p. 1.

by the older physicians are now very properly looked upon with ever-increasing disfavor; for not only are they less certain in their action than the practical procedures just described, but, in addition, they are attended by undesirable, and in some cases even dangerous, by-effects on the stomach and on the heart, and this objection applies especially to the more efficacious of the group. The least objectionable internal diaphoretics are *hot drinks*, either of pure hot water or hot milk; hot teas with or without brandy; rum and the like, or hot mulled wine; they are, in fact, quite useful as adjuvants to baths and hot packs. [Cream of tartar, one teaspoonful dissolved in a pint of hot water, is an excellent diuretic, and is taken readily by the patient when lemon juice and sugar are added to the water—*i. e.*, when made into a lemonade. This can be taken freely. Too much of the cream of tartar may cause looseness of the bowels, a result not undesired in this condition.—Ed.]

Among medicinal diaphoretics *liquor ammonii acetatis* was formerly esteemed very highly, but in reality has very little value; the effect of *Dover's powder*, which formerly enjoyed a similar reputation, is also uncertain, and its action as a diaphoretic is overshadowed by its other less desirable properties. A much more trustworthy remedy is found in *pilocarpin*, given internally in doses of 0.01 to 0.02 gm. ($\frac{1}{6}$–$\frac{1}{3}$ gr.) and more, or hypodermically up to 0.01 gm. ($\frac{1}{6}$ gr.) once a day or oftener. The *salicylates*, of which sodium salicylate, in the dose of 1 gm. (15 gr.) several times daily, is the best, may also be tried. Both drugs, however, disturb the digestion and are apt to cause symptoms of collapse; pilocarpin has the additional disadvantage of causing profuse salivation, which makes it very disagreeable to some patients, and the salicylates sometimes irritate the kidneys. In recent cases of nephritis the latter drug is therefore contra-indicated; in fact, both remedies should be used only in selected cases, and then with due caution and for a short period at a time.

Diuretics may also be used with good effect not only in chronic but also in acute cases, as the writer wishes to emphasize in spite of the contrary opinion of many authors. It is needless to say that the more severe, irritating diuretics—"*diuretica acria*"—are to be avoided in acute and, for that matter, in chronic cases as well; although such remedies have been recommended by some of the older authors—Rayer and others—who gave the preference to tincture of cantharides. The practice is to be deprecated on theoretic grounds, and in the cases in which the writer tried the tincture after all other remedies had failed he was not able to convince himself of its utility.

On the other hand, there is no objection to the use of the so-called *refrigerant diuretics*, especially the *carbonates* and *vegetable acid salts*, which are converted into carbonates in the body. They are free from the risk of aggravating the irritation in the kidneys, as they contain nothing foreign to the blood and tissue juices and merely modify their concentration. Experience is altogether in favor of their efficiency. Heading the list are *potassium* and *sodium acetates*, 1 to 2 gm. (15–30 gr.) and more several times daily for adults; next the *tartrates*—potassium

tartrate and bitartrate—and *citric acid*, either pure or in saturated solutions, or citrate of potassium, 10 to 30 gr. There are also certain *vegetable diuretics*, which, however, are more suitable in subacute and chronic than in acute cases, because they are somewhat more irritating than the above-mentioned salts; but owing to their undeniable efficacy in many cases they cannot well be dispensed with. This class includes the various well-known diuretic decoctions of *juniper berries* (baccæ juniperi, *parsley* (fructus petroselini), *restharrow* (radix ononidis), *lovage* (radix levistici or ligustici), *birch leaves* (foliæ betulæ), bean husks of the species *diuretica*, and above all *digitalis* and *squills*. A combination of one of the latter or both with *potassium acetate* is often very efficacious, as in the following formula:

R. Foliarum digitalis . . . . . (1.2–1.5) gr. xx–xxv;
Radicis scillæ . . . . . (3.0) gr. xlv.
Add boiling water and percolate to . . . . (170.0) about 5 oz.
Potassi acetatis . . . . . (8.0–12.0) ʒij–iij;
Syrupi . . . . . (30.0) ʒj.—M.
Sig.—One tablespoonful every three hours for an adult.

Another very efficacious drug, which need not be feared even in acute cases, is *diuretin* (theobromin sodium-salicylate), in the dose of 4 to 6 gm. (1–1½ dr.), in a little tea or hot milk. Combinations of theobromin with *lithium benzoate* and *salicylate* ("uropherin" compounds), 1 gm. four times a day, have a similar action. In addition there are numerous remedies which act either by increasing blood-pressure or by their direct influence on the renal epithelium, and these may be tried in chronic cases when other drugs have failed. This class includes the *caffein salts*, *Convallaria majalis* (lily of the valley), *Adonis vernalis*, *Blatta orientalis* (cockroach), and *strontium lactate;* the last of the list has recently been recommended against albuminuria, but, judging from the author's own rather scanty observations, it has merely a gentle diuretic action; the daily dose is about 4 to 6 gm. (1–1½ dr.). *Calomel*, which has also been recommended in doses too feeble to produce catharsis, the writer has found useful only in combination with digitalis; about 0.1 gm. (1.5 gr.) of the latter should be given in capsules or wafers, not in powder form, three times a day until ten doses have been taken.

[The dose of calomel recommended by the author (1½ gr. three times a day) will often produce free catharsis. The diuretic effect will often be better secured if, along with calomel, a small amount of opium be given, say ¼ to ½ gr. of powdered opium or a few drops of laudanum.—Ed.]

In rare instances edema has been observed to disappear as the result of *profuse salivation* or sialorrhea (v. Leube), and for this reason the above-mentioned sialagogue and diaphoretic, pilocarpin (p. 91), might be tried in desperate cases.

Mention should finally be made of the *thirst* or *dry cure* much in vogue among the ancients, and after a long interval of oblivion revived by Schroth and lauded by him as a wonderful cure in a number of diseases, including dropsy. When carried out as a routine measure, with-

out regard for the patient's strength and other individual conditions, this method of treatment may do more harm than good; although the underlying principle of withholding liquid, if applied with caution and in accordance with the condition of the digestive organs and the heart's action, and if the quantity of fluid allowed is very slowly and gradually reduced, no doubt hastens the absorption of serous effusions. Serre's[1] advice to combine the administration of a diuretic with the abstraction of fluid is, in the writer's opinion, worth considering.

[Widal and Javal, and after them many others, have called attention to the fact that in nephritics with dropsy a withholding of chlorids will often be followed by a decrease in the dropsy. Nephritics eliminate chlorids poorly—*i. e.*, there is undue chlorid retention. This may alter the molecular concentration of the blood and tissues in such a way as to produce edema, according to Widal and Javal. Large amounts of common salt seem to increase the albuminuria in nephritis, and may be followed by increase of edema and the appearance of drowsiness and other symptoms not unlike uremia. These observations have been confirmed by many observers, though there are also conflicting reports. It is worth while, however, to try in the cases with dropsy the giving of food with the minimum amount of salt—*e. g.*, milk, unsalted bread, etc. Two grams of salt a day meet the requirements of the animal economy.—Ed.]

When all other remedies fail, *venesection* sometimes acts favorably by inducing perspiration and diuresis, thus influencing the absorption of effusions.

Unfortunately there are many cases in which none of these remedies or methods, or even a combination of them, is successful in removing the edema; and if the disturbances and alarming indications previously described make their appearance, the fluid must be withdrawn by *mechanical means.*

Cutaneous dropsy may be relieved by making one or more *incisions* 1 to 2 cm. (about 0.5 in.) in length wherever the tension is greatest, usually the dorsum of the foot or leg, prepuce, scrotum or vulva; or by a resort to *capillary drainage,* first recommended by C. Bock,[2] which is best performed by means of Southey's needles. The upper extremity of the needle having been inserted into a rubber tube, the point is introduced into the outer side of a limb until it enters the subcutaneous cellular tissue, and the rubber tube allowed to drain into a vessel standing on the floor by the side of the patient's bed. When incisions are used, the effect may be reinforced by applying cups once or twice over the site of the incisions. Dehio[3] has devised for the same purpose a rubber bandage provided with an aspirating funnel, which appears to work very well. Needless to say, both of these methods demand strict asepsis, and scrupulous cleansing of the skin as well as of the instruments, in order to guard against infection, erysipelas, and the like conditions. Incisions should be covered with gauze saturated with a

[1] *Bull. de Thérap.*, July, 1853. [2] *Reichert u. du Bois-Reymond's Archiv*, 1873, p. 620.
[3] *Petersburg. med. Woch.*, 1900, No. 51.

1 : 1000 solution of bichlorid, and the part wrapped in salicylated cotton or ordinary absorbent cotton to take up the serum; the dressing is renewed as fast as it becomes soaked. After capillary drainage it is well to cover the puncture with a little salicylated cotton and seal the wound with iodoform collodion. The latter procedure is less painful and cleaner than simple incisions; the patient is spared the discomfort of being soaked through; and the quantity of fluid abstracted can be accurately determined. Depending on the degree of tension, the latter amounts to several liters (quarts) in twenty-four hours. During capillary drainage the patient must be under constant supervision, to guard against the needle becoming displaced and thereby enlarging the punctured wound, as such an accident increases the risk of infection and might lead to hemorrhage. It is therefore necessary in some cases to withdraw the needle at night; and in any case it is wiser not to leave the apparatus in place day after day; the puncture should be carefully sealed with collodion, and if the procedure has to be repeated after a time a new puncture should be made. The former practice of effecting evacuation by puncturing the skin in a number of places with a fine needle is not to be recommended and should be resorted to only in cases of emergency, as the risk of infection is even more difficult to guard against than in the other methods, and, owing to the ease with which the punctures heal over, the evacuation of fluid is much smaller. On the other hand, the writer has seen some good results follow the method of applying vesicants to the edematous areas, which is a popular remedy in some regions.

[In private practice among people where the services of a skilled nurse are not obtainable and where economy in the matter of surgical dressings has to be considered, multiple simple puncture wounds on the legs can be dressed with liberal amounts of cotton or linen cloth that has been recently boiled, and that is frequently changed when soaked with discharge and reboiled. In this way a sterile dressing that is absorbent can be kept on the leg and infection will rarely occur.—Ed.]

Whenever the accumulation of fluid in serous cavities attains an alarming degree, the affected cavity (pleura, peritoneum) must be evacuated by puncture according to recognized rules of practice. Edema of the vocal cords, which is often an alarming condition, must be treated by intralaryngeal scarification, and if that method fails, tracheotomy must be performed. Lastly, pulmonary edema is to be treated after the usual well-known methods.

UREMIA.

By the term "uremia" we designate a symptom-complex which makes its appearance when the function of the kidney is deficient, and which consists chiefly in disturbances of the nervous system and of the digestive organs.

The renal insufficiency is caused either by disease of the organ itself or by some affection situated in the urinary passages, somewhere between

the pelvis of the kidney and the urethra, which interferes with the evacuation of urine. Among diseases of the kidneys themselves, the inflammatory conditions, both acute and chronic, are the ones that are most apt to produce uremia.

The renal insufficiency manifests itself usually by a *diminution in the quantity of urine excreted*, more or less sudden in onset, or even by complete anuria. In rare cases the reduction fails to take place, and in still rarer instances the outbreak of uremia is preceded by an increase in the quantity of urine.

Bartels[1] observed the appearance of uremia from the sudden absorption of serous effusions after large quantities of fluids had been abstracted by diaphoretic and laxative measures; he attributed the uremia to the absorption of excrementitious materials contained in the dropsical fluid.

Two forms of uremia, the *acute* and the *chronic*, are distinguished according as the symptoms come on suddenly and rapidly, or develop insidiously and persist for some time; but it is impossible to draw a sharp line of distinction between the two forms. Chronic uremia, of course, develops only in chronic conditions of some duration, in which the renal function is lost gradually. Partly because of this gradual diminution of the kidney function and because the organism to a certain extent accustoms itself to the functional disturbances, the resulting symptoms develop slowly, one after another, instead of all at once, and the course of the disease is less stormy. Acute uremia, on the other hand, occurs both in acute and in chronic conditions whenever the renal insufficiency suddenly reaches the level necessary to bring on the disturbance.

In its most pronounced form, *acute uremia* presents a complete picture of a typical epileptic attack—so-called uremic eclampsia—and is usually preceded by certain more or less characteristic prodromes which often escape observation, or more rarely it begins with absolute suddenness. The commonest prodromal symptoms are headache or a sense of pressure and dizziness in the head, obscuration of the visual field, somnolence, vertigo, and absolute anorexia, combined with nausea and a tendency to retching and perhaps epigastric pain. The headache is sometimes unilateral and, with the other phenomena, gives the impression of migraine. Sometimes the attack is preceded by insomnia and a resulting sense of great lassitude and depression, by dyspnea and a feeling of oppression, drawing or even painful neuralgic sensations in the entire body or the course of individual nerves, ringing in the ears, and all kinds of other phenomena analogous to the aura which precedes an epileptic attack. Sooner or later, in rare cases more than a day after the first onset, complete *unconsciousness* sets in with more or less general *clonic* and *tonic* convulsions, beginning now in one extremity, again in the face or in the muscles of the neck, and in severe cases attacking the muscles of the chest and abdomen and threatening the patient with asphyxia, or causing cyanosis and involuntary evacuation of urine and feces.

[1] *v. Ziemssen's Handb. der spec. Path.*, xi., 1, 1875, p. 122.

In very rare instances the convulsions are unilateral, or very much more violent on one side than on the other.

After a short time—a few minutes to a quarter of an hour—the convulsions subside, while unconsciousness and coma continue for some time. The patient may never wake from the coma, and death takes place with stertorous, irregular respiration, often of the Cheyne-Stokes type, and increasing cardiac weakness. In other cases the patient may feel comparatively well after he comes out of the coma, or some of the prodromal symptoms continue with variable severity until a new attack occurs, or, finally, the patient may develop chronic uremia.

At the height of the attack the *pupils* are dilated and react sluggishly or not at all to light. The skin is frequently covered with sweat, although in other cases it may be dry and hot; *before* the convulsion the *pulse* is often tense and slow, but *during* the attack it is small and accelerated and often irregular; as a rule, however, it cannot be counted accurately until after the attack, when it is also retarded in most cases. If the *temperature* is taken after the convulsive attack, it is usually found to be elevated—and according to Rosenstein the elevation begins during the convulsions—but comes down to the normal again within a few hours unless a second attack follows; or it may become subnormal in very rare cases which rapidly terminate fatally. Bourneville's[1] statement that the temperature is always abnormally low in uremic eclampsia is only exceptionally applicable to the cases with tumultuous onset and course.

The frequency and mode of recurrence are variable. A patient rarely dies in the first attack, but it is equally rare for a single attack to be followed by prompt recovery; both these events are most likely to be observed after attacks occurring in the course of an acute nephritis; as, for instance, that of scarlet fever. As a rule, the attacks recur after intervals of variable duration; sometimes so frequently and at such intervals, especially in acute nephritis, that the patient never gets out of the coma and finally dies in an attack.

Instead of these fully developed attacks which the writer has just described, incomplete rudimentary attacks may occur alone or in alternation with the former. There may be coma without convulsions, or the convulsions may be less violent and extensive, and consciousness may be preserved or but little disturbed; or, finally, the two symptoms, coma and convulsions, may be replaced by other disturbances of the nervous system and of the organs of special sense as a kind of *uremic equivalents*, much as in the case of epilepsy.

These equivalents consist chiefly of *delirium* and *conditions of psychic excitement*, which may go on to *mania*. Very rare in children, they occur somewhat more frequently in adults in the course of chronic nephritis, and may either alone or during or following convulsions take the place of the coma. The excitement may be followed by *psychic depression*, which in rare cases has been known to result in a psychosis lasting many months.

[1] *Étude clinique et thermomètr. sur les maladies du syst. nerveux*, Paris, 1872.

In this connection should be mentioned *aphasia*, also associated, as a rule, with convulsions or coma with or without simultaneous hemiplegia (see p. 98), and transitory; in rare cases it forms the first symptom and is the forerunner of an eclamptic attack.[1]

Amaurosis is another frequent phenomenon. It is always bilateral, and may be the precursor of the attacks, but more frequently follows in their wake or is not observed until the patient regains consciousness. In rare cases it is the only noticeable symptom of uremia. With the exception of an already existing *albuminuric retinitis*, the ophthalmoscope reveals no striking alteration. The reaction of the pupils is variable; sometimes it is normal, especially in scarlatinal nephritis, in others it is sluggish or absent; sometimes the reaction is different in the two eyes. When the reaction is preserved, the vision usually returns after a few hours or days and the diminution of the visual field gradually becomes less (H. Schmidt[2]). In the other cases also the vision may be more or less completely restored; but if the eclamptic attacks are repeated, the blindness may become permanent. The cause of the blindness in cases in which the pupils failed to react was thought to be edema of the sheath of the optic nerve, and in the other cases edema somewhere beyond the corpora quadrigemina in the cortex. But M. Rothmann[3] pointed out that the absence of pupillary reaction is not an argument against the edema being situated peripherally in the sheath of the optic nerve, and that the existence of edema in the cortex is very improbable, because unilateral edema in the cortical center for sight produces hemiopia, and to explain complete blindness the lesion must be confined accurately to the two visual centers, which is very unlikely. It is more common to find hemorrhages in the central optic pathways (Zimmermann[4]).

Hemiopia has also been occasionally observed, as by Fr. Pick[6] in a case in which there was a focus of softening in the corresponding occipital lobe. In most cases hemiopia is probably also dependent upon unilateral edema.

Disturbances of the sense of hearing in uremia are much less common; they are either irritative in character, as ringing, whistling, and buzzing noises in the ears, and the like, or paralytic, ranging from hardness of hearing to complete deafness; they are said to be either unilateral or bilateral and ephemeral in character.

In connection with the *motor sphere*, mention should be made of certain tonic contractions of individual groups of muscles, as those of the calf of the leg, for example, of tremors similar to those of *paralysis agitans*, and actual *palsies*, which occur much more rarely in acute than in chronic uremia. Palsies were not known as uremic symptoms until quite recently, and even experienced observers regarded their occurrence as one of the most important points of distinction between uremia and cerebral apoplexy. But the observations of the last few years have upset the older teaching and have shown that, while uremic palsies are

[1] U. Rose, *Berlin. klin. Woch.*, 1898, No. 9. [2] *Ibid.*, 1870, p. 575.
[3] *Ibid.*, 1894, No. 30. [4] *Arch. f. Ophthalmol.*, vol. xxvii., No. 8.
[5] *Deutsch. Arch. f. klin. Med.*, vol. lvi.

rare, they are not by any means rarer than many of the above-mentioned symptoms. With the exception of paralysis of the external muscles of the eye, resulting in temporary strabismus, these palsies in the majority of cases consist of *hemiplegia* bearing the character of an ordinary cerebral paralysis, although in a few cases the palsies observed suggested more the bulbar type, presenting as they did anarthria, partial paralysis of the tongue and of the muscles of mastication, or paralysis of the face on one side and of the extremities on the other. The paralysis may develop and persist after a convulsive attack, or may develop without any convulsion having taken place.[1]

The anatomic findings in all these cases consisted simply in cerebral edema of varying intensity and possibly of localized anemia; no gross focal lesion has ever been found. As, however, none of these cases, so far as the writer knows, was examined microscopically, the possibility of finer structural alterations, such as capillary hemorrhages, softenings, and the like, being present cannot be excluded.

The **symptomatology** of chronic uremia includes all the symptoms of the acute variety in an attenuated and less violent form, and in addition certain other phenomena which presumably require for their development the action of more protracted and gradually progressing injurious influences on the organs. Owing to this insidious development, the beginning of chronic uremia cannot be sharply determined and the earliest phenomena are not characteristic, the true nature of the affection being recognized only by the coincidence of various symptoms, their peculiar grouping, and their refractoriness to treatment.

As regards nervous symptoms, the motor disturbances, especially convulsions, are more in the background, while the *psychic* manifestations come more to the front. The patient becomes apathetic and somnolent, or may be confused for days at a time. *Headaches* of various kinds constitute some of the earliest and most obstinate symptoms, and when they occur in renal patients should always arouse a suspicion of uremia; in addition, all the other above-described nervous disturbances may make their appearance. Another noteworthy point of distinction from acute eclamptic uremia is the frequency of *myosis*.

Next in order of frequency are the *disturbances* of the *digestive apparatus*, persistent anorexia with nausea and occasional attacks of vomiting. At first the vomiting occurs only after taking food or in the morning when waking, but later the patient vomits also during the day when the stomach is empty. In the more advanced stages the vomited material has a neutral or even an alkaline reaction and sometimes a urinous odor, caused by ammonium and perhaps also by amin (trimethylamin). These substances are derived from the decomposition of

[1] The writer observed 3 cases of hemiplegia of this type during the last eleven years, 2 of which were reported in Clemens Jäckel's dissertation: "Beiträge zum Symptomencomplex der Urämie insbesondere über urämische Lähmungen," Berlin, 1884; cases 1 and 3. The dissertation also cites 2 cases reported by another observer. See also Paetsch, *Zeit. f. klin. Med.*, iii., 1881, p. 209; Chantemesse and Tenneson, *Revue de méd.*, 1885, No. 11; Dunin, *Berlin. klin. Woch.*, 1889, No. 7; Raymond, *Revue méd.*, Sept., 1885; Boinet, *Ibid.*, Sept., 1892.

the nitrogenous constituents of the urine—urea and the like—and are excreted vicariously by the mucous membranes of the intestine instead of by the insufficiently functionating kidneys. They are probably responsible for the burning and dryness in the throat complained of by the patients. Finally, there occur obstinate attacks of diarrhea which may alternate with the vomiting. This diarrhea is also attributable to irritation of the intestinal mucous membrane by the above-mentioned decomposition products, which may produce not only catarrh, but also ulcerative processes in the bowel, so-called "uremic intestinal ulcers," and dysenteric manifestations.[1] Boucheron[2] asserts that he found uric acid in the *saliva* of uremic patients.

Respiratory disturbances directly attributable to uremia and not due to demonstrable alterations of the respiratory organs or the heart are very rare. Most complaints of this kind observed in the course of chronic kidney disease are caused by organic disease of the bronchi or the pulmonary parenchyma, and especially of the heart muscle. So-called *uremic or renal asthma* is in reality almost always a form of cardiac asthma on an arteriosclerotic base. Occasional suffocative attacks suggesting bronchial asthma or associated with laryngeal dyspnea devoid of any anatomic foundation are said to be observed (G. Sée,[3] Bartels,[4] E. Wagner[5]). In some somnolent or comatose patients Cheyne-Stokes breathing is not infrequent.

A symptom that is not rarely observed in chronic uremia is a *peculiar "urinous" odor of the breath* and of the exhalations of the skin. Christison[6] mentions it in connection with a case of Bright's disease of the kidney; Hemmernik[7] reports having noticed the odor in the breath and perspiration in the typhoid stage of cholera, which is frequently attributed to uremia; and Frerichs[8] believes that ammonium is contained in the expired air and possibly also in the exhalations from the skin. His theory will be referred to later. The writer's own impression is that the odor resembles trimethylamin more than ammonium. He has seen a number of cases in which the odor was unmistakable, especially before an eclamptic attack, and is therefore inclined to ascribe to it a certain prognostic significance.[9]

The *quantity of urine* excreted is usually, but not always, diminished shortly before and during a uremic attack. The urine during a pronounced attack of uremia contains an abundance of ammonium (Gumlich, P. Fr. Richter[10]), while the proportion of urea is more

[1] J. Fischer, *Virchow's Archiv*, vol. cxxxiv.; P. Grawitz, *Deutsch. med. Woch.*, 1898, No. 20.

[2] *Comp. rend.*, vol. c., and *Semaine méd.*, 1896, No. 23.

[3] *Gaz. hebdom.*, 1869, No. 1, and *Wien. med. Presse*, 1869, No. 7.

[4] "Krankheiten der Harnapparate," in *v. Ziemssen's Handb. der spec. Path.*, ix., 1875, p. 100.

[5] "Der Morbus Brightii," *ibid.*, 3d Ed., 1882, p. 70.

[6] *On Granular Disintegration of the Kidneys*, Edinburgh, 1839, p. 202.

[7] *Die Cholera epidemica*, Prague, 1850.

[8] *Die Bright'sche Nierenkrankheit*, 1851, p. 101.

[9] v. Kaup and Jürgensen (*Deutsch. Arch. f. klin. Med.*, vi., 1869, p. 54) had under their observation a patient with vesical catarrh, who emitted a markedly urinous odor. They were unable to demonstrate ammonium in the expired air.

[10] *Zeits. f. physiol. Chem.*, vol. xvii.; P. Fr. Richter, *Charité-Ann.*, vol. xxii., 1897.

likely to be diminished. The entire quantity of nitrogen content includes, in addition to urea, ammonium, alloxur bodies and other extractives, and appears to be diminished as the result of the toxic decomposition of protoplasm (P. Fr. Richter).

In chronic uremia the *skin* is usually dry and frequently the seat of intolerable itching, which makes the patient scratch himself, and sometimes results in an erythematous scratch-marks eruption. The itching is attributed, and probably with reason, to the overloading of the blood with urinary constituents, which represent an abnormal irritant to the sensory cutaneous nerves. The theory finds support in the fact that—as was described long ago in connection with cholera typhoid by Schottin, Drasche, and sometimes with chronic kidney disease, as by v. Kaup and Jürgensen, Deininger, and Jahnel[1]—a short time before death urea is deposited in fine crystalline scales on the skin around the openings of the sweat ducts. In all these cases, to be sure, the question of itching either before or during the excretion of uric acid was not discussed.

Other disturbances of the skin in subjects of kidney disease have been pointed out by Alibert[2] and Dieulafoy,[3] among which may be mentioned "dead fingers" ("le doigt mort"), or a feeling of formication or convulsive rigidity, which he has personally observed in several cases of chronic uremia. The symptom probably depends on a vasomotor disturbance which may under certain conditions go on to the production of symmetric asphyxia or Raynaud's disease.

The *body temperature* in chronic uremia, in contradistinction to what occurs in the acute form, is never elevated unless there is some febrile complication, and even then fever is not always present; on the contrary, the temperature is usually diminished and may fall to an extremely low level. An extreme fall in the temperature is usually a sign of impending death, or may in exceptional cases occur some time before death and alternate with periods of somewhat higher temperature.

Thus, in the case of a locksmith, fifty-three years of age, suffering from contracted kidney and uremia, the writer observed an axillary temperature of 33.8° C. (92.8° F.) twenty-three days before death; on the following day. the eighteenth before death, the temperature, after some oscillations, fell to 35.6° C. (94° F.) and 32° C. (89.6° F.), and then rose again to 33° to 34.7° C. (91.4°–94.4° F.), and shortly before death it again sank to 32.5° C. (90.5° F.); the pulse rate during that time ranged between 40 and 70.

Bourneville[4] and Netter[5] saw the temperature go as low as 30° C. (86° F.).

In the hope of determining the condition of the *blood* in uremia a number of experiments were made, which will be detailed later in connection with the discussion in regard to the theories advanced for the explanation of uremia (see p. 103). As a point of some practical importance, the writer may mention that the molecular concentration of

[1] v. Kaup and Jürgensen, *loc. cit.*; Deininger, *Deutsch. Arch. f. klin. Med.*, vii.; Jahnel, *Wien. med. Presse*, 1897, No. 46.

[2] "Contribution à l'étude clinique du mal de Bright," *Thèse*, Paris, 1880.

[3] *Union méd.*, 1886, No. 106.

[4] *Loc. cit.*

[5] Cited by Brault, "Maladies du rein", in *Traité de médicine*, by Charcot, Bouchard, and Brissaud, v., 1894, p. 589.

the blood and of the edematous fluid, as found by determining the freezing-point, is, although not without exception, in the great majority of cases of uremia increased—that is to say, the freezing-point falls below the normal—*i. e.*, below —0.56° to —0.58° C.

Blood-pressure is usually increased shortly before the onset and during the course of uremia, but falls with the appearance of collapse and the approach of the agonal period.

In the majority of cases *acute uremia* ends in *death*, a very small minority end in recovery, and the outlook for the latter is better in proportion to the infrequency of the attacks and the length of the free intervals. *Chronic uremia* practically always ends fatally when the symptom-complex is well pronounced; coma, a decided fall in the temperature, and palsies are evil prognostic omens. On the other hand, individual symptoms, which by themselves cannot always be recognized as uremic in character, such as headache, obstinate anorexia, and itching, may persist for some time without immediately threatening the patient's life, and then pass away.

In order to establish a **diagnosis** of uremia, the fact that the kidney action is deficient must first be demonstrated. The cause of this functional disturbance is in most cases a disease of the kidneys, as the writer has already pointed out, especially diffuse inflammation. But the primary cause may be some such condition as a calculus, tumor or scar outside of the kidneys, as in the pelvis of the kidney, ureters, bladder, or even the urethra, or in the neighborhood of these structures, impeding the flow of urine and thus impairing the function of the kidneys. If the physician has had the patient under observation during the course of the kidney disease or the extrarenal disease responsible for the retention, it is usually not difficult to recognize the uremia when it occurs, especially if other organic conditions can be excluded. But even under such circumstances certain phenomena may lead to error in the diagnosis, particularly *hemiplegia*, which not infrequently occurs in chronic kidney disease as the result of *cerebral hemorrhage* attended with coma and sometimes with convulsions, and *thrombosis* or *embolism* of the cerebral arteries. In all such cases changes are usually present in the arterial system and in the heart, and may thus suggest the correct diagnosis; but it is not always possible to avoid errors.

When, on the other hand, the patient's previous history is not known, it is often impossible to make a positive diagnosis when a sudden accident occurs in the course of disease, particularly an attack of coma and convulsions; the most the physician can do is to suspect uremia among a number of other conditions. The provisional diagnosis receives some confirmation, although it is not by any means rendered positive, when, on examination of the urine, which may have to be obtained by compressing the bladder or by the use of the catheter, signs of one of the above-mentioned kidney diseases are found; in other words, when the urine contains albumin. Even in that case, however, the diagnosis of "uremia" is not absolutely certain, because, on the one hand, other conditions which produce the same cerebral symptoms—coma and con-

vulsions—such, for example, as hemorrhage, an epileptic attack, meningitis, poisoning with narcotics or with santonin (Binz),[1] or profound alcoholic intoxication, may be accompanied by temporary albuminuria; and, on the other hand, because these or similar affections may be present as *complications* of a disease of the kidneys. In such a case of doubt the demonstration of *albuminuric retinitis*, and especially of decrease in the molecular concentration of the urine with *increase in the molecular concentration* of the blood or edematous fluid, is of the greatest value. The presence of these two conditions is distinctly in favor of uremia. The absence of retinitis does not negative the diagnosis, and if the molecular concentration is not increased the diagnosis of uremia is not thereby upset; but any existing suspicion will be reinforced.

In general, when only a few ambiguous symptoms, such as headache, anorexia, insomnia, and the like, are present, uremia may be suspected, but its presence cannot be positively asserted unless other symptoms are superadded and a careful examination of all the organs fails to reveal any other cause for the condition.

In regard to the **nature of uremia,** a number of theories have been constructed since the discovery that its most frequent cause is to be found in the diseases of the kidneys described by R. Bright, and the object of these theories has always been to explain the connection between the deficient kidney action and the uremic symptoms. Most of these theories assume that the blood and tissue fluids become vitiated by the presence of substances which the kidneys have failed to excrete; in other words, that the body becomes *overloaded with urinary constituents*. In addition to these so-called *chemical* theories, there is another known as the *mechanical* or *physical* theory, which seeks the true cause of the uremia, not in the poisoning of the blood, but in *hydremia* and *edema of the brain*.

The latter theory has been chiefly defended by Traube,[2] after Owen Rees[3] had pointed out as a cause of the convulsions and coma the watery condition of the blood and consequent edema of the brain. Traube expanded the theory, and formulated as the second important factor hypertrophy of the left ventricle, "which becomes added to the kidney disease soon after the development of the latter and, in conjunction with the thinning of the blood-serum, brings about an abnormally high tension in the aortic system. If from any accidental cause the tension is *suddenly* increased or the density of the blood-serum *suddenly* diminished even more than it was already, a transudation of serous fluid takes place through the walls of the small vessels into the brain substances and *edema of the brain* is produced. But as the blood-serum when it escapes is under the mean pressure prevailing in the aortic system, which is higher than the pressure in the capillaries and veins, the latter vessels are compressed, and their contents are diminished by a quantity equivalent to the volume of the escaping blood-serum. The

[1] *Trans. Second Congress for Internal Medicine*, 1883, p. 203.
[2] *Allg. med. Centralzig.*, 1861, No. 103.
[3] *On the Nature and Treatment of Diseases of the Kidney*, etc., London, 1850, p. 67.

inevitable consequence of edema of the brain produced in this wise is *anemia of the brain substance*. Traube attributes the coma to the edema and anemia of the cerebrum, and the convulsions to the same conditions in the midbrain; if one only becomes edematous and anemic to the exclusion of the other, either coma or convulsions will be present separately.

This theory seems *à priori* faulty, because it starts out with the utterly untenable assumption that edema and anemia may be produced by a rise in the arterial pressure; and, in the second place, because uremia may occur with or without hypertrophy of the heart and when cardiac action is weak. The hardness and tension of the pulse at the beginning of the attack is not due to increased heart action, but to the contraction of the smallest arteries. It is quite true that edema of the brain is frequently found in the bodies of those who have died of uremia; but the mere fact that this edema of the brain is not constantly found proves that at most it is the cause in only part of the cases, providing, as Bartels believed, the edema is not the result of the convulsions. The writer does not think, however, that Bartel's view is correct; for edema of the brain is not always found even after the most violent convulsions produced by a great variety of poisons. But the fact that edema of the brain is a frequent occurrence in uremia does not in itself justify the conclusion that the two conditions have a causal connection, although it lends a certain modicum of probability to such a view. Ph. Munk's [1] attempt to demonstrate experimentally this causal connection and to prove the correctness of Traube's theory can only be characterized as a complete failure. For by ligating the ureters and the jugular vein in dogs—and thereby producing *venous* congestion of the brain—and, in addition to that, injecting water or defibrinated blood into the carotid, he produced such an overwhelming influence on the organism that his conclusions cannot be said to prove anything whatever.

But it does not need to be proved that edema of the brain, especially when it develops suddenly, may produce the same phenomena as those which occur in uremia, particularly coma, vomiting, and perhaps also convulsions; and it may therefore be admitted that edema of the brain in many cases is partly responsible for the development of uremia, although other factors are probably present also. The writer is very much inclined to regard a circumscribed edema of the brain as the cause of many *focal manifestations*, particularly amaurosis and hemiplegia, for which it would be difficult to find another explanation.

As regards the *chemical* theories which assume that some of the urinary constituents are retained in the body, it may be said that nearly all the specific constituents have been in turn made responsible for uremia. First *urea* by A. Wilson [2] and a number of English authors, who based their assumption on the fact—first demonstrated by Bostock and Christison and later confirmed by many others—that the blood in Bright's disease contains an unusually large percentage of urea. It

[1] *Berlin. klin. Woch.*, 1864, No. 11.

[2] *London Med. Gaz.*, 1833.

was soon found, however, that the increase in urea was not constant, and especially that the blood of uremic patients by no means always contained a large quantity of urea; on the contrary, it may be very poor in urea (Bartels[1]); and, on the other hand, Babington,[2] Christison, Owen Rees,[3] Frerichs, and others demonstrated an abnormal percentage of urea in the blood of kidney patients who did not present any uremic symptoms. Finally, numerous experiments made by injecting urea into the blood or into the cavities of the body have shown that the substance is harmless even in excessively large quantities, and does not hasten the occurrence of death even when the kidneys are excluded from the circulation or the ureters are ligated (Stannius and Scheven,[4] Frerichs, Petroff,[5] Richet and Moutard-Martin,[6] Astaschewsky,[7] Feltz, and Ritter.[8]

Since, then, urea could not cause uremia, other authorities laid the blame on some of the *extractives*, especially *creatinin*, and on other substances that are said to accumulate in the body as the result of incomplete combustion, such as leucin and tyrosin. Schottin[9] was the first to utter this opinion, and was followed more or less closely by Hoppe-Seyler, Oppler[10] and Perls.[11] As a matter of fact, an accumulation of creatin or creatinin in the blood and in the tissues was found in a few cases of uremia. But in a number of other cases no creatinin was found, and v. Meissner,[12] Feltz and Ritter, Astaschewsky, and others combated the theory that the injection and accumulation of creatinin are capable of producing uremic symptoms. It is now, however, generally admitted, as the result of most recent investigations (see p. 108), that the blood of uremic patients contains an increased quantity, at least of the *nitrogenous* substances or so-called extractives.

Next the *potassium salts* were regarded as the essential cause of uremia. Voit[13] was one of the first to regard them as the principal factor in the production of uremia, although he also accorded to other excrementitious substances a certain share in its production. Feltz and Ritter are the chief exponents of this view, and Astaschewsky also adopted it at the same time. The former found that the injection not only of urea, urates, creatinin, hippuric acid, leucin and tyrosin, and the like substances in a quantity equal to three times the normal daily excretion, but also the injection of all the organic constituents together into dogs was quite harmless, while the potassium salts were found to be exceedingly poisonous; sodium and calcium combinations were not found to possess any injurious property. These facts were known,

[1] *London Med. Gaz.*, p. 116. [2] Bright, in *Guy's Hosp. Rep.*, 1836, p. 360.
[3] Bright in *Guy's Hosp. Rep.*, 1836, p. 360.
[4] Stannius, *Vierordt's Zeit.*, 1849, p. 201, and Scheven, "Ueber die Ausschneidung der Nieren" *Diss.*, Rosstock, 1858.
[5] *Virchow's Archiv*, vol. xxv., p. 91. [6] *Gaz. hebdom. de méd. et de chi.*, 1881, No. 12.
[7] *Petersb. med. Woch.*, 1881, No. 27. [8] *De l'urêmie expérimentale*, Paris, 1881.
[9] *Arch. f. physiol. Heilk.*, xiii., 1853, p. 170. [10] *Virchow's Archiv*, xxi., 1861, p. 260.
[11] *Königsberger med. Jahrb.*, 1864, iv., p. 56, and *Berlin. klin. Woch.*, 1868, No. 19.
[12] *Zeits. f. rationelle Med.*, v. Henle and Pfeuffer, 1866, xxvi., p. 225.
[13] *Sitzungsb. der Bayr. Akad. der Wissensch.*, 1867, i., p. 364, and *Zeit. f. Biol.*, iv., 1868, p. 140.

however, before the experiments referred to were made. Astaschewsky also succeeded in producing uremia with potassium salts, but failed with urea, creatinin, and the other urinary salts; A. Beck [1] and Herringham [2] report a like experience. It was also urged in support of the theory that an accumulation of potassium is found in the blood in uremic eclampsia, although this was denied by others (Horbaczewski,[3] Snyers,[4] Bruner [5]).

Finally a theory was advanced by Bouchard [6] that uremia was caused chiefly by the retention of certain organic metabolic products normally contained in the urine, conjointly with the accumulation of potassium salts and possibly of urea. Some of these organic poisons—ptomain, urotoxin—are said to produce convulsions, others to act as narcotics; to a third class is attributed the power of reducing the temperature; while a fourth contracts the pupils, and a fifth produces ptyalism. Normal urine is said to owe its toxicity chiefly to these substances, of which the quantity of urine voided in fifty-two hours contains enough to poison an adult. The urine from uremic patients, on the other hand, is said to be harmless, because the above-mentioned substances have been retained in the body. Now, aside from the fact that these ptomains and urotoxins have never been positively demonstrated, their occurrence has been directly disputed by Stadthagen.[7] As Lecorché and Talamon [8] justly remark, the theory is refuted by the fact that complete anuria has been observed to last much longer than would be necessary, according to Bouchard, to poison the individual, without giving rise to any uremic symptoms. Finally it has been shown by numerous investigators, from the time of Bichat, Courten, Gaspard,[9] Frerichs, down to most recent times, that filtered urine, although not quite innocuous, is not by any means so poisonous as Bouchard would have us believe. The only constant effect of the injection of urine noted by Fleischer [10] was persistent vomiting; and Albu [11] found that when the renal function was normal the injection of urine, unless too overwhelming, was almost entirely harmless.

In opposition to all these views, we have the theory erected by Frerichs, in 1851, to the effect that the manifestations of uremia are not produced by any urinary constituent, not even by a combination of all the excrementitious substances in the urine, but by *ammonium carbonate* generated from the accumulated urea in the blood by the action of a special ferment. In support of his theory Frerichs states (1) that he found ammonium in the expired air, as had already been observed in uremic patients (see p. 99), in the vomit, and in the blood and secre-

[1] *Pflügers Archiv*, vol. xxxi. [2] *Wien. med. Presse*, 1899, No. 32.
[3] *Med. Jahrb. der k. k. Ges. der Aerzte in Wien*, 1883, p. 385.
[4] *Pathologie des nephrites chroniques*, Brussels, 1886, p. 144.
[5] *Centralbl. f. inn. Med.*, 1898, No. 18.
[6] *Leçons sur les auto-intoxications*, Paris, 1887.
[7] *Zeit. f. klin. Med.*, xv., 1889, p. 383.
[8] *Traité de l'albuminurie*, etc., Paris, 1888, p. 578.
[9] Cited by Frerichs, *loc. cit.*, p. 106.
[10] *Trans. Fourth Congress for Internal Medicine*, Wiesbaden, 1885, p. 307.
[11] *Virchow's Archiv*, vol. clxvi.

tions of nephrectomized animals after intravenous injection of urea, and (2) that he was able to produce the symptoms of uremia in animals by injecting ammonium carbonate. Whether the manifestations are those of acute or chronic uremia will depend on the rapidity with which ammonium carbonate is formed from urea in the body.

These assertions have met with more contradiction than assent. Demjankow,[1] however, expressed himself in entire accord with Frerichs. He found that in nephrectomized dogs the injection of urea with ferment was rapidly followed by uremia, although neither of the two substances alone produced the same effect with the same rapidity; and he also succeeded in demonstrating ammonium in blood taken from the carotid artery, regularly after the attack and with somewhat less constancy during the attack.

The latter statement—about the occurrence of ammonium in uremic patients—gave rise to lively discussions. Schottin[2] first objected on the ground that Frerichs had inferred the presence of ammonium in blood from the fact that he had found it in the expired air—which in turn was inferred from the generation of fumes of ammonium chlorid when a glass rod moistened with hydrochloric acid was held in front of the mouth; for he said that ammonium might be produced in the oropharynx or in more deeply situated cavities by the decomposition of stagnating nitrogenous material. While such a possibility is conceded, the writer must say from his own experience that the occurrence of ammonium chlorid fumes is much more frequent in uremic patients than in others, a difference which, as Schottin surmises, may be due to the decomposition of the urea contained in the saliva and other fluids in the mouth. Such an event is rendered even more likely by the experiments of Schiffer,[3] Rosenstein,[4] and others, who showed that little if any of the injected ammonium is excreted by the lungs.

After Oppler and Petroff[5] had made contradictory statements about the occurrence of ammonium in the blood, Kühne and Strauch[6] asserted that the blood of uremic animals is free from ammonium, and Rosenstein later confirmed this statement with regard to human blood. On the other hand, Spiegelberg[7] succeeded in demonstrating ammonium in the blood of an eclamptic pregnant woman beyond the possibility of a doubt, and Winterberg[8] also found it later in the blood of uremic patients, although not in larger quantities than are found in persons who are not uremic; and, according to the investigations of H. Strauss (see p. 109), ammonium would really appear to be found in increased quantities in uremia. As, however, in addition to ammonium certain other nitrogenous bodies, which are neither albumin nor urea, are found in the blood in abnormal quantities, ammonium, while it may share to a certain extent in the production of uremia, cannot possibly be regarded as the sole cause of the condition.

[1] *Petersb. med. Woch.*, 1881, No. 28. [2] *Arch. f. physiol. Heilk.*, xii., 1853, p. 170.
[3] *Verhandl. des Vereines f. inn. Med.*, iii., 1883–84, p. 13.
[4] *Virchow's Archiv*, lvi., p. 383. [5] *Ibid.*, xxv., 1862, p. 91.
[6] *Centralbl. f. die med. Wissensch.*, 1864, Nos. 36 and 37.
[7] *Arch. f. Gynäk.*, i., 1870, p. 383. [8] *Zeit. f. klin. Med.*, vol. xxxv.

But as this destroys the foundation of Frerichs' theory, the second question—whether ammonium carbonate is really capable of producing symptoms similar to or identical with those of uremia—possesses little interest. According to Rosenstein's experiments it should be answered in the affirmative, in contradiction to the statements of Hoppe-Seyler and Oppler, as well as those of Ph. Munk.

Another theory that belongs to the same category as that of Frerichs has been upset by the examination of the blood. It is the theory advanced by Treitz,[1] and assumes that the production of ammonium is not, as Frerichs asserted, due to a special ferment occurring in the blood, but to the decomposition of urea in the intestine or, under certain conditions, in other portions of the body; as, for example, in the bladder. He applied the term *ammoniemia* to the condition produced by absorption of the ammonium carbonate. It is not to be denied that such absorption is possible, and it is, in fact, frequently observed in patients with chronic vesical catarrh when the evacuation of urine is insufficient and the accompanying manifestations in many respects resemble uremia, especially the chronic form.

It is to be remembered in connection with these conditions which have been termed "ammoniemia" that, as the writer pointed out years ago,[2] other decomposition products besides ammonium, among them trimethylamin, are formed and may play a part in the production of the symptom-complex; but at present nothing is known of their mode of action, which has so far received little consideration.

It may be worth mentioning briefly that *sodium chlorid*, *lactic acid*, *carbonic acid*, and *uric acid* have been found in abnormally large quantities in the blood of uremic patients by some investigators, while others failed to detect their presence; and that the *alkalinity* of the blood in uremia is diminished, according to v. Jaksch, and not notably altered according to v. Limbeck.[3]

More productive than the search for toxins and related substances in the blood is the investigation of other changes in the fluid, particularly such as affect the *physical conditions* and *percentages* of its various constituents.

Among the most important of these changes is the *increase in the molecular concentration of the blood, or of the serum and the dropsical transudates*, bringing the freezing-point of those fluids below the normal, which is —0.55° to —0.57° C. The investigations pursued by A. v. Korányi, Lindemann, M. Senator, Strubell, Rumpel, and especially the numerous ones carried on in the writer's own clinic by H. Strauss and others, demonstrate that this increase occurs in all cases of uremia with very few exceptions.[4]

[1] *Prager Vierteljahrsschr.*, 1859, iv., p. 143.

[2] "Ueber Selbstinfection durch abnormal Zersetzungsvorgänge," etc., *Zeits. f. klin. Med.*, 1884, vii., p. 235.

[3] R. v. Jaksch, *Zeits. f. klin. Med.*, vol. xviii.; v. Limbeck, *Arch. f. exper. Path.*, etc., vol. xxx.

[4] For the literature consult Strauss: *Die chronischen Nierenentzündungen in ihrer Einwirkung auf die Blutflüssigkeit*, etc., Berlin, 1902, p. 59.

Bruner[1] and Biernacki[2] determined an increase in the amount of water or, more strictly, a decrease in the solids, especially the albumin, in uremia; although it appears from the investigations of H. Strauss[3] that there are cases of uremia without any marked decrease in the percentage of albumin. On the other hand, the latter's investigations show beyond the possibility of a doubt that, while the salinity of the serum in uremia undergoes no change, the quantity of nitrogenous constituents contained in the serum after removal of the albumin—in other words, the residual or "retention" nitrogen—is, as a rule, increased, even to an extraordinary degree, and the same is true of the dropsical effusions.

In uremia A. Bickel[4] found that the electric conductivity of the blood-serum was not increased to the same degree as the molecular concentration is in some cases. This confirms the argument that the latter is not due to the accumulation of electrolytes—salts, bases, and acids.

It follows, therefore, that uremia, as a rule, is characterized by an increase of the molecular concentration with unchanged normal salinity, normal or diminished albumin content, and an increase of residual or "retention" nitrogen. Hence the increase in the molecular concentration is caused chiefly by an increase of those nitrogenous bodies which are not albumin, but are normal or abnormal derivatives of albumin.

But the increase in the molecular concentration cannot be held solely responsible for the production of uremia; for, in the first place, a high degree of concentration has been observed in a variety of other conditions, including nephritis without uremia; and, in the second place, the concentration of the blood can be artificially increased by suralimentation, or even better by the administration of large quantities of salt or sugar or even urea, without producing any symptoms of uremia even when nephritis is present, and the kidneys, whose task it is to maintain the normal molecular concentration of the blood, are therefore totally or partially incapacitated from performing that duty (Nagelschmidt,[5] Knapp[6]).

If, therefore, any significance at all for the occurrence of uremia is to be attributed to the above-described changes in the blood, the increase of the substances contained in the residual or "retention" nitrogen, which are in some way related to the kidney disease, must be regarded as the cause of the uremia.

But how is this connection to be explained? A simple retention in the blood of normal urinary constituents as the result of insufficient kidney action cannot be admitted, because undoubted cases of complete anuria lasting from a day to several weeks have been observed without uremia. In some of these cases an attempt has been made to explain

[1] For the literature consult Strauss: *Die chronischen Nierenentzündungen in ihrer Einwirkung auf die Blutflüssigkeit*, etc., Berlin, 1902, p. 59.
[2] *Zeits. f. klin. Med.*, vol. xxxii., p. 49. [3] *Ibid.*
[4] *Deutsch. med. Woch.*, 1902, No. 28. [5] *Zeits. f. klin. Med.*, vol. xlii.
[6] *Verhandl. der deutsch. Ges. f. Gynäk.*, 1901.

the absence of uremia on the ground of vicarious excretion of the noxious constituents through other channels (vomiting and diarrhea); but, in the first place, such vicarious excretion does not take place in every case, and, in the second place, the phenomenon does occur quite frequently in uremia without producing any appreciable benefit; and in general this vicarious excretion is a very imperfect substitute for kidney action.

Even the assumption that in such cases of anuria the quantity of metabolic products which ought to be excreted by the kidneys is diminished on account of the lessened food-supply is not a satisfactory explanation, although the significance of this factor is not to be underestimated.

So far as the writer can see, the only possible explanation remaining is the following: In the first place the residual or retention nitrogen may contain noxious substances, the nature of which is still unknown, which produce the uremia. The residual nitrogen of the blood always contains, in addition to urea, uric acid, and ammonium, a respectable array of other substances, among which the cause of uremia is possibly to be sought. According to H. Strauss,[1] *that* particular portion of the residual nitrogen is not increased much above the normal in uremia and nephritis, as compared with the urea, uric acid, and ammonium. If the peccant bodies are then contained in the above-mentioned portion of the residual nitrogen, they cannot be normal substances that have accumulated to an abnormal degree, since no such apparently abnormal accumulation takes place; they must be abnormal bodies, the products of faulty metabolism. This brings us back to the assumption which more closely approaches the older theories—namely, that *uremia depends on an intoxication with abnormal nitrogenous metabolic products.* This view is supported by the above-mentioned facts (see p. 100) that the nitrogen content of the urine is increased in uremia, not, however, through an increase of the urea, but through an increase of the ammonium and other nitrogenous (alloxuric) bodies. Such a process, particularly an increase of the excreted ammonium, is observed in the conditions designated "*acidosis*," profound disturbances of metabolism that lead to abnormal production of acid and abnormal decomposition of albumin (*plasmolysis*). Unfortunately this brings up the further question, which we should like to have answered—namely, What is the cause of this plasmolysis which leads to acidosis?

A key to the answer of this question might possibly be found in the doctrine recently promulgated, according to which the kidneys are possessed of a second function or so-called "*internal secretion*," in addition to the secretion of urine. But the existence of such a secretion from the kidneys has not by any means been proved, for the experiments carried out by the discoverer of internal secretion (Brown-Séquard), and after him by E. Mayer, Vanni and Manzini,[2] for the purpose of

[1] *Verhandl. der deutsch. Ges. f. Gynäk.*, 1901, p. 43.

[2] *Arch. de physiol.*, etc., 1893, v.; E. Mayer, *ibid.*, p. 761; Vanni and Manzini, *Gaz. degli ospedali*, xii., 1893.

proving the theory are anything but convincing. Nevertheless, it cannot be denied that there is much in favor of the doctrine, such as the analogy existing between the kidneys and other glands that are universally acknowledged as possessing "internal secretions," and the fact already referred to, that anuria may persist a long time without producing uremia; the latter might be explained by means of this doctrine on the assumption that the internal secretion has not been impaired, although the other function of the kidneys, the excretion of urine, is abolished.

According to this doctrine, uremia is not produced in diseases of the kidneys unless the internal secretion also becomes abolished or perverted.

With the assumption that all the results of the investigations which have been made recently will be confirmed, *uremia may be defined as an auto-intoxication by nitrogenous substances, depending on a disturbance of the renal function and accompanied by the decomposition of albumin (plasmolysis), leading to abnormal acid formation (acidosis).*[1] The functional disturbance of the kidneys probably includes that of an "internal secretion," the significance of which is not as yet very well known.

The substances elaborated in the kidneys during functional disturbance which produce uremia, and by causing contraction of the vessels gradually bring about hypertrophy of the heart, are called "nephrolysins."[2] The theory that the functional renal disturbance depends on a disturbance of the "internal function" appears to be supported by the experiments of Vitzou, who observed that animals which had been rendered uremic by nephrectomy could be kept alive an extraordinary length of time by means of injections of venous blood-serum obtained from normal kidneys.

[On the subject of nephrolysins or nephrotoxins, one may consult articles by Pearce.[3] He found that the renal cells of the dog are altered both anatomically and functionally by the injection of blood-serum taken from rabbits which had been previously treated with emulsion of dog's kidney. Also serum from dogs in which a spontaneous nephritis was found was nephrotoxic for healthy dogs. This work is suggestive, but still offers little definite explanation of the development of most cases of nephritis in man.—Ed.]

In the great majority of cases the functional disturbance of the kidneys is brought about by disease or destruction of the glandular parenchyma, leaving an inadequate remainder; more rarely it is induced mechanically by obstruction either of the urinary tubules or of the larger urinary passages, preventing sufficient evacuation of the excrementitious substances and injuring the renal parenchyma through stagnation of the contents.

[1] "Die Auto-intoxicationen" in *v. Leyden's* and *F. Klemperer's Deutsch. Klinik*, i. 1, p. 25.

[2] Lindemann, Nefédieff, Bierry, Ascoli, and Figari, *Berlin. klin. Woch.*, 1902, Nos. 24 and 27.

[3] *Univ. of Penn. Med. Bull.*, 1903, xvi.

The moment when metabolic disturbances may manifest themselves by clinical symptoms—in other words, the *time of occurrence of uremic symptoms*—depends, as in other disturbances, partly on the severity of the irritation and partly on the degree of individual irritability—*i. e.*, uremia occurs only when the limit of tolerance has been overstepped. The irritability of the *nervous centers* is of the first importance, especially for the onset of a typical acute uremic attack; for the nervous disturbance dominates the clinical picture, and treatment directed against this irritation of the nervous system is of undoubted utility (p. 113); while, on the other hand, conditions that increase the irritability of the nervous system—such, for example, as parturition—hasten the outbreak of the uremic attack. The immediate effect of the irritability appears to be a contraction of the small arteries, causing acute anemia of the brain, which is a possible factor in the production of the attack, although it is probably not followed by cerebral edema, as v. Traube asserts.

[Some clinical observations seem to indicate that there is an element of cerebral pressure, perhaps due to edema, in cases of uremic coma, for by lumbar puncture during coma considerable quantities of cerebrospinal fluid have been withdrawn with temporary symptomatic improvement.[1]—ED.]

Whether the course of uremia is *acute* or *chronic* depends on whether the blood becomes overloaded with the injurious substances suddenly or gradually. As regards the *varied character of the symptoms*, Traube (see p. 102) ascribed it to the fact that *different* regions of the brain are involved; and Landois[2] succeeded, by irritating *different* parts of one or both halves of the cerebral hemisphere and of the medulla oblongata with various urinary constituents, in producing almost all the manifestations observed in the clinical picture of uremia in so far as they can be reproduced in animal experiments. There is, of course, a difference between direct localized irritation of individual portions of the brain and an irritation emanating from the general blood-stream, the effects of which must necessarily be more diffuse; and the writer has therefore pointed out above (see p. 103) that certain focal symptoms, which in the absence of gross anatomic changes are regarded as uremic, are more probably produced by local disturbances of the circulation and circumscribed edema than by a general intoxication.

Uremia, whether acute or chronic, is always a serious condition and the **prognosis** is accordingly always grave. It depends first of all on whether the cause—that is, the functional disturbance of the kidneys—can be removed. But this is possible only in a small minority of the cases, in which the cause is some mechanical obstruction, as a calculus, a kinking of the ureter, a growth, and the like. In such cases the prognosis of uremia is less unfavorable, as it is also in pregnant and parturient women, providing it is possible to bring on labor. But

[1] *Cf.* Scherb, *Revue neurologique*, x., No. 1, p. 19, and Willson, *Jour. Am. Med. Assoc.*, 1904.

[2] *Die Urämie*, Wien and Leipzig, 1889, 2d ed., 1891.

in the majority of cases of uremia produced by true renal disease the cause cannot be removed. Nevertheless, it is not infrequently possible, particularly in acute nephritis, to combat the uremia, and, if recovery from the nephritis takes place, to achieve a permanent cure. Even in chronic cases the physician sometimes, although more rarely, succeeds in bringing his patient through one or several uremic attacks; but in the end the patient will succumb to such an attack unless some other intercurrent disease or accident terminates life. The danger to life in chronic uremia is not so immediate as in the acute form; but, on the other hand, complete recovery is more difficult to bring about.

Treatment.—In the *prophylaxis* of uremia the indications are to remove the functional disturbance of the kidneys, or, if that is impossible, to open up other outlets for the impeded excretion of urine or urinary constituents. In active uremia of sudden onset the same treatment, as a rule, accomplishes the latter object and combats the basal disease; and in chronic uremia also the first indication, as a rule, is the same as for the basal disease, and need not be discussed in greater detail. Whenever the excretion of urine is very scanty and the onset of uremia is therefore to be dreaded, an attempt might be made to stimulate diuresis by means of remedies that do not irritate the kidneys, the so-called refrigerant diuretics, which have already been discussed in connection with the treatment of dropsy (p. 91). Among these Leube[1] gives a preference to digitalis, especially in cases with weak heart action, as there is a prospect of stimulating diuresis by improving the action of the central organ and at the same time raising the blood-pressure. The drug may be advantageously combined with camphor, 0.1 gm. (1.5 gr.) several times a day; or the digitalis may be given internally, and camphor with or without ether (oleum camphoratum, æther sulfuricum, āā) may be given hypodermically. It is particularly important always to keep the *bowels active*, and not only to guard against constipation by every means, but even to induce copious catharsis unless there are special contra-indications. For the purpose the saline cathartics or strong bitter waters, such as Hunyadi, Apenta, and the like, are to be used, partly because by this means injurious urinary constituents are eliminated through the intestine—although such vicarious excretion is very inconsiderable—and partly because constipation, as has been remarked on p. 41, may have an injurious influence on the kidneys, besides leading to the formation of harmful decomposition products within the intestine, which irritates the canal; and finally because it is a matter of experience that such intestinal "derivation" has a favorable influence on the central nervous system.

On the theory that uremia depends on intoxication with *nitrogenous* substances, the ingestion of albumin should be restricted as a prophylactic measure, particularly meat, a procedure that is found to be desirable by experience also in acute nephritis and in acute exacerbations of chronic nephritis (*q. v.*). Clinical experience in this matter finds support

[1] *Verhandl. des Cong. f. inn. Med.*, Wiesbaden, 1883, p. 189.

in the investigations of Strubell,[1] who found that nephrectomized dogs which were fed on carbohydrates showed milder symptoms of uremia than dogs in a state of starvation or such as were given a large quantity of albumin or fat. Hence, when uremia is impending and in cases of chronic uremia, the patient should receive milk in not too large quantities (1.5 liters—or quarts—should be the limit for an adult), *carbohydrates*, and *fat*. Instead of milk, *buttermilk* may be given on account of its laxative and diuretic properties. *Cream, sour milk, almond milk, fruit juices,* and *lemonade* are also to be recommended.

The second indication consists in providing another outlet for the urinary constituents. To meet this indication many authorities adopt the same means to stimulate the function of the intestine and of the skin as are ordinarily employed in the treatment of dropsy (p. 89). *Pilocarpin* has been widely recommended because it is both a diaphoretic and a ptyalagogue, and urea has been found occasionally both in the sweat and in the saliva. Unfortunately, however, the drug, like other agents intended to stimulate excretion through the intestine and through the skin, often fails to act; in fact, the value of such vicarious excretion in threatening or existing uremia is not to be rated too highly. These methods may be adequate to the task of supplying the deficient elimination of water and, to a limited extent, of the urea, which is quite soluble, but they have little or no effect on the extractives and other urinary constituents, as has already been remarked.[2] According to Knapp's investigations,[3] the evacuation of injurious substances in uremic animals is secured much better by *vomiting* than by diaphoresis and salivation. He therefore recommends *lavage*. Warm baths of the temperature of 27° to 28° R. (92.7°–95° F.), gradually raised to 30° (99.5° F.) or a little higher, act very beneficially, even if they are not followed by profuse sweating. They quiet the nervous system and thus produce a very good effect on the patients' general condition.

The treatment that has just been outlined is suitable not only in the prophylaxis of uremia, but also in the insidious, slowly developing chronic form, the onset of which cannot be determined accurately.

When severe uremic manifestations, especially *eclamptic* attacks, make their appearance, narcotics are, of all the remedies that have been recommended, the most serviceable; by means of *chloroform inhalation* it is almost always possible to terminate the convulsions at once. Next in order of importance is *morphin*, given hypodermically, or by the mouth if the patients are able to swallow; the drug is particularly well adapted for preventing the return of the attacks for a considerable period and for relieving certain irritative symptoms, particularly the violent headache, the twitching, the distressing restlessness and anxiety, vomiting, and the

[1] *Wien. klin. Woch.*, 1901, No. 29.

[2] According to F. Köhler (*Deutsch. Arch. f. klin. Med.*, vol. lxii.), the sweat contains normally 0.14 per cent. of urea and 0.08 per cent. of nitrogen, so that very little is left for other nitrogenous bodies. A relation between the elimination of nitrogen in the sweat and urea could not be determined.

[3] *Loc. cit.*

like.[1] It may be used in alternation with *chloral hydrate*, which should be given as an enema with or without a few drops of tincture of opium, as it is not well borne by the stomach.

Unless the patient is very debilitated, *venesection* or venopuncture is to be recommended; in the case of little children, cups may be applied to the nape of the neck, or leeches behind the ears. An adult may be relieved of from 300 to 500 c.c. (say from 10 oz. to a pint) at one venesection.

Venesection probably acts by withdrawing a part of the poisonous blood from the body. To what extent other factors—such as the lowering of the blood-pressure, which only lasts a very short time, diminution of the viscosity of the blood, and therefore of the obstacles to the circulation and the production of sweat—are concerned is difficult to decide; at all events the influence of these factors is distinctly less important than the actual withdrawal of poison. The molecular concentration of the blood, which, as has been remarked (p. 107), is a frequent concomitant of uremia, without, however, being regarded as its cause, is not affected by venesection, as has been shown by P. F. Richter, Schreiber and Hagenbeck.[2]

It is advisable immediately after venesection to inject a solution of sodium chlorid, either isotonic with the blood or hypotonic with regard to it (0.9–0.6 per cent.), under the skin or into the intestine or directly into the vein that has been opened for the purpose of blood-letting. Such an infusion prevents too great lowering of the blood-pressure, and collapse, dilutes the blood and stimulates excretion, especially through the kidneys.

Deep coma is to be combated with *cold affusions in a warm bath*, with *stimulants* and *derivatives to the skin and mucous membranes* by means of sinapisms; dry cups to the nape of the neck, vinegar-water enemata, cold compresses, and cold sponging.

Although a great many internal remedies have been recommended, none, with the exception of the above-mentioned narcotics, has proved itself of any value. At the most, hydrochloric acid may be of some use in correcting gastric disturbances when they are to be regarded as uremic. Renal extract is recommended by Ajellon and Parascandole,[3] on the strength of Brown-Séquard's theory.[4]

CHANGES IN THE VASCULAR APPARATUS.

The frequent occurrence of hypertrophy of the heart, with or without valvular lesion or thickening of the walls of the aorta, in diseases of the kidney was first pointed out by R. Bright in connection with his investigations on the connection between the renal disease and dropsy.

[1] R. C. M. Page (paper read before the Medical Society of the State of New York, Albany, 1893) recommends the injection of veratrin (10 to 20 drops of Norwood's tincture of veratrum) either immediately after or together with the morphin; the drug is said to act by diminishing the blood-pressure.

[2] P. F. Richter, *Berlin. klin. Woch.*, 1900, No. 7; Schreiber and Hagenbeck, *Centralbl. f. Stoffwechselkrankh.*, 1901, No. 11.

[3] *Wien. med. Woch.*, 1896, No. 12.

[4] Bright, *Guy's Hosp. Rep.*, i., 1836, p. 396.

Among his 100 cases, 27 were found to be free from any form of cardiac disease, while in 6 the point is not mentioned, and it may therefore be assumed that no marked abnormality was present. Of 52 cases of cardiac enlargement, 34 were free from valvular lesion, although 11 of these presented thickening of the aorta, leaving 23 cases in which there was probably no organic cause for the pronounced hypertrophy, which in most cases had affected the left ventricle. This observation led Bright, as he said, to look for a less local cause for the unusual exertion to which the heart is spurred on. He believed that the change in the constitution of the blood acted as an irregular and unusual stimulus on the organ directly, or that it affected the smaller vessels and the capillaries in such a way as to require a greater exertion to drive the blood through the terminal ramifications of the vascular system. Cardiac hypertrophy, to a certain extent, may be observed to advance *pari passu* with the progress of the renal affection.

This very lucid explanation of Bright's, and particularly his segregation of the cases of hypertrophy of the left ventricle without disease of the valves or of the aorta occurring in the course of kidney diseases, was not at first generally accepted. Rayer[1] disputed the frequency of cardiac hypertrophy without valvular lesion or pulmonary disease; Frerichs[2] refused to admit the effect of the constitution of the blood on the development of cardiac hypertrophy, and was of the opinion that most cases of cardiac hypertrophy precede the development of Bright's disease. On the other hand, G. Johnson[3] confirmed Bright's assertions in regard to the occurrence of hypertrophy of the left ventricle in chronic renal disease without valvular or vascular lesion, and adopted the second of the two possibilities proposed by Bright as an explanation. He even went a step farther, and divided the cases of valvular lesion and kidney disease into those in which the latter occurs as the result of the former or sometimes of pulmonary disease, and those which are secondary to the toxic condition of the blood. S. Wilks[4] also distinguished a special group of renal affections occurring as the result of heart disease, particularly valvular lesions, and confirmed the occurrence of hypertrophy of the left ventricle in Bright's disease, and the thickening and rigidity of the arteries, which he regarded as the cause of the cardiac hypertrophy.

The question was finally cleared up by Traube in his celebrated treatise, "On the Connection between Disease of the Heart and of the Kidneys."[5] In his time little attempt had been made to classify the numerous kidney affections associated with heart disease. In addition to *infarction*, a condition which was then already well known, Traube separated from the mass of renal affections associated with heart disease *the congested kidney* which results, during insufficient cardiac activity, from the increased pressure in the venous system and simultaneous

[1] Bright, *Guy's Hosp. Rep.*, ii., pp. 234 and 259.
[2] *Loc. cit.*, p. 119.
[3] *Diseases of the Kidney*, 2d ed., 1856.
[4] *Guy's Hosp. Rep.*, viii., 1853.
[5] Berlin, Hirschwald, 1856, and "Nachträgliche Bemerkungen über den Zusammenhang," etc., *Deutsch. Klinik*, 1859, Nos. 31 and 32.

diminution of the arterial tension, and which in his opinion does not predispose to "*true Bright's disease*," that being an inflammatory condition. Traube[1] also described the clinical symptoms of congested kidney as well as those of *amyloid degeneration of the kidneys*, which he also separated from the general picture of Bright's disease; and finally he insisted upon the frequent occurrence of cardiac hypertrophy, particularly of the left ventricle, in chronic nephritis, and especially with the contracted kidney, the diagnosis of which he also placed on a solid foundation.

Traube's work, particularly his subdivision and clinical description of the various renal affections, which up to his time had been included under the term Bright's disease, soon won universal recognition. On the other hand, his explanation of the mechanism of cardiac hypertrophy in nephritis, to which the writer will revert presently, elicited lively discussions and led to a number of clinical, anatomic, and experimental investigations which have resulted in the accumulation of a very large supply of material available for the study of the cardiovascular changes occurring in diseases of the kidney, but so far have not resulted in any generally accepted explanation.

As regards the occurrence of cardiac hypertrophy, the analysis of a large number of cases proves that it occurs not only in cases of contracted kidney, but also, although less frequently, in other forms of chronic or subchronic disease, and even in some of the acute inflammations, particularly scarlatinal nephritis; this was demonstrated by F. Sibson,[2] and especially by C. Friedländer,[3] and has been confirmed by many others. In regard to the frequency of cardiac hypertrophy and its distribution among the individual forms of nephritis, the statements of authors are conflicting, partly because the dividing lines between the individual forms are difficult to establish and are variously laid down by different authorities. There is no doubt that in cases of contracted kidney cardiac hypertrophy is the rule, the percentages given ranging between 50 and 90 per cent. And, as was to be expected, increase of arterial tension as determined by studying the sphygmographic curve is likewise most frequent in cases of contracted kidney, but is also observed in all other forms of acute, subacute, and chronic inflammation of the kidneys (Galabin,[4] F. A. Mahomed,[5] Fr. Riegel[6]); and the rise in blood-pressure occurs, as appears from Riegel's observations in various forms of acute nephritis, early, before enlargement of the heart can be demonstrated, and even in cases in which enlargement never develops at all.

[1] Berlin, Hirschwald, 1856, and "Nachträgliche Bemerkungen über den Zusammenhang," etc., *Deutsch. Klinik*, 1859, Nos. 31 and 32, and *Allg. med. Centralztg.*, 1858, No. 65, and 1859, Nos. 1, 7, and 8.

[2] *Lancet*, March and April, 1874.

[3] *Arch. f. Anat. u. Physiol., Physiol. Abth.*, 1881, p. 168, and *Fortschr. der Med.*, 1883, No. 3.

[4] Thesis for the degree of M. D., London, 1873.

[5] *Brit. Med. Jour.*, May 2 and 23, 1874.

[6] *Volkmann's Samml. klin. Vorträge*, Nos. 144 and 145; *Berlin. klin. Woch.*, 1882, No. 23, and *Zeit. f. klin. Med.*, 1884, vii., p. 260.

The hypertrophy may involve the entire heart, including the auricles and the right and left ventricles, or the left ventricle alone, the last form being somewhat more frequent. The enlargement is never confined to the right ventricle. According to the generally accepted view, which is based chiefly on the assertions of Bright and Traube, hypertrophy of the left ventricle alone occurs with by far the greatest frequency in cases of *contracted kidney;* although this assertion appears to be contradicted by the very comprehensive statistics of v. Bamberger,[1] an abstract of which is given in the following table:

Primary form of Bright's disease.	Eccentric, simple hypertrophy of the entire heart.	Eccentric, simple hypertrophy of the left ventricle.	Percentage of hypertrophy of left ventricle.
Acute	5	6	54.5
Chronic	54	62	53.4
Atrophic	94	104	52.5
Total	153	172	53.0

It is to be observed, however, in this connection that v. Bamberger's "primary form" includes those cases of Bright's disease which develop from cold or some unknown cause, and which he distinguishes from all others. But it is impossible to carry out such a distinction consistently; nor does v. Bamberger distinguish between true contracted kidney the result of primary chronic interstitial nephritis or arteriosclerosis and the secondary form which develops during the terminal stage of chronic "parenchymatous" nephritis. While this distinction is not always easy to make in the cadaver, it is nevertheless an important one, because the antecedent parenchymatous nephritis may have something to do with the hypertrophy of the heart; and, finally, it is to be observed that the methods employed by v. Bamberger and the older authors for determining the size of the different portions of the heart yield inaccurate results.

The later investigations by C. Hirsch,[2] carried out by W. Müller's method, show that in 4 cases of genuine contracted kidney which developed after interstitial nephritis, and in 9 cases complicated with arteriosclerosis, or 13 cases in all, the hypertrophy was confined exclusively to the left ventricle in 4 cases, and the average increase in size was 43 per cent.—minimum 21 and maximum 67 per cent. In 7 cases the hypertrophy of the right ventricle was, on the average, 18 per cent. —minimum 10 and maximum 37 per cent.; while that of the left ventricle was 56—minimum 52 and maximum 91 per cent.; and in 2 cases the increase was 74 and 129 per cent. on the right and 76 and 188 per cent. on the left side respectively. C. Hirsch points out that during the early stage of contracted kidney (following parenchymatous nephritis) only the left ventricle and auricle are hypertrophied, while the right, instead of being hypertrophied, is atrophied. As we shall

[1] *Volkmann's Samml. klin. Vorträge*, 1879, No. 173, p. 1552 (20).
[2] *Deutsch. Arch. f. klin. Med.*, lxviii., p. 597.

see presently, it can be shown by clinical examination that the same process occurs in beginning *genuine* contracted kidney (following interstitial nephritis). Finally, it appears from the investigations of C. Hirsch that the heart may undergo hypertrophy during the later stages of chronic parenchymatous nephritis, as was also indicated by the older measurements, and that in this form of nephritis also the hypertrophy of the *left* ventricle is greater, and in some cases very much greater, than that of the right. Thus, in 1 case the increase of the right ventricle was 5 per cent., while that of the left was 63 per cent. The hypertrophy of the ventricles is shared by the auricles.

To sum up, it appears that the cardiac hypertrophy which occurs during and in connection with diseases of the kidneys at times affects the left half of the heart exclusively; in other cases to a preponderating degree; and that with contracted kidney particularly, the left ventricle alone hypertrophies in the beginning.

The enlargement of the heart is effected by an increase of the myocardium as a whole, with or without dilatation of the cavities (eccentric hypertrophy or simple concentric hypertrophy). Simple dilatation without hypertrophy is very rare and occurs usually in conditions of general marasmus, fatty degeneration of the myocardium, pericarditis, and the like.

Years ago the writer,[1] from observations of his own and those of others (Galabin,[2] Ewald[3]), proved by actual figures that in cases of contracted kidney, particularly so-called "genuine contracted kidney," which is regarded as the *typical form of chronic interstitial nephritis*, the increase in the mass of the heart is relatively much greater than its dilatation; or, in other words, that simple cardiac hypertrophy more frequently accompanies genuine contracted kidney, while eccentric hypertrophy is more frequent in other forms of Bright's disease.

Since that time the attention of observers has been directed to this condition, and the literature now contains more observations on the subject than were at the writer's disposal at that time. Hanot, like the writer, emphasizes the absence of dilatation in genuine forms of contracted kidney. Among 207 cases of enlargement of the heart with "atrophy" of the kidneys, Bamberger found hypertrophy of the left ventricle 39 times; and if we deduct 9 cases of simple dilatation without hypertrophy —since dilatation, as has been remarked, implies the presence of some special condition—the ratio as computed on 198 cases is 19 to 20 per cent. Even this figure is large enough to deserve attention; but it does not correspond to the conditions which the writer has in mind, because, as he has said, the analysis embraces *all* forms of contracted kidney, the so-called "secondary" as well as the genuine primary form, and in addition the arteriosclerotic contracted kidney; although the latter two varieties, as the writer explained at the time, are associated in the majority of cases, and the arteriosclerotic variety almost regularly with *eccentric* hypertrophy. If these cases were deducted from the total

[1] *Virchow's Archiv*, lxxiii., 1878. [2] *Ibid.*, lxxi., 1877.
[3] *Arch. gén. de méd.*, August, 1878, p. 172.

number (207, or, as the writer has suggested, 198), the percentage of simple hypertrophy with genuine primary contracted kidney would be considerably increased. These remarks apply even more forcibly to Spatz's [1] collection of cases. Among 54 cases of "granular atrophy" ("Granularschwund") he found 4, or 7 per cent., with simple hypertrophy; but in 30 out of 54 of these cases the patients were between fifty and seventy-nine years of age; in other words, many of the cases were complicated with senile arteriosclerosis.[2] Da Costa [3] states that simple hypertrophy predominates in cases of contracted kidney, and the eccentric form in parenchymatous nephritis; and Josef Bauer [4] expresses the same opinion. A few authors have disputed my assertion; so far as the writer can see, chiefly on the strength of Cohnheim's [5] authority, who, speaking from recollection, says that the relation given by me is the exception and the opposite is the rule. His memory, no doubt, deceived him, for even E. Wagner,[6] on the strength of his observations collected in the same place, which for years was the scene of Cohnheim's activity, asserts that a hypertrophied left ventricle *rarely becomes dilated* and rarely concentrically contracted, being most frequently of normal volume or but little dilated.[7]

In many respects *clinical* observation is better adapted to settle this question than is anatomic investigation. For, in the first place, the size of the cavities of the heart in the cadaver affords no positive criterion as to their size during life. When death has occurred while the heart is in systolic contraction, the cavity may appear smaller than it was during life. Moreover, it is more difficult to determine by the post-mortem findings which form of contracted kidney was present; and finally, when death occurs, changes have not infrequently developed as the result of disease of the coronary arteries, which lead to nutritive disturbances and relaxation of the heart muscles.[8]

But when one has the opportunity of observing cases of nephritis for a number of years, especially in children and young persons, developing from apparently insignificant beginnings and attended only by intermittent so-called "cyclic" albuminuria (see p. 33), the signs pointing to the occurrence of renal contraction and simple left-sided cardiac hypertrophy—that is, increased work *without demonstrable increase in volume* on the part of the heart—can be studied at leisure, and if death occurs during this stage the diagnosis can be confirmed by autopsy.[9] In other cases the development of dilatation may be observed during the subsequent course of the disease if conditions arise which, under other circum-

[1] *Deutsch. Arch. f. klin. Med.*, xxx., 1882, p. 156.

[2] The same statement applies to some extent to the above-mentioned figures given by Galabin and Ewald.

[3] *N. Y. Med. Rec.*, May 5, 1888.

[4] "Die idiopathische Herzvergrösserung," *Festschrift f. M. v. Pettenkofer*, München, 1893, p. 19.

[5] *Allg. Path.*, 2d ed., ii., 1882, p. 352.

[6] "Der Morbus Brightii," *v. Ziemssen's Handb. der spec. Path.*, ix., 1882, p. 88.

[7] Elsewhere (*loc. cit.*, p. 274) Wagner says the opposite of this.

[8] Adami, "Notes on Cardiac Hypertrophy," *Montreal Med. Jour.*, 1895, No. 12.

[9] For the diagnosis of hypertrophy of the heart without dilatation, see Traube, *Ges. Abh.*, ii., pp. 978 and 979; iii., pp. 232 and 440; and Senator, *Virchow's Archiv*, lxxiii., 1878, p. 327.

stances, lead to *secondary* dilatation of a hypertrophied heart. These causes include any temporary or permanent interference with the nutrition of the heart muscle, leading to relaxation, and permanent or repeated increase of intracardial pressure above a certain limit as the result of the manifold complications which may occur in the course of chronic renal diseases.

In cases of genuine contracted kidney such causal conditions usually develop as the result of changes in the arteries during the advanced stage of the disease—later than in other forms of chronic nephritis, particularly so-called "parenchymatous" nephritis, and later than in the case of the arteriosclerotic contracted kidney. In the parenchymatous form the hydremia and the general impairment of nutrition favor the relaxation and dilatation of the ventricle; and if later secondary contraction takes place, usually associated with improvement in the nutrition, the increasing hypertrophy may partially obscure the dilatation in the cadaver. In the arteriosclerotic form the nutrition of the heart muscle is, as a rule, directly impaired by disease of the coronary arteries. Both these factors may be operative in genuine contracted kidney, but much later, as has been stated, since the nutrition for a long time is perfectly well preserved and arterial changes occur late—*i. e.*, after the development of cardiac hypertrophy in consequence of continued increase of aortic tension.

The etiologic significance of arterial diseases in relation to the cardiac hypertrophy of kidney disease is variable. In the kidneys themselves arterial disease may be the result of inflammation, and does not markedly differ from the vascular changes observed in acute or chronic inflammatory processes elsewhere in the body. Sometimes atheromatous and arteriosclerotic changes precede the renal disease and may become the cause of contracted kidney—the so-called arteriosclerotic form.

Changes in the blood-vessels, both in the kidneys and outside of the kidneys, have been variously interpreted. Under the name "*arterio-capillary fibrosis*," Gull and Sutton[1] have described a "hyaline fibroid" formation in the walls of the smaller arteries, occupying, as a rule, the intima and adventitia, the muscularis escaping, and a "hyaline granular" change in the corresponding capillaries. They consider this disease of the vessels primary and the contraction of the kidneys as a sequel or a concomitant, because they found the same vascular disease with cardiac hypertrophy in cases with healthy kidneys. It is probable, however, that these changes are artefacts and to be attributed to the methods of investigation employed by Gull and Sutton. The writer has never been able to convince himself[2] that the changes may be limited to the intima or adventitia to the exclusion of the muscularis, or, in other words, to the exclusion of other parts of the vessel walls, and judging from the investigations of others (Sotnitschewski,[3] Leyden,[4] Lemcke,[5] Rosen-

[1] *Med.-Chi., Trans.*, lv., 1872.
[2] *Berlin. klin. Woch.*, 1880, No. 29, *Sitzungsb. d. Med. Ges.*
[3] *Virchow's Archiv*, lxxxii., 1880. [4] *Zeits. f. klin. Med.*, ii., 1881, p. 131.
[5] *Deutsch. Arch. f. klin. Med.*, xxxv., 1884, p. 148.

stein [1]), it appears to be, to say the least, extremely rare. On the contrary, all the coats of the artery take part in the thickening; the intima and adventitia are chiefly implicated, while the muscularis may be unchanged or atrophic or also thickened, as, in fact, Gull and Sutton themselves observed in a few instances.

G. Johnson [2] and Ewald [3] describe a simple hypertrophy of the muscularis in the smaller arteries, *also outside of the kidneys*, which, as appears from the latter's analysis, is overwhelmingly more frequent in "chronic interstitial nephritis" without "parenchymatous" inflammation, the form, therefore, which probably corresponds to the genuine contracted kidney. Ewald regards this hypertrophy of the muscularis as the result of the cardiac hypertrophy, because he never found it without the latter, although he frequently observed cardiac hypertrophy without vascular changes. But the objection which has been made to Gull and Sutton's description, that its occurrence in the adventitia and intima alone is very rare, applies to this observation as well. According to the writer's own investigations as well as others (W. H. Dickinson,[4] Saundby,[5] Auld [6]), it is usually found associated with changes of the adventitia and intima, an observation that is confirmed by the careful investigations of U. Friedmann.[7] According to the latter, the condition is often accompanied by arteriosclerosis of the smaller arteries, which differs from arterial hypertrophy by the fact that the thickening of the media is caused by an increase of the connective tissue and not of the muscle fibers. In the intima there is found in the inner side of the newly formed elastic membranes a more fibrous or hyaline layer presenting signs of degeneration in the elastic tissue elements, and sometimes vascularization and localized necrosis.

In order to get at the bottom of the connection existing between all these changes, more particularly to determine whether the kidney diseases are primary and the cardiac hypertrophy and vascular changes are to be regarded as sequelæ, studies were made on animals to learn the effect on the heart of excluding a portion of the renal parenchyma from the circulation. Thus, S. Rosenstein [8] failed to observe any increase of pressure in the aortic system or hypertrophy after the extirpation of one kidney in rabbits and dogs, the remaining kidney becoming hypertrophied in some cases and not in others. Similar results were obtained by G. Simon [9] and Gudden; [10] the latter operated on newborn rabbits exclusively. On the other hand, Grawitz and Israel [11] observed that after obliterating the kidneys by occluding their arteries, or extirpating one kidney, in full-grown rabbits, hypertrophy of the heart developed in some cases and not in others; while in young animals extirpation of

[1] *Path. der Nierenkrankh.* [2] *Med.-Chi. Trans.*, li., 1867.
[3] *Virchow's Archiv*, lxxi., 1877.
[4] *Diseases of the Kidney*, ii., p. 539; *Albuminuria*, London, 1877, p. 539, and *Lancet*, July 20, 1895.
[5] *Trans. of Internat. Cong.*, ii., p. 398. [6] *Lancet*, May, 1894.
[7] *Virchow's Archiv*, vol. clix. [8] *Ibid.*, liii., 1871, p. 141.
[9] *Chirurgie der Nieren*, Erlangen, 1871, p. 72. [10] *Virchow's Archiv*, lxvi., 1876, p. 55.
[11] *Virchow's Archiv*, lxxvii., 1879, p. 315, and lxxxvi., 1882, p. 299.

one kidney was followed by compensatory hypertrophy of the fellow organ. Lewinski[1] also observed cardiac hypertrophy in dogs whose kidneys he had caused to contract by occluding the artery. R. Zander,[2] in a number of cases of unilateral extirpation of the kidney in rabbits, both young and full-grown animals, observed enlargement of the remaining kidney in most cases, but never cardiac hypertrophy. On the other hand, J. Straus,[3] after causing contraction of the left kidney by ligating the corresponding ureter, observed hypertrophy of the left ventricle and hypertrophy of the other kidney developing in the course of two to six months in young as well as in full-grown animals. The smaller arteries outside of the kidney were normal. Before that time Beckmann[4] had observed enlargement of the right kidney and cardiac hypertrophy, especially of the left ventricle, in a dog after ligation of the left ureter, which was followed by contraction of the kidney. Finally, de Dominicis[5] concluded from experiments performed by ligating a renal artery that the cardiac hypertrophy which accompanies renal diseases is not a result of the renal disease, but a co-ordinate result of a form of blood-poisoning.

It will be seen, therefore, that these experiments have failed to yield any decisive result in regard to the relation between cardiac hypertrophy and diseases of the kidney. The positive and negative findings balance each other, and, so far as postmortem findings alone are concerned, we should not conclude that there was any connection between the two conditions were it not for the clinical observations already referred to, and the frequency of cardiac hypertrophy in Bright's disease which makes it probable that more definite factors than a mere accident are at work. Again, in other diseases which lead to loss of renal parenchyma, cardiac hypertrophy, particularly of the left side, is also observed; such conditions are protracted urinary stagnation from occlusion of the ureters by calculi, tumors, exudates, or kinks; also in hydronephrosis and cystic kidney, as well as congenital absence of one kidney. When hypertrophy of the heart is not present in these conditions, the explanation is that in disease of one kidney the other kidney makes up the deficiency, or that the low state of the nutrition has prevented the development of hypertrophy. Depraved nutrition is also regarded as the cause of absence of cardiac hypertrophy in *amyloid degeneration of the kidneys* except when contraction is present at the same time, in which case the latter probably leads to hypertrophy before the amyloid degeneration develops.

In any case, it may be stated as an axiom that the loss of functionating renal parenchyma, up to a certain degree, is followed by hypertrophy of the heart, which may be exclusively or to a preponderating extent confined to the left ventricle, unless its development is prevented by a depraved state of nutrition.

[1] *Zeits. f. klin. Med.*, i., 1880, p. 561.
[2] *Ibid.*, iv., 1882, p. 101.
[3] *Arch. gén. de méd.*, January, 1882.
[4] *Verhandl. der Würzburger Physikal.-med. Ges.*, ix., p. 142.
[5] *Wien. med. Woch.*, 1894, Nos. 47–49.

Traube published the first clearly thought-out theory in regard to the development of this hypertrophy. It is as follows: In contracted kidney two factors influence the rise in the aortic pressure, (1) the destruction of numerous blood-vessels in the shrunken parenchyma, or the compression of the vessels by an exudate in recent inflammation; and (2) the diminution in the total quantity of the fluid withdrawn in a given time from the aortic system on account of obliteration of the secreting parenchyma. Now, while it is conceded that in kidneys the seat of recent inflammation and in contracted kidneys the blood-current meets abnormally great resistance—in the case of the contracted kidney the fact has indeed been demonstrated by injection experiments by W. H. Dickinson[1] and Thoma[2]—yet it is not true that any kind of resistance in the renal arteries raises the mean aortic pressure; for we have learned through the investigations of C. Ludwig and his disciples and successors that not even the ligation of both renal arteries is sufficient to produce a permanent increase of pressure in the aorta. As for the second factor —the diminution in the quantity of fluid—the excretion of water through the urine is not diminished in contracted kidney, which is the form that Traube particularly had in mind; on the contrary, it is increased from the very beginning in so-called genuine kidney, or, at least, does not diminish. Nor is it proved or even probable that diminution of the quantity of water excreted by the kidneys raises the blood-pressure. In the first place the vascular system has other channels by which to get rid of any excess of water, as daily experience shows; nor is it possible by injecting physiologic salt solution to raise the aortic pressure. In the second place, even if the vascular system should become overfilled, it has the power to adapt itself quickly and completely to the altered conditions by the simple process of dilatation.

v. Bamberger believes that at some time in the course of an inflammation of the kidneys the body must accumulate water, as shown by the polyuria which occurs later, and therefore at some time the quantity of blood is absolutely greater, and, in spite of the tension in the vessels, the heart is obliged to work harder in order to move the increased quantity of blood, and thus becomes hypertrophied. But, in the first place, polyuria does not prove that the quantity of blood is abnormally large, since it occurs from a variety of causes when the quantity of blood is normal, as, for example, in diabetes insipidus; again, the water which at some time has accumulated in the body and is later evacuated is not contained within the vessels, but forms the serous effusions; and if it were really contained in the vascular system and the quantity of blood increased, we should have *hydremic plethora*, a condition that has never been demonstrated (see Dropsy, p. 83); and it is more than doubtful that the heart would have to work harder to move such hydremic blood.

A more plausible theory is that the serous effusions, by compressing the vessels, embarrass the circulation and cause the heart to work harder. It is possible that this factor has something to do with the production of cardiac hypertrophy in the renal diseases accompanied by dropsy—

[1] *Med.-Chi. Trans.*, 1860, p. 243. [2] *Virchow's Archiv*, lxxi.

that is, especially in the so-called parenchymatous and in many forms of acute nephritis; but it fails to explain the development of this hypertrophy with contracted kidney in which dropsy is usually absent.

In short, the theories based on purely physical considerations are not tenable, especially Traube's theory, and least of all in the case of contracted kidney. Nor is Cohnheim's modification [1] of that theory, which is somewhat difficult to understand, satisfactory. The latter contends that in spite of the resistance in the kidneys the same quantity of blood enters the small branches of the renal arteries, the tone of which is regulated by the quantity of materials in the blood that should be eliminated through the kidney (harnfähig), so long as the amount of these substances is not changed. Hence, the size of the small arteries and the quantity of blood that enters the kidney remain the same, and the increase in arterial tension is a necessary consequence of the abnormal resistance within the renal circulation behind the small arteries. Aside from other considerations, it is enough to say in response to this theory that the small arteries to which Cohnheim assigns such an important part are extensively diseased in contracted kidney.

In opposition to Traube's theory, which is purely physical, all the other theories advanced to explain cardiac hypertrophy assume a *faulty condition of the blood*, this altered blood acting as a direct irritant to the heart in the way indicated by Bright, and spurring it on to greater activity, or acting first on the vessels and indirectly, by the resistance opposed to the blood-stream, on the heart.

G. Johnson was the first to attempt to explain hypertrophy of the left side of the heart in contracted kidney in this way. The blood, which as a result of the renal disease is surcharged with excrementitious material, stimulates the smaller arteries to contraction under the influence of the vasomotor nerves, and thus stimulates the heart to perform more work in order to keep the circulation going. The resultant of these antagonistic forces is a simultaneous hypertrophy of the muscular layer of the arteries and the left ventricle (p. 121). This explanation is based on the doctrine, which the writer has also accepted, that certain materials contained in the blood are capable of acting as irritants upon the vessels. But hypertrophy of the muscular layer is not regularly found, as has already been said, and if contraction of the vessels were the first and only consequence of the irritation, the quantity of blood brought to the kidneys would have to be diminished, and therefore the quantity of urine would also have to be diminished from the very beginning, a condition that is not observed in genuine primary contracted kidney, which is the form in which Johnson made his observations on the arteries. Later in the course of the disease the increase in the quantity of urine might be explained by the secondary hypertrophy of the left side of the heart. Finally, Johnson's theory explains neither the hypertrophy of the right ventricle, which is quite frequently observed, although the enlargement is less than on the left side, nor the hypertrophy of the auricles.

[1] *Allg. Path.*, 2d ed., ii., p. 258.

Ewald, who, like Johnson, found only that the muscular layers of the arteries were hypertrophied (see p. 121), believes that the arterial condition is dependent upon the cardiac hypertrophy and excessive tension. He seeks the cause of the hypertrophy in the increased resistance in the capillaries due to friction, which in turn he ascribes to changes in the blood brought about by the renal disease. But as Ewald himself acknowledges, there is no proof that the blood-flow in the capillaries is impeded, and his theory also fails to explain the hypertrophy of the auricles.[1]

The explanation offered by O. Israel[2] dodges this difficulty of the auricles. To complete his previous experimental work with Grawitz, he fed rabbits on increasing quantities of urea for a certain length of time, and found in the animals hypertrophy not only of the kidneys, but also of the heart, from which he concludes that the accumulation of metabolic products in the body stimulates the heart to greater activity, which finally results in hypertrophy. The explanation does not particularize as to the hypertrophy of the vessels, nor is any account taken of the difference in the clinical course of genuine contracted kidney and parenchymatous nephritis.

A theory differing from all its predecessors was developed by Gull and Sutton. They regard the kidney disease not as the cause of the cardiovascular changes, but merely as a concomitant of their "arterio-capillary fibrosis" (p. 120), which may occur without renal disease. This, they say, is the cause of the cardiac hypertrophy. Now, it is quite true that in arteriosclerotic contracted kidney the arterial disease precedes the kidney lesion, but it is not true of the other forms of kidney disease, in which the arterial disease often bears no relation whatever to the hypertrophy of the heart. This theory also fails to explain the hypertrophy of the right ventricle and of the auricles.

The theory advanced by v. Buhl also differs from most of the others. He does not regard the kidney disease as the cause of the cardiac hypertrophy, but believes both conditions to be the co-ordinate effects of an unknown cause, producing inflammatory processes in the heart and in the kidneys. Inflammation of the myocardium, aside from pericarditic and endocarditic changes, was found by v. Buhl in no less than 65.7 per cent. of all cases of granular atrophy of the kidneys. Myocarditis, according to him, leads to dilatation and, later, to hypertrophy of the heart; simple hypertrophy without dilatation was found by him only in rare cases. A relative narrowing of the aorta also takes place, according to v. Buhl's theory,[3] and this is a further cause of cardiac hypertrophy. Changes in the smaller arteries are regarded as secondary and dependent upon the hypertrophy of the heart. v. Buhl's observations have not been confirmed by other observers, and he evidently takes no account of the cardiac hypertrophy which occurs in other diseases of the kidneys besides "granular atrophy."

[1] C. Hirsch and Beck failed to find any relation between the viscosity and increased pressure of the blood on the one hand, and the cardiac hypertrophy on the other (*Deutsch. Arch. f. klin. Med.*, lxxii.). [2] *Virchow's Archiv*, 1881, lxxxvi., p. 299.
[3] *Mittheilungen aus dem. path. Institut zu München*, 1878, p. 38.

Debove and Letulle[1] also regard the inflammatory changes in the heart as primary. Both in the heart and in the kidneys these changes, they say, begin as a periarteritis and go on to sclerosis with disappearance of the parenchyma. The sclerosis of the myocardium, which they found in the left ventricle and, to a lesser degree, in the left auricle and right ventricle, is then followed by hypertrophy of the heart. These changes in the heart, however, are but seldom found, nor can the pathologic process in the kidneys be compared to a periarteritis and its consequences.

Da Costa and Longstreth[2] report having found, in cases of contracted kidney and mixed nephritis (interstitial and parenchymatous), in the solar ganglia or, rather, in the renal ganglia degenerative atrophy of the nerve cells, with proliferation of the interstitial connective tissue and thickening of the vessels; and the same changes were demonstrated by Da Costa in the cervical ganglia of the sympathetic, especially the lower ones, which give off the cardiac branches. They attribute the renal disease as well as the hypertrophy of the heart to these changes in the nervous system, and therefore consider the two conditions as co-ordinate effects of an injury to the nervous system, especially the vasomotor nerves. Their findings have never been confirmed as being characteristic of chronic nephritis, and it is probable that some of the changes in the ganglionic apparatus which they describe are due to age.

The conclusion to be drawn from the above review is that some of the theories of the connection between renal disease and hypertrophy of the heart lack sufficient foundation in fact, being based either on rare conditions or findings that have never been positively demonstrated, and can therefore claim only a limited application to exceptional cases. This statement applies particularly to those theories which are based on the inflammatory changes in the myocardium or sympathetic ganglia. Nor is there a single one among the remaining theories that does full justice to all the facts; some of them fail to take into account the difference in kidney affections, while others explain only the hypertrophy of the left ventricle and pass over the hypertrophy of the right ventricle and of the auricles, which is quite frequently present at the same time.

Long ago the writer[3] pointed out that in view of the many anatomic and clinical differences in diseases of the kidneys, it is not probable that the accompanying hypertrophy of the heart can be explained in the same way for all of them, and he accordingly assumes for the cardiac hypertrophy in primary or genuine contracted kidney a different mode of origin than for the hypertrophy which occurs in the chronic parenchymatous form and secondary contracted kidney to which it gives rise. Recent investigations on cardiac hypertrophy and the constitution of the blood have confirmed the existence of such differences, but at the same time they have necessitated the modification of my earlier expla-

[1] *Arch. gén. de méd.*, 1880, i., p. 278.
[2] *Am. Jour. Med. Sci.*, July, 1880, and *N. Y. Med. Rec.*, May, 1888.
[3] *Virchow's Archiv*, lxxiii., 1878.

nation in several respects. In view of the facts now in our possession, the mode of origin of cardiac hypertrophy can be explained as follows:

Typical "chronic parenchymatous" nephritis so closely resembles acute nephritis in its development, clinical course, and symptomatology that it is impossible to draw a sharp dividing line between the two forms, hence the term "subchronic nephritis" applied to the former (see p. 224). Typical "genuine (primary) contracted kidney or chronic interstitial nephritis," on the contrary, develops much more insidiously and is characterized by a slower course, and presents various marked clinical differences, particularly as regards the constitution of the urine and the absence of dropsy. In addition to this, the investigations of H. Strauss (see p. 107) have developed distinct differences in the constitution of the blood in typical cases of the two forms. The following table, showing the composition of the serum in each of the two forms, makes these differences very evident:

	Chronic parenchymatous nephritis.	Chronic interstitial nephritis.
Salinity.	Usually normal; sometimes increased.	Fairly normal.
Molecular concentration.	Not increased.	Normal or slightly increased.
Residual (retention) N.	Not increased.	Usually increased.
Specific gravity.	Lowered.	Fairly normal.
Percentage of albumin.	Diminished.	Fairly normal.
Toxicity.	Not increased; sometimes diminished.	Not diminished; sometimes rather increased.

The effect of taking methylene-blue is also different in the two forms of the disease, but in this respect the variations observed under normal conditions are so great that no trustworthy conclusions can be deduced from the differences observed in disease.

In comparison with chronic interstitial nephritis, the course of the *chronic parenchymatous* form may be said to be stormy; the kidneys are in a greater state of irritation and the vessels outside of the kidneys suffer more severely, probably owing to the irritation of metabolic products retained in the blood on account of the disturbance of renal function; and these substances also irritate the heart muscle. As the result of this injury the vessels become more permeable, dropsy develops, and by that means the blood is relieved of part of the injurious substances that have been retained as the latter escape with the fluid into the tissues and cease to accumulate in the blood.

If the morbid process in the kidneys ceases entirely, as happens in favorable cases of acute nephritis, the irritation of the vessels and of the heart subsides, dropsy disappears, and complete recovery takes place. If the disease goes on to the subchronic stage, or if its onset is less tumultuous and life is sufficiently prolonged, the intensity of the irritation gradually diminishes, without, however, ceasing altogether; the dropsy disappears and an improvement takes place in the vessel walls. Nevertheless, as the irritant continues to be operative, contraction of the vessels, sometimes associated with thickening of their walls, takes place with hypertrophy of the heart, both of the right and of the left half, since

both are exposed to irritation by the blood. The left ventricle hypertrophies more than the right, because it not only responds by increased activity to the direct stimulus of the blood, but also has to overcome the resistance caused by the contraction of the arteries in the entire body; the right ventricle is spared this resistance because, as is well known, the pulmonary vessels possess very little tonus. Such is the mechanism in chronic parenchymatous nephritis and in secondary contracted kidney.

In *primary chronic interstitial nephritis*, owing to the insidious onset and slow course, the irritation of the vascular apparatus is no doubt correspondingly more feeble. Accordingly the injury to the vessels is not, as in parenchymatous nephritis, severe enough to produce dropsy; but the persistent irritation eventually results in contraction of the vessels. The result is hypertrophy of the heart, that of the left ventricle again being very much greater than that of the right, for the same reason as in secondary contracted kidney. The ultimate effect in both is the same—increased pressure in the aortic system.

The effect of this increased pressure is the excretion of a larger quantity of water and soluble urinary constituents by the kidneys, while the nitrogenous constituents, which are dissolved with greater difficulty, are excreted in lesser quantities, and accumulate in the blood in proportion to the extent of renal parenchyma destroyed.

The theory that the retention of nitrogenous metabolic products is irritating to the vascular system is supported by the experiments of Ustimowitsch,[1] Grützner,[2] Cavazzani and Rebustello,[3] from which it appears that the injection of urea into the blood produces an increase of pressure through arterial spasm. Of course, this increase of pressure is only temporary, as the urea is soon eliminated by the blood and arterial spasm does not last indefinitely. Hypertrophy of the heart is only produced by repeated attacks of heightened tension persisting for a considerable period, not by one such attack alone. This theory is also supported by the above-mentioned experiments of O. Israel (p. 125), in which he administered urea continuously for a considerable time.

What is true of urea is probably true also in a higher degree of many other urinary constituents, and it is readily conceivable that these substances, even if they are present in comparatively small quantities, may by their combined action produce an increase of the blood-pressure, although in animal experiments a large quantity of urea must be given to produce that effect.

In the case of *primary chronic interstitial nephritis* (genuine contracted kidney), it is questionable whether the irritation of the vascular system is primarily due to the kidney affection and consequent retention of injurious substances in the blood. For, in view of the fact that in the beginning of the disease and for some time after—in some cases for years—the changes in the kidneys are very slight, their function for a considerable period is practically not interfered with at all, especially

[1] *Arbeiten der physiol. Anstalt. zu Leipzig*, 1871, p. 198. [2] *Pflüger's Archiv*, xi., 1875.
[3] *Archivio per le science med.*, xv. and xvi.

as the destruction of parenchyma is so slight that it is readily compensated for by extra work on the part of the healthy tissue. (See Section V.) Hence retention can only occur when the renal disease has advanced to a certain point, when it regularly develops, as is shown by the investigations of H. Strauss, which the writer has so often referred to.

It is also conceivable, however, that instead of the irritation being primarily initiated by the kidney affection itself and the consequent disturbance of the metabolism, the primary irritant might be found outside of the kidney in some other injury, as, for example, *lead or the poison of gout.* Of these we know that they may exert an injurious effect on the vascular system without the intervention of a kidney disease. It must be admitted that it is possible for an injury of this kind to affect the vascular system *primarily*, whether it be the arteries first or the heart or the kidneys; or the effect may be produced on all these structures at the same time, and in the subsequent course of the disease the increasing functional failure of the kidneys may bring about the retention of excrementitious substances in spite of the copious excretion of water, as in the case of secondary contracted kidney, and thus reinforce the already existing irritation.

Lastly, as regards the *arteriosclerotic contracted kidney*, the hypertrophy of the heart in that condition is brought about by the rigidity of the vessel walls and consequent obstruction in the circulation, forcing the left ventricle to greater exertion. A. Hasenfeld[1] asserts that only severe arteriosclerosis of the splanchnic arteries, or of that portion of the aorta which lies above the diaphragm, is capable of alone producing hypertrophy, and that sclerosis of the remaining vascular regions is not followed by that result. For his part, however, the writer does not regard it as impossible that sclerosis of other arteries might lead to hypertrophy, especially if a large portion of them are affected at their point of origin from the aorta; for obstruction at the entrance offers a much greater obstacle to the blood-stream than rigidity of the walls in the subsequent course of the vessel.[2]

[1] *Deutsch. Arch. f. klin. Med.*, lix.

[2] According to Ascoli and Figari (*Berlin. klin. Woch.*, 1902, Nos. 24–27), "nephrolysins" are the cause of the cardiac hypertrophy.

SPECIAL PORTION.

MALFORMATIONS OF THE KIDNEYS.

THIS subject possesses but little clinical interest.[1] *Total absence or rudimentary "Anlage" of both kidneys* never occurs in viable children, and is nearly always associated with malformations elsewhere in the body.[2] On the other hand, *absence or congenital maldevelopment of one kidney*—the left a little more frequently than the right—is not rarely found in otherwise well-formed individuals and does not necessarily give rise to any disturbance, as the other kidney is usually enlarged and compensates for the functional or actual absence of its fellow by increased activity. (See below, Hypertrophy, p. 163.) The absence of one kidney is of practical importance because, when a single organ becomes diseased or injured, the danger is very much greater than when one of two available kidneys is attacked by disease. The sudden abolition of function—for instance, from occlusion of the pelvis of the kidney or of the ureter by calculi, kinks, and the like—may be followed by disastrous results when only one kidney is present. The occurrence of renal colic with complete anuria lasting for some time may in some cases suggest the correct diagnosis, which is confirmed by finding *only one* ureteral orifice on cystoscopic examination.

The question whether one or both kidneys are present is one of practical importance also in deciding the propriety of operative interference, especially in nephrectomy, which would, of course, be promptly followed by death if only one kidney were present. Before such an operation is performed, one should not neglect to determine by a careful cystoscopic examination whether there are one or two ureteral orifices; for when a kidney is wanting the corresponding ureter as well as the artery and vein are usually absent also. Whenever, therefore, it has been positively determined that the bladder has only one ureteral orifice, nephrectomy must not be performed. Conversely, however, the finding of two ureteral orifices is not absolute proof that two kidneys are present; for in a few cases—rare, it is true—two ureters have been found

[1] For the literature, besides the text-books on pathologic anatomy, see Rayer, *Traité des maladies des reins*, iii., 1861, p. 756; Lancereaux, article, "Rein," in the *Dict. encyclopédique des sciences méd.*, by Dechambre; Ebstein in *v. Ziemssen's Handb. der spec. Path.*, ix., 2; R. Beneke in *Zülzer-Oberländer's klin. Handb. der Harn- u. Sexualorgane*, i., Leipzig, 1894, p. 128; E. Ballowitz, *Virchow's Archiv*, clxi.

[2] A few cases without malformations elsewhere have been reported by Zaufal (*Prager med. Woch.*, 1898) and Rud. Bayer (*Wien. med. Woch.*, 1899). Moulon (cited by Rayer) says that he observed complete absence of both kidneys, ureters, and bladder in a child fourteen years of age. Rayer quite rightly regards this assertion with suspicion.

with a single enlarged kidney; or two ureters may pass upward from the bladder, but one of them ends blindly because the corresponding kidney is wanting (Bauchhammer,[1] Eppinger,[2] Paulicki,[3] Zaaijer[4]).

[In operations where the removal of one kidney is contemplated, the presence of the other kidney should be determined by palpation, by cystoscopy, or, it may be, by exploratory incision; this method has been practised by some surgeons by palpating the organ through an abdominal or lumbar opening.—Ed.]

Adhesion and fusion of both kidneys is a somewhat more frequent condition. A number of grades have been observed. In the mildest cases the lower extremities of the kidneys are somewhat nearer than under normal conditions and connected by a bridge of connective tissue or true renal parenchyma; the halves of the kidney are longer and narrower than ordinary kidneys and, with the connecting bridge, which lies in front of the vertebral column, form a curve with its convexity presenting downward—*horseshoe kidney* (ren arcuatus)—which lies somewhat lower than the level of normal kidneys. The ureters in this variety are normal. There are other, rarer forms of fusion, which are nearly always associated with displacement of the kidneys, resulting in a right- or left-sided double kidney.

Double kidney as described by v. Hansemann[5] is exceedingly rare.

These changes may give rise to the greatest diagnostic difficulties and even to the most serious errors, because the fused and dislocated kidneys give the impression of a tumor, and may therefore lead to the performance of an operation; in fact, such a thing has actually happened, and the error was discovered only at the time of the operation. Finally, if the deformed organ becomes diseased and enlarged—as, for instance, from hydro- or pyonephrosis or the presence of a neoplasm—the diagnostic difficulties may become insuperable.

The existence of a developmental error, such as absence or maldevelopment of one or both kidneys, may be suspected when there is some anomaly of the sexual organs. This often accompanies renal malformation, and when the latter is unilateral is found on the same side.

Of *acquired* malformation is to be mentioned the so-called *constricted lobe* (Schnürlappen) of the kidney, which, as J. Israel[6] tells us, is caused in *scoliosis* of the thoracic portion of the vertebral column by the pressure on the corresponding kidney of the lowest ribs, whose course is abnormal. The condition may simulate a tumor.

DISPLACEMENTS OF THE KIDNEY.

Either one or both kidneys may be displaced, and the condition may be *congenital* or *acquired*. In either case the abnormally situated kidney may become fixed at the abnormal site—*ectopia, fixed dislocation*—

[1] *Arch. f. Anat. u. Entwicklungsgeschichte*, 1879, i., 2.
[2] *Prager med. Woch.*, 1879, Nos. 26 and 27.
[3] *Allg. med. Centralztg.*, 1868, No. 57. [4] *Arch. neerland. des sci. nat.*, 1872, vii., p. 449.
[5] *Berlin. klin. Woch.*, 1897, No. 4.
[6] *Deutsch. med. Woch.*, 1896, No. 22, and *Chi. Klin. der Nierenkrankh.*, 1901, p. 14.

or it may be more or less movable. Ectopia is the rule in cases of congenital dislocations, while in the acquired cases the kidney usually possesses a variable degree of mobility.

1. **Congenital dislocations**[1] very rarely affect both kidneys except in the above-mentioned cases of *simultaneous fusion* (p. 131); it is much more frequent for one kidney, usually the left, to be dislocated. The condition is found more frequently in men than in women; according to W. Stern,[2] in the proportion of 20 to 9. The dislocated kidney is almost always abnormally depressed and lies in the false or true pelvis, usually on the promontory. Quite frequently abnormalities of the intestine or sexual organs are present at the same time. But, as a rule, there are no symptoms of any consequence, and congenital dislocations of the kidney are interesting rather from an anatomic than from a clinical point of view; they are very rarely discovered during life. Occasionally a displaced kidney interferes with labor, and in such cases, as well as in a few others, has been mistaken for a tumor.[3]

A positive *diagnosis* of this condition is well-nigh impossible. Dislocation of the kidney might be suspected if, the patient being under an anesthetic, on examining the supposed tumor, the outline of the kidney, and possibly also the pulsation of the renal artery, can be made out by palpation through the abdominal walls, or through the rectum and vagina; or if an exploratory puncture withdraws urine or a fluid containing characteristic urinary constituents, such as urea. Such fluid was found by Wölfler,[4] from Billroth's clinic, in a case of suppuration of the right kidney which was dislocated into the true pelvis.

2. **Acquired dislocation** is either produced by the pressure of tumors in the neighborhood of the kidney or is the result of abnormal mobility of the viscus. The first variety, in which the dislocation of the kidney either produces no symptoms at all or leads only to secondary disturbances, will not be discussed here; the second class of cases, on the other hand, deserves a full discussion on account of its great clinical importance.

WANDERING KIDNEY.

(Movable Kidney; Ren Mobilis; Ectopia Renis Acquisita.)

Under normal conditions the kidneys possess a certain degree of mobility, and when the abdominal walls are flaccid and thin, it is often possible during deep breathing to palpate the lower poles of the organs, especially of the right, which normally is somewhat lower than the left. In women palpation of the kidneys is easier than in men. In view of this normal mobility and the low position of the kidneys, the term "wandering kidney" is applied only to a condition of abnormally great

[1] See G. Strube, *Virchow's Archiv*, lxxxvii., 1894, p. 227; Graser, *Deutsch. Arch. f. klin. Med.*, lv., 1895, p. 473.

[2] Diss. inaug., Berlin, 1869.

[3] Schütz (*Deutsch. Zeit. f. Chi.*, xlvi.) describes a case of congenital dislocation of the right kidney to the left and underneath the left kidney, without fusion.

[4] *Wien. med. Woch.*, 1876, No. 7.

mobility of one or both kidneys, in which the *entire* viscus can be palpated through the abdominal walls.

The first description of this condition, which contains all the essential points, is that of Rayer, based on a few observations in the older literature and a number of cases of his own.[1] His dictum, that the condition is much more frequent than was commonly believed at that time, has been fully borne out since the attention of physicians has been directed to the subject, and the condition is being more and more frequently recognized since the methodic examination of the abdominal and pelvic organs, especially of women, has become a general practice and has been perfected by the aid of anesthesia. An abundant literature, embracing many hundred cases and a number of monographs by E. Fritz, Becquet, E. Rollet, L. Landau, Linder, and others, is now available.

Etiology.—Although, as has just been remarked, wandering kidney is by no means a rare disease, it is nevertheless difficult for various reasons to speak positively in regard to its frequency. In the first place, postmortem records yield a much lower percentage of cases than clinical observations on the living subject, chiefly, as Lancereaux[2] points out, because a movable kidney will return to its normal site when the cadaver is laid on its back, and unless the pathologist's attention is specially directed to the condition, abnormal mobility of the kidney is easily overlooked. But the figures in regard to the incidence of the disease, derived from clinical observations, are equally contradictory and untrustworthy, partly because, as a rule, no search for the condition is made unless there is some special reason for doing so, and partly because it is not always possible to detect the disease; while a third reason, no doubt, is the fact that the material at the disposal of the various observers varies in the matter of sex, age, and social condition.

The most important etiologic factor is the sex. Since Rayer's time, all observers, without exception, are agreed that wandering kidney is far more frequent in women. The relation of incidence in women as compared to men is variously given as 100 to 17.8 (Schütze[3]), 100 to 12.3 (Glénard[4]), 100 to 15 (Ebstein), and 100 to 1 (Dietl[5]). Judging from his own observations of 300 cases, the writer would say that the last-

[1] *Traité des maladies de reins*, 1841, iii., p. 783; *Gaz. méd.*, 1846, No. 54. For further literature see E. Fritz, *Arch. gén. de med.*, August, 1859; Becquet, *ibid.*, January, 1865; E. Rollet, *Path. u. Therap. der beweglichen Niere*, Erlangen, 1866; L. Landau, *Die Wanderniere der Frauen*, Berlin, 1881; H. Lindner, *Ueber die Wanderniere der Frauen*, Neuwied, 1888; C. Schütze, *Die Wanderniere, Statistische Untersuchungen*, Berlin, 1888; Conti, *Nefroptosi Gaz. Lombarda*, 1891; L. Knapp, *Klin. Beobachtungen über die Wanderniere bei Frauen*, Berlin, 1896; C. Keller, *Die Wanderniere der Frauen*, Halle, 1896; Wolkow and Delitzin, *Die Wanderniere*, Berlin, 1899. Furthermore in Rosenstein's *Path. der Nierenkrankh.*; Ebstein in *v. Ziemssen's Handb. der spec. Path.*, ix., 2; J. Prior in *Zülzer-Oberländer's Klin. Handb. der Harn- u. Sexualorgane*, 1894, ii. p. 211; also E. Küster, *Deutsch. Chi.*, Lief, 52b, 1896, p. 132.

[2] *Dictionn. des sciences méd.*, by Dechambre, article, "Rein," p. 177.

[3] *Loc. cit.*

[4] *Les ptoses viscérales*, Paris, 1899, p. 307.

[5] *Wien. med. Woch.*, 1864, Nos. 36 and 37.

mentioned relation, while greatly exaggerated in favor of women, is nevertheless nearer the truth than any of the others.[1]

Middle age, embracing the third, fourth, and fifth decades, contributes the greatest number of cases. According to Landau, of 100 cases 6 occurred during the first decade, 2 during the second, 15 during the third, 43 during the fourth, 21 during the fifth, 9 during the sixth, and 4 during the seventh.

Schütze[2] found that up to the end of the year 1888, 8 cases, which were probably congenital, were known to have occurred in children under ten years of age, 1 of them in a child six months old. C. Baron[3] also believes that wandering kidney is not so very rare in children, especially in girls; but that it usually gives rise to very few symptoms.

Among women, *those who have born children* suffer more frequently than others. The condition is also said to be more frequent in women of the lower (working) classes than among those in better circumstances; but personally the writer does not consider that this assertion has ever been proved. It cannot be denied that wandering kidney is more frequently *observed* among the members of the former class, but the writer doubts whether we are thereby justified in concluding that it *actually occurs* more frequently; because women of the lower classes, for various reasons, present better opportunities for examination and for the *recognition* of the disease.[4]

In the great majority of cases it is the *right* kidney that is displaced, rarely both together, and rarest of all, as the writer finds by his own observations, which agree with Fritz's statement, the left kidney alone.[5] The cases the writer has observed among men have practically all been left-sided.

The cause of the dislocation is sometimes found in distortion of the vertebral column or enlargement of the kidney by a *tumor*, rendering the viscus abnormally heavy and dragging it downward. Wolkow and Delitzin succeeded in dislocating the kidney by injecting mercury until the weight of the viscus was doubled. Pressure on the kidneys from above by descent of the diaphragm, as in the presence of pleural effusions and similar conditions, may cause descent of the corresponding kidney; or the viscus may be dragged down by cicatricial processes in the peritoneum (Riedel[6]). Finally, dislocation of one kidney has been observed in a few isolated cases after direct external violence applied to the region of the kidneys and after severe concussion of the pelvis.

[1] The writer refrains from giving more accurate figures, because he has doubts about the diagnosis of a wandering kidney in men in general, and does not consider it established beyond the possibility of a doubt in all his own cases. (See Diagnosis.)

[2] *Loc. cit.*

[3] *Festschr. zur Feier des 50-jährigen Bestehens des Krankenhauses Dresden-Friedrichstadt*, 1899.

[4] In this connection see H. Senator in *Charité-Ann.*, viii., 1883, p. 312.

[5] Among 107 cases that were observed in the Polyclinic of the Berlin University during four and one-half years (1890–95), 101 were right-sided, 4 bilateral, and 2 left-sided (S. Krischewski, "Die Wanderniere und ihre operative Behandlung," *Diss.*, Berlin, 1895).

[6] *Arch. f. klin. Chi.*, lvii.

The origin of such cases is therefore regarded as *traumatic*.[1] But on the whole traumatism plays a small part in the production of wandering kidney, as is shown by the rarity of the disease among men, who are much more exposed to injuries than women, although E. Küster[2] explains their comparative immunity by the fact that men have much stronger abdominal muscles.

Two factors appear to be of the greatest significance, a congenital *predisposition and diminution of the intra-abdominal pressure.*

As regards *predisposition*, it has been found by W. Becher and R. Lennhoff,[3] as well as by Wolkow and Delitzin, that the space normally occupied by the kidneys—the kidney niches—may be flatter, and in the erect position more cylindric, on the right side, especially in women, and more open below, so that dislocation more readily takes place. Such a condition of affairs is observed especially in women of slender build with narrow thorax and slightly flattened abdomen, falling away gradually in the flanks.

Another sign of congenital structural predisposition was pointed out by B. Stiller,[4] and is known as the "*tenth floating rib.*" As the term implies, the tenth rib is not attached to the costal arch as in normal individuals, but ends in a free extremity, like the eleventh and twelfth. This floating rib is often found in entero- and splanchnoptosis, of which wandering kidney and dislocations of other organs are concomitant conditions. J. Rosengart[5] regards as a potent factor in the production of enteroptosis persistence of the fetal and infantile position of the intestines in which the liver fails to undergo its normal development and to occupy a higher position in the abdomen, and thus to allow the kidney to move inward and upward.

Intra-abdominal pressure, which under normal conditions is always positive, assists in keeping the kidneys in their normal positions by pressing them against the posterior abdominal wall.[6] The significance of this factor is shown by the investigations of Wolkow and Delitzin, who, after dividing the abdominal muscles, observed ptosis of the large and small intestines, and especially of the kidneys—the right more than the left—when the cadaver was placed in the erect posture. Everything that tends to relax the abdominal walls—repeated pregnancies, relaxation after the removal of ascitic fluid or tumors, and the like—favors the development of wandering kidney; and the same conditions that had previously distended the abdomen tend to dislocate the organs in the vicinity of the kidneys, and thus strain and twist the connections existing between those organs and the kidneys.

In this respect, an etiologic factor pointed out by Landau—*displace-*

[1] In a case under the writer's observation, that of a lady, twenty-eight to thirty years old, who had never born children, the development of wandering kidney on the right side was attributed to a very trying sleigh ride over a hard, rough road, because the symptoms developed immediately after that experience.

[2] *Arch. f. klin. Chi.*, l. [3] *Deutsch. med. Woch.*, 1898, No. 32.

[4] *Arch. f. Verdauungskrankh.*, 1896, ii. [5] *Zeit. f. diätet. u. physikal. Ther.*, 1898, i.

[6] H. Senator, *Charité-Ann.*, viii., 1883.

ments of the female sexual organs, prolapse, distortions and flexions of the uterus—is of importance.

The causes just enumerated sufficiently explain why the condition occurs so much more frequently during middle age, and, if the assertion should be confirmed, among the poorer classes of women, who have to work hard (see p. 134); for, as they are unable to take proper care of themselves, especially during the puerperium, involution of the sexual organs as well as of the abdominal organs frequently becomes arrested before it is complete.

Cruveilhier regarded the wearing of *tight corsets*, or *tight lacing*, as a cause of wandering kidney on the right side in women. The pressure on the liver, which records itself in the well-known furrow, is directly transmitted to the right kidney lying underneath, the left being somewhat more protected by the stomach, which lies in front of it. Fischer-Benzon[1] found a furrow on the liver in 11 of 21 cases of wandering kidney. But tight lacing can only act as a contributory cause in the presence of a congenital predisposition; for movable kidneys are also found in women who never lace or even wear corsets, as, for example, among Samoan women (Becher and Lenhoff[2]).

Extreme emaciation with the loss of fat from the renal capsule is also regarded by Oppolzer[3] and others as a possible cause of wandering kidney, on the ground that it may loosen the kidney from its bed. But even this factor by itself is of slight importance, for in children whose renal capsules do not contain any fat, wandering kidney is relatively rare, just as it is in men, who are subjected to rapid emaciation quite as frequently as women. When a predisposition exists, rapid emaciation may no doubt contribute to the loosening of the kidney, and the loss of fat from the omentum and mesentery as well as from the abdominal walls may also play a part, since it has a certain effect on the degree of fulness of the abdominal cavity and the tenseness of the abdominal wall, and therefore on intra-abdominal pressure.

The fact that the right kidney is more often affected than the left is probably due, in addition to the structure of the vertebral column and the growth of organs in the abdominal cavity, factors that have been referred to on page 134, to differences between the peritoneal and connective-tissue attachments on the two sides of the body. For Gerota[4] has shown that the anterior portion of the renal fascia, or *lamina prærenalis*, is reinforced on the left side by a triple layer of peritoneum, and, in addition, the descending colon, which lies close to the lateral margin of the left kidney, affords considerable support to the viscus. The left kidney also has a somewhat shorter artery than the right, and is somewhat more intimately connected with the suprarenal vein which empties into the left renal artery; and finally the left renal vessels are more closely attached to the pancreas by cellular tissue than are the vessels on the right side. Landau finally points out that the hepatic flexure of the colon is more subject to fecal accumulation, and, there-

[1] Diss., Kiel, 1887.
[2] *Ibid.*
[3] *Wien. med. Woch.*, 1856.
[4] *Arch. f. Anat. u. Physiol. Anat. Abth.*, 1895, p. 256.

fore, is more readily dragged downward because it forms an obtuse angle or even a loop.

Pathologic Anatomy.—Wandering kidney, as has already been stated on page 133, is frequently overlooked or discovered only by accident, for it probably never proves fatal in itself. The description of the pathologic anatomy is therefore partly based on the findings obtained during life.

The capsule almost always contains less fat than under normal conditions, and the organ is found either in its normal site, owing to the dorsal position of the cadaver, or lower in the abdomen, covered with loops of intestine; rarely immediately beneath the abdominal walls. When the organ is displaced, the pedicle formed by the blood-vessels is twisted and the organ is rotated outward on its long axis, sometimes so far that the outer border is horizontal and presents downward, while the inner border is directed upward. The blood-vessels are elongated and the ureter bent or kinked. In some cases the kidney has been found attached to its abnormal bed and to neighboring organs by connective-tissue adhesions (*ectopia renis fixata*); thus, in one case it was adherent to the gall bladder, and in another to the transverse colon. The kidney itself is only exceptionally diseased, *hydronephrosis* being the most common pathologic condition when there is any.

The *suprarenal body* is usually in its normal position.

Wandering kidney is usually associated with other visceral displacements, particularly displacements of the uterus and its adnexa, which have been already mentioned (p. 136). The effect of uterine displacements, as Virchow[1] has pointed out, is to distort the base of the *trigonum vesicæ* where the ureters enter the bladder, and in that way, assisted probably by kinking of the ureter, to cause stagnation of the urine, and distention of the pelvis of the kidney and of the kidney itself, going on to hydronephrosis. Among other structures the *transverse colon* and the *stomach* are chiefly at fault, as they often occupy an abnormally low position in the abdomen. The stomach is usually rotated about its long axis, so that the pylorus is abnormally low and placed somewhat laterally, while at the same time the stomach presents a variable degree of dilatation. Finally, the liver may be depressed, or the dislocation may be so great as to produce a true wandering liver, such as the writer had the opportunity to see in one case in which the viscus extended as far as the true pelvis. In short, wandering kidney is frequently associated with the condition designated "*splanchnoptosis*," "*visceroptosis*," or "*enteroptosis*," which, as has been mentioned, is largely due to the same causes as the displacement of the kidney (compare p. 135).

Symptomatology.—In not a few cases wandering kidney, especially if the right, gives rise to no symptoms whatever, or the symptoms only begin to appear when the dislocation has attained a certain degree, sometimes quite suddenly after some violent bodily movement, concussions, or the like. In other cases the dislocation itself may be unproductive of symptoms, but when the patients discover the tumor in the

[1] *Gesammelte Abhandlungen*, Frankfurt, 1856, p. 812.

abdomen they begin to worry, become depressed, and fall into a hypochondriac state.

In most cases, however, the patients experience a variety of unpleasant oppressive, dragging or painful sensations, and cases are not very rare in which there are violent pains and colicky attacks of various kinds. The symptoms become intensified when the patient assumes certain positions or goes through certain movements that tend to exert severe traction on the renal nerves or the organs connected with the kidney, during walking, leaping, dancing, and the like. On the other hand, they disappear in the dorsal position and when the patient lies on the affected side. Overloading of the stomach sometimes gives rise to the characteristic discomfort.

The pain may be localized in that portion of the body which corresponds to the displaced kidney or it may radiate in various directions; it may be constant or may occur paroxysmally in the form of cardialgia, intestinal colic or some variety of neuralgia—intercostal, lumbar or crural neuralgia, or sciatica. At the same time there may be digestive disturbances of every kind—anorexia, nausea and vomiting, irregular action of the bowels, and the like.

As the condition is nearly always associated with other troubles, especially in the sexual organs or with enteroptosis and a general neuropathic condition, it is often difficult to decide how much of the patient's discomfort is due to the kidney displacement. Conversely, in other cases these symptoms may be primary and bring about *extreme nervous perturbation* and lead to *neurasthenia* or *hysteria*.[1]

The *jaundice* which is sometimes observed has been explained in various ways. Bartels and Müller-Warneck[2] believed that the displaced right kidney exerts pressure on the descending portion of the duodenum and thus prevents evacuation of the bile as well as of the stomach contents, and through the latter becomes the cause of gastric dilatation which is not infrequently present (see p. 137). On the other hand, it has been objected with perfect justice that in the great majority of cases the kidney itself is extremely movable and cannot, therefore, very well exert pressure. As to the relation between *wandering kidney* and *enlargement of the stomach*, or, as the writer is led to believe by his investigations, *forcible downward displacement* of the stomach, which is even more frequent and is probably the primary condition, it appears to him that both are manifestations of enteroptosis—*i. e.*, independent of one another and due to a common cause. It is quite possible that the traction exerted by the kidney on the duodenorenal (hepaticorenal) ligament may increase the distention of the descending portion of the duodenum, which is already stretched by the displacement of the stomach, and thus cause a narrowing of the orifice of the common bile duct and pancreatic duct, and permit the development of jaundice.

[1] Edebohls (*Centralbl. f. Gynäk.*, 1898, No. 40) believes that the symptoms observed with wandering kidney are produced by appendicitis, which frequently accompanies the renal condition.

[2] *Berlin. klin. Woch.*, 1877, No. 30.

The complication of wandering kidney with *gall stones* and jaundice depending upon their presence is not infrequent.

Other symptoms may be caused by the traction of the downwardly displaced kidney. In the case of a woman, fifty years of age, with bilateral wandering kidney, the writer saw an aneurismal dilatation of the abdominal aorta which was possibly due to the traction of the two renal arteries on the wall of the aorta.

On the other hand, *pressure symptoms* are rarely caused by the displaced kidney, which usually rests upon and between loops of intestine. Nevertheless E. Hahn and Franck [1] repeatedly observed symptoms of *ileus* which they attributed to wandering kidney; and Girard, cited by Rayer, observed in a phthisical woman edema of the right leg which he believed to be due to the pressure of a wandering right kidney.

The occasional occurrence of *pain and weakness* in both lower extremities, which had been observed in Rayer's time, is worthy of being mentioned; the pains are suggestive of tabes, and are possibly due to distortion and inflammatory irritation of the lumbar plexus.[2]

The symptoms are frequently worse during *menstruation*, but almost always in women who continue their usual mode of life and occupation during the period; while in those who keep quiet and lie down the influence of menstruation is less noticeable.

In strong contrast to these disturbances and discomforts, the *function of the kidneys* usually goes on undisturbed; at the most the patients may complain of frequent micturition, a symptom that is perhaps more correctly explained by the displacement of the pelvic organs than by that of the kidney. In a case observed by Apolant [3] there was marked polyuria, which disappeared after the kidney was replaced.

Stagnation of the urine caused by kinking of the ureter, as already referred to, and leading to *hydronephrosis*, is a somewhat more frequent occurrence. If kinking of the ureter takes place suddenly, with twisting of the vessels and the nerves supplying the kidney, an acute and stormy picture develops, which was first described by Dietl [4] as "compression of the kidney," because he believed that the kidney became wedged between connective tissue and peritoneum; Gilewski,[5] on the other hand, thought that the condition was due to compression of the ureter between the kidney and the vertebral column. The attack resembles renal colic; the urine is scanty and high-colored and contains either from the outset or, more generally, as the attack subsides, mucus or pus and sometimes blood. The abdomen is hard and tense, and if palpation is possible a tumor corresponding to the distended kidney can be recognized. With appropriate treatment copious diuresis takes place and the symptoms soon subside.

[1] *Berlin. klin. Woch.*, 1889, No. 10, p. 208.

[2] The writer has seen 2 cases of pronounced tabes in women with right-sided wandering kidney; Schwerdtfeger, Diss., Greifswald, 1886 (cited by Franck), mentions a similar case, and Habel (*Centralbl. f. inn. Med.*, 1897, No. 7) found among 68 cases of tabes 6 cases of wandering kidney, all of them among the 24 women.

[3] *Wien. med. Woch.*, 1864, Nos. 36 and 37.

[4] *Ibid.*

[5] *Oesterr. Zeit. f. prakt. Heilk.*, 1865, No. 18.

In other cases the symptoms are less violent and stormy, stagnation of the urine develops with moderate distress to the patient, disappears again only to return at the slightest provocation, and a condition correctly designated by Landau as *periodic hydronephrosis* develops, the commonest cause of which is wandering kidney.

Owing to the kinking of the vessels and the resulting vascular stasis, albuminuria with or without casts, and even a variable degree of hematuria, may make its appearance.[1]

The *objective* symptom of wandering kidney is a tumor in the abdomen, which can be felt through the abdominal walls whenever the conditions are not too unfavorable for examination. The latter is best performed with the patient in the dorsal or lateral position, with the trunk slightly raised and the feet also somewhat elevated to relax the abdominal muscles.[2] The examiner then places one hand—the left in cases of right-sided wandering kidney, and *vice versâ* on the lumbar region, and the other on the corresponding side of the abdomen (usually the right), and gently presses the soft parts from behind forward against the hand on the abdomen, which is pressed in as deeply as possible, or the patient is told to take a deep breath at the same time. Unless the abdominal walls are exceedingly tense or loaded with fat, the displaced kidney will be felt as a smooth tumor, presenting the characteristic shape and consistence. Sometimes the examiner will be more successful if he will have the patient suddenly change from the dorsal to the lateral position, or ask her to walk up and down before the examination, so as to displace the kidney downward and forward. On the other hand, the writer is not much impressed with the expediency of examining the patient while she is standing or bending over, or is in the knee-elbow position, all of which positions have been recommended, because in these positions the abdominal walls are more distended or else the patient involuntarily renders them rigid. The tumor is readily movable, especially in the upward direction toward its normal site; gentle pressure is not painful, but by exerting downward traction a pain can be elicited. The percussion note over the tumor is dull with a tympanitic element, the intensity of which will depend on the degree to which the organ is covered with coils of intestine. In very much emaciated individuals the lumbar region on the side corresponding to the wandering kidney appears flattened or depressed when the patient is standing or lying in the prone position or in the knee-chest position, and a similar difference is sometimes observed in the percussion note of the two sides over the region of the kidney. In the rare cases in which displaced kidney is adherent to the surrounding structures, and when the kidney is diseased (hydronephrosis), the physical signs are, of course, correspondingly modified. (See also under Diagnosis.)

Course and Termination; Prognosis.—Wandering kidney

[1] It has been shown by Menge (*Münch. med. Woch.*, 1900, No. 23) that pressure on the displaced kidney, as during palpation, may easily produce hematuria and albuminuria.

[2] The usual method of bending the knees is often accompanied by a contraction of the abdominal muscles which renders them rigid, and the writer therefore prefers the above-described position.

may develop suddenly or gradually, and when left to itself usually persists until death occurs from some other cause, as the condition itself is not fatal; at least not directly fatal. If the above-described symptoms and the disturbances of digestion and nutrition are severe and the condition last a long time or is greatly protracted, the health may eventually become undermined or the kidney may become the seat of a fatal disease, such as pyonephrosis.

Fluctuations in the clinical course and in the symptoms are extremely common and usually depend on the causal influences enumerated. In itself the displacement does not cause fever, which, aside from accidental complications, occurs only with so-called "compression" of the kidney, or "Dietl's crisis."

The *prognosis*, so far as life is concerned, is therefore favorable, although during an attack of compression of the kidney, such as has been described, the possibility of a fatal issue from collapse or the development of peritonitis cannot be absolutely excluded. As a matter of fact, such a termination has been seldom or never observed. The prospect of recovery since the introduction of nephrorrhaphy is better than formerly (see Treatment); recovery without operation is not impossible, although it rarely takes place; while, on the other hand, an amelioration of the symptoms is quite frequently achieved.

Diagnosis.—A positive diagnosis of wandering kidney is based on the demonstration of the dislocated organ, which is possible in many cases by careful examination, if necessary repeated under anesthesia (see p. 140), for when the abdominal walls are very fat or sensitive, examination may be practically impossible without the aid of narcosis. If the entire organ can be palpated and the typical shape, the hilus, or even the pulsation of the renal artery be felt (Eichhorst), and if the viscus can be pushed up under the liver, all doubt in regard to the nature of the tumor is at once removed. But even when the outline of the tumor is only approximately like that of a kidney, the diagnosis can be made with a fair degree of certainty by taking into consideration the symptoms and changes produced by changes of posture; by considering, too, that the patient is a woman, especially one with relaxed abdominal walls; that the tumor is in the right side of the abdomen and exhibits the other characteristics of wandering kidney, such as mobility and a moderate degree of sensitiveness; and that possibly flattening of the right lumbar region or disappearance of dulness on percussion is noted when the patient is erect or in the prone position. The condition is most likely to be confounded with a *constricted hepatic lobe* (Schnürlappen), particularly the tongue-shaped prolonged anterior lobe, or with the thickened gall bladder frequently found after repeated attacks of gall-stone colic. There is a notch between such a lobe and the head of the gall bladder which closely simulates the hilus of a kidney; the lobe can often be turned over so that it apparently occupies the position of the kidney; and the symptoms produced by gall stones are quite similar to the symptoms of wandering kidney—for all these reasons a mistake is quite possible. In order to avoid it, the suspected region

must be carefully examined by palpation and percussion, preferably with the patient lying on her left side, so as to decide whether the tumor is connected with the liver and merges with the viscus or not. Inflation of the intestine with air may assist in removing any existing doubt, as in most cases an inflated colon will force the liver and gall bladder against the abdominal wall, while the kidney is rather more likely to be pushed backward.

Tumors of the omentum, on account of their great mobility, and, to a lesser degree, tumors of the intestine and stomach, especially if the latter organ has been pushed down, are next in importance as possible sources of error. By a careful consideration of all the subjective and objective symptoms bearing on the question of diagnosis, and of any changes in size observed during a protracted period of observation, the diagnosis can usually be arrived at in these doubtful cases; but if the question of operation is to be determined, examination under anesthesia, with inflation of the stomach or intestine or both, should never be neglected. The differentiation from ovarian tumors or even fecal accumulations seldom presents any great difficulties.

It is well to be very conservative in diagnosticating mobility of the left kidney alone, because the condition is extremely rare. The differential diagnosis in such a case must, in addition to the conditions mentioned, take into account tumors of the splenic flexure and descending portion of the colon, and downward displacement of the spleen (wandering spleen); the latter differs from wandering kidney inasmuch as it is usually in close contact with the abdominal wall, and therefore yields dulness on percussion.

As for the diagnosis of *wandering kidney in men*, one should be doubly cautious.

When no tumor can be felt and the usual symptoms and etiologic factors are ascertained to be present a provisional diagnosis only may be made.

While the existence of wandering kidney may be surmised when the viscus is fixed or otherwise diseased and swollen or enlarged, it is impossible to make a positive diagnosis unless the fact of the kidney having been movable had been previously known.

Treatment.—The *prophylaxis* of wandering kidney includes the avoidance of all the conditions or influences that favor its production, the prevention of any traumatism, and above all great caution in allowing the woman to get up after childbirth until the expiration of the puerperal period, and careful attention to everything calculated to further the involution of the distended and displaced structures.

The treatment may be *curative* or *palliative*. Complete recovery, in the sense of replacing the organ and securing its attachment in its normal position, may be brought about in cases that have not gone too far by keeping the patient as much as possible in the dorsal position for a long time—that is, a number of weeks. An appropriate *mast-cure* or forced feeding, which causes a deposition of fat not only in the capsule of the kidney, but also in the omentum, mesentery, and sub-

cutaneous cellular tissue of the body, and thus increases intra-abdominal pressure and the tension of the abdominal walls, will materially contribute to the success of the treatment, besides being indicated by the nervous and neurasthenic symptoms which are commonly present. As massage usually forms part of a mast-cure, it is well to add a caution against using pressure on the kidney, on account of the possibility of thus inducing albuminuria and hematuria (p. 140). Such a course of treatment requires a great deal of patience, and this often proves an insuperable obstacle in the case of many sufferers from the disease, otherwise it would probably be more successful than it actually is.

The condition can also be cured by *operative procedures*, the most successful of which is nephrorrhaphy or nephropexy, which was first performed by E. Hahn.[1] For the technic of this operation the reader is referred to text-books on surgery. The immediate result of this operation is almost always excellent, and the subjective symptoms caused by the wandering kidney are at once removed. As regards the permanency of the cure, however, the results are somewhat less favorable, for in a portion of the operative cases the kidney, after a variable length of time, again becomes dislocated. But, as in other cases, recovery is permanent or, at least, there is no return for a number of years, as the writer's own observations have shown him; and as the operation in itself is practically free from danger, it may be recommended in every case in which the symptoms are severe and entirely or chiefly dependent on the mobility of the kidney and have been relieved only in part or not at all by palliative treatment.[2]

In accordance with his above-mentioned view (p. 138), Edebohls recommends the operation for appendicitis, either alone or in combination with nephropexy.

Palliative treatment consists in the employment of mechanical contrivances designed to push the kidney backward and upward and to prevent any further downward descent. To accomplish this purpose a variety of abdominal binders, bandages with or without pads, contrivances like hernia trusses and corsets, have been recommended. Most of these appliances are very uncomfortable to the patient and are not more effective than a simple elastic abdominal binder, made to order, with tapering extremities that are laced over the sacrum with elastic laces; the binder is provided with soft elastic perineal straps or covered rubber tubing. When the abdominal walls are very much relaxed a soft pad or folded towel may be placed between the binder and the body over the region of the kidney. The long corset extending to the pubis, recommended by Landau, is usually well borne and is equally effective; the same may be said of Philipp's corset. The writer has recently adopted the plan of having his patients wear a kind of *bathing-trunks* with a broad elastic front, which has proved to

[1] *Centralbl. f. Chi.*, 1881, No. 2.

[2] In regard to the permanent results of nephropexy, P. Geiss (18 *Jahre Nieren chirurgie*, Marburg, 1900), quoting from Küster's statistics, gives 29 recoveries out of 34 uncomplicated cases, or 85.2 per cent. R. Wolff (*Deutsch. Zeits. f. Chi.*, xlvi.) saw the good result persist in 1 case for fourteen years.

be quite comfortable. During the night, when the patient is in bed, all these appliances may be taken off. It is needless to say that even when these binders, corsets, and other appliances are worn, the patient must avoid sudden movements and concussions of the body. During menstruation the woman should keep her bed.

It is important to say that regularity in digestion and the action of the bowels is to be maintained, and if, notwithstanding these precautions violent attacks of pain occur and cannot be relieved by rest, wet compresses or some other simple measure, narcotics, especially morphin, either internally or hypodermically, may be necessary. *Extirpation* of the kidney, which used to be recommended and even carried out in cases of this kind characterized by severe and obstinate symptoms, has become superfluous since the introduction of nephropexy. It could only be considered in conditions in which nephrectomy is indicated for other reasons. The so-called "*compression phenomena*" can usually be relieved by rest in bed, hot compresses, and, if necessary, morphin.

[Senator's views on movable or floating kidney are so clearly stated and are so sound that they must meet with the general approval of physicians, except perhaps those who radically and, we believe, unwarrantably advise operation in nearly every case of obscure abdominal or nervous complaint in which they are able to palpate the right kidney. Operation ought not to be advocated until other remedial measures have been attempted. The rest cure with forced feedings, dietetic cure for the mucous colitis that is occasionally present and is, in reality, of greater importance than the prolapse of the kidney, encouraging suggestive therapy, the wearing of the simple abdominal supporter—all these agencies should be tried before the resort to the knife. And it must be remembered, too, that not a few failures either to keep the kidney in place or to relieve symptoms have followed nephropexy. When the operation is deemed necessary and there is marked diastasis of the recti muscles, at the same time as the operation on the kidney these can be brought together with edges freshened, and in this way the tone and firmness of the abdominal wall can be restored. J. Clarence Webster[1] has called especial attention to this point.

The writer's own experience is that in the majority of women patients seen in office, home, and hospital practice, the right kidney can be palpated, very rarely the left. In most of these cases no symptoms attributable to the kidney are to be discovered. In a goodly proportion of these patients the kidney can be felt as a whole—*i. e.*, its upper and lower poles can be felt, and there is plainly to be made out inspiratory descent of the organ. In many of these there is no discomfort arising from its free mobility. Of value in the examination is the fact that the kidney, when displaced from its bed by the left hand of the examiner and by the patient taking a deep breath, can be held down between the two examining hands, so that it will not rise on expiration until it is freed by a gradual loosening of the bimanual grasp, when it suddenly and with a little jerk, which is often

[1] *Jour. Am. Med. Assoc.*, 1903.

felt by the patient and startles her, slips back into place. A gall bladder or a tumor of the intestine will not behave in this manner. A movable kidney always feels "slippery." The writer can heartily approve of Senator's advice as to not having the knees drawn up while examining for the kidney. Occasionally this procedure helps relax the abdominal muscles, but very often it brings about the opposite result. It is generally preferable to have the patient lying flat upon the back, with the thighs and legs extended, or, as Senator suggests, with the feet propped up, as on one or two pillows.

While a movable or even a palpable kidney in man is much rarer that in woman, it is occasionally seen—the writer should say in about 1 in 50 of men examined. He has seen in 3 men bilateral nephroptosis, and with the ordinary Glénard's complex of symptoms. In his own experience the right kidney in men, as in women, has been oftener palpable than the left.

It is often unwise in talking to the patient to refer in any way to the fact that there is a floating kidney. The laity do not always discriminate as they should between this simple dislocation of the kidney and an organic affection. Too often with them any disease of the kidney is synonymous with Bright's disease, and Bright's disease to them means certain death. Or, owing to the prevalence of the fad for operating on floating kidneys, the moment they are told that they have this dreaded condition they are constantly haunted by the vision of a serious surgical procedure. The effect of all this on the neurasthenic possessor of the movable kidney is anything but pleasant or beneficial. The treatment of this condition is truly on the border line between medicine and surgery, and it often takes the combined wisdom and tactful effort both of physician and surgeon to carry an aggravated case to a successful issue.—Ed.]

NEURALGIA OF THE KIDNEY.

(Renal Colic; Nephralgia.)

Pain in the kidneys in the majority of cases is caused by gross anatomic disease of the organs. Violent colicky attacks of pain are such frequent attendants on the passage of foreign bodies, usually concretions, as well as on neoplasms, that physicians have contracted the habit of regarding these conditions as the only cause of renal colic and the frequently associated hematuria (*nephralgia hæmaturica*). But since operations on the kidney have become more frequent in recent times, it has been ascertained that other conditions which frequently receive but little attention are capable of producing renal colic with or without hematuria, and that in very rare cases no cause whatever is to be found.

Among such conditions capable of causing renal colic are: *dislocations* of the kidney, which, even though it may not overstep the physiologic limit, or exceed it but little, may cause violent attacks of pain in sensitive persons with hyperesthesia of the abdominal sympathetic

nerve (Talma[1]); *twisting of the pedicle* of the dislocated kidney (see Wandering Kidney, p. 139); *adhesions*, which may be strained in different positions of the body, and even by respiratory or severe peristaltic movements, so as to bring on attacks of pain (H. Senator[2]); and finally it has been reported by J. Israel,[3] as well as by Guyon, Albarran, Legueu,[4] that one of the most frequent causes of hematuric nephralgia is an acute congestive swelling of the kidney, which frequently begins in old inflammatory foci, leads to distention of the capsule, and may be relieved by incising that structure. Against this theory may be urged, in the first place, that the severest forms of swelling of the kidney with distention of the capsule, such as are frequently observed in renal congestion and in acute diffuse nephritis, are never, or only in exceptional cases, attended by true colicky pains; and in the second place, that in many of the cases said to be cured or improved by splitting the capsule, the corresponding kidney was not found to be swollen at all, but, on the contrary, small and relaxed, and the success of the operation had to be attributed to other factors, such as separations of adhesions and anchoring of the kidney which had been abnormally movable.[5]

It should also be borne in mind that attacks of pain referred to the region of the kidney may have their origin in affections of neighboring structures, such as aneurism, disease of the vertebral column, and the like.

But after excluding all such conditions there still remains a small number of cases of renal colic, with or without hematuria, in which it is impossible by the most careful macro- and microscopic examination to discover a cause, and which must be accepted as cases of true neuralgia of the kidney or nephralgia. (See also Hematuria, p. 54.) This neuralgia may occur *secondarily*—the so-called deuteropathic form—as a sequel to or concomitant of other nervous affections; or it may occur quite independently—*i. e.*, it may be *primary* or idiopathic.

Among the secondary renal neuralgias should be included the form of colic described at the same time by Raynaud[6] and Lereboullet[7] which occurs in the course of tabes, and to which they gave the name "crise nephrétique," on the ground that it is analogous to the "gastric crises." It is said to resemble closely the colic occasioned by renal calculi, and to differ from the latter by the absence of hematuria and of the passage of concretions. According to Raynaud, the pain in this disease appears to show a predilection for the left kidney.

It is possible that many of the neuralgias and colicky attacks that occur in *hysteria* also belong to this category; the pain in these forms radiates from the loins toward the bladder and is accompanied by strangury. Many of the hyperesthesias designated as "*ovarian*" are probably of the same character. B. Guisy[8] believes that these neural-

[1] *Deutsch. Arch. f. klin. Med.*, xlix., p. 236.
[2] *Deutsch. med. Woch.*, 1902, No. 8, and discussion thereof in No. 9.
[3] *Loc. cit.* [4] *Ann. des mal. des organes gén.-urin.*, 1898 and 1899.
[5] The same opinion has just been expressed by Th. Rovsing (*Hospital-stidende*, 1902, Nos. 1–4, abstract in *Deutsch. med. Woch.*, 1902, No. 6, Literaturbeilage).
[6] *Arch. gén. de méd.*, October, 1876. [7] *Goz. hebdom. de méd. et de chi.*, 1876, No. 31.
[8] *Progrès med.*, 1897, No. 17.

gias in hysteric subjects may be occasioned by spasmodic contraction of the ureters.

The term *idiopathic* or *primary renal neuralgia* must be reserved for the rare cases in which all the causes here enumerated can be excluded, although that is rather difficult when no operative autopsy is performed. For, as the pain of neuralgia in nowise differs from that of renal colic which is not of purely nervous origin, being caused by some gross alteration, except possibly by some change in the urine—which, however, may be entirely absent for a variable length of time or even permanently in the last category of cases—it is practically impossible to make a positive diagnosis from the symptoms alone; at best a *provisional diagnosis* may be made if, notwithstanding long-continued observation, no indication of any gross renal affection, especially the formation of concretions, tumor, or abscess, can be found.[1] In these obstinate cases the diagnosis can be made only by exposing the kidney, and if that fails to reveal a cause for the pain, such as adhesion or twisting of the pedicle, by laying the viscus open. The *therapeutic* indications ascertained by this *exploratory* intervention can be satisfied at the same time.

It is needless to say that these operative procedures are not to be employed unless the *medical treatment*, which is always to be tried for the relief of the ordinary and much more frequent kinds of renal colic, has proved useless and the symptoms become intolerable or the hemorrhage, which is frequently present, becomes alarming. As a rule, some suspected or unsuspected anatomic lesion is found in such cases, and if it is removable a radical operation may be performed at the same time.

It is a noteworthy observation that operative interference, when made for the purpose of establishing the diagnosis, is sometimes followed by cure or, at least, an amelioration of the symptoms lasting for a variable period in many of those rare cases in which no cause for the pain and hemorrhage is found. This unexpected result may be explained in part by the fact that in the act of removing the kidney from its bed, inflammatory exudates and adhesions dragging upon and compressing the renal nerves are broken up; otherwise it would have to be assumed that the operative intervention acts by suggestion.

These unintentional therapeutic effects present some similarity to the results often obtained by bloody or bloodless *stretching* of the nerves or even of the spinal cord in tabetic and other forms of neuralgia, and it is a debatable question from this point of view whether in the above-mentioned renal crises of tabes and in the severe renal neuralgia of hysteria simple exposure of the kidney followed by reattachment of the organ may not be justifiable as a last resort. Such a procedure may be characterized as almost without danger when the present methods of operation are employed.

[In nephritis neuralgic attacks are extremely rare, yet they are occa-

[1] Gowers (*Handb. der Nervenkrankh.*, translated by Grube, Bonn, 1892, iii., p. 230) relates a case in which periodic attacks of pain in the region of the kidney continued for forty years, although the presence of calculi could never be demonstrated.

sionally seen, as in cases described by Martens,[1] in which periodic pain referred to one kidney, with hematuria, led to the suspicion of stone, yet at the operation only chronic parenchymatous nephritis was found.

The possibility that the nephralgia with or without hematuria is one of the visceral manifestations of the erythema group of diseases should also be kept in mind, and search for other evidence of this condition should be made.[2]—ED.]

CIRCULATORY DISTURBANCES OF THE KIDNEY: THROMBOSIS AND EMBOLISM; HEMORRHAGIC INFARCT.

ACTIVE HYPEREMIA.

Active hyperemia of the kidneys which is the result of increased pressure in its arterial system has little clinical importance, because it is practically always a concomitant or sequel of other conditions.

The attempt has been made to study the effect of active hyperemia by *experimentation*, but the methods employed for this purpose, consisting in ligation of the aorta below the renal arteries, division of the renal nerves, and the injection of blood into the vascular system, are either uncertain in their action as regards raising the pressure in the kidneys, or they give rise to numerous secondary disturbances. Judging from the experiments that appear to be the most successful and from experiments on surviving kidneys through which blood is forced artificially, the chief effect of a rise in arterial pressure in itself is an increase in the quantity of urine excreted and an increase in its most important solid constituents—urea, etc.[3]

The pathologic conditions in which active hyperemia of the kidney occurs are: (1) *Inflammations* of various kinds, the inception of which is, of course, marked by dilatation of the vessels and acceleration of the blood-stream, as well as by other changes in the vessels. (2) *The loss of one kidney*, which causes an increased flow of blood to the other kidney with increased functional activity, unless such a result is antagonized by disturbing influence. (3) *Increased activity of the left ventricle* in the absence of any obstacle in the aorta or renal arteries to the access of a greater quantity of blood to the kidneys. (4) *Diabetes mellitus and insipidus* (probably), as well as many diseases of the nervous system (medulla oblongata, sympathetic) in which, on account of paralysis of the constrictor or irritation of the dilator nerves of the renal vessels, more blood passes through the kidneys. (5) The direct effect on the renal vessels of certain *diuretic* (harntähiger and diuretischer) substances; a group that may as well be added here, although it does not represent a pathologic cause of active renal hyperemia.

The increased blood-supply and more liberal nutrition bring about a greater functional activity of the tissue elements, which, if protracted, lead to hypertrophy of the organ. (See Section V.)

[1] *Deutsch. med. Woch.*, xxx., 45; *Vereinsbeilage*, p. 1665.
[2] *Cf.* Osler, *Am. Jour. Med. Sci.*, cxxvii., No. 5, May, 1904.
[3] H. Senator, *Albuminuria*, 2d ed., Berlin, 1890, p. 57.

Active renal hyperemia requires no treatment, especially in cases in which it is the result of a compensatory process beneficial to the organism, as in (2) and (3). In other cases the hyperemia disappears at the same time as the disease of which it is a feature.

PASSIVE HYPEREMIA; CONGESTION OF THE KIDNEYS.

Passive or venous hyperemia of the kidneys develops whenever there is some obstacle to the venous circulation. The commonest cause of such obstruction is cardiac insufficiency, leading to stasis of the blood in the right heart and *general venous hyperemia;* much more rarely the obstruction affects only the inferior vena cava or only one or both renal veins, in which case the venous stasis is *local*, being limited to the corresponding region.

CONGESTION OF THE KIDNEYS IN GENERAL VENOUS HYPEREMIA.

Etiology and Pathogenesis.—This form of congestion occurs during the stage of so-called disturbances of compensation in cases of valvular disease or disease of the myocardium or pericardium, and may complicate any form of congestion in the pulmonary circulation, whatever its cause. From the nature of things, it is always associated with a lowering of the arterial pressure, and consequently with deficiency of the arterial blood-supply to the organs, since the strength of the heart is diminished in all the conditions enumerated.

The effect of the circulatory disturbance in general venous stasis is therefore made up of two elements—the obstruction to the venous flow from the kidneys and the diminution in the supply of arterial blood to the organs. Both have been studied experimentally. Although clinical conditions cannot be perfectly reproduced in animal experiments, because the insult in the latter must be more intense and of shorter duration than morbid changes which develop more slowly, yet by taking care not to carry the obstruction to the venous or arterial flow too far and removing it from time to time or keeping it incomplete, conditions approximately comparable to clinical conditions can be achieved, and such experiments contribute not a little to the elucidation of the processes that take place.

It has been shown by experiments performed by the writer,[1] Frylinck,[2] and Alb. Seelig[3] that, when the venous circulation in the kidneys is interrupted for a short space of time, hyperemia develops first in the medullary layer and is chiefly confined to that region, the vascularity of the cortical substance at first showing little if any increase. The *excretion of albumin* likewise takes place first in the uriniferous tubules of the medullary substance.

On the other hand, incomplete or temporary interruption of the arterial blood-supply produces venous hyperemia in the cortical sub-

[1] *Die Albuminurie*, etc., 2d ed., p. 73.
[2] *Onderzeukingen over veneuze Stavingen in de Nier*, Leiden, 1882.
[3] *Arch f. exper. Path. u. Pharmakol.*, xxxiv., 1894, p. 23.

stance, the glomerular vessels in particular become greatly engorged, and albumin is excreted into the capsules of the Malpighian bodies.

Under clinical conditions, therefore, general venous hyperemia, which is usually attended by a diminution of the blood-supply, should lead to engorgement both of the cortical and of the medullary substance; and if, in addition, the excretion of albumin takes place, the latter would be expected to occur both in Bowman's capsule and in the uriniferous tubules of the medullary substance. When the circulation is interfered with for any length of time, the evil effects produced on the tissues, the glomerular vessels, and on the epithelial cells of the capsules and uriniferous tubules, especially in the cortex, are due chiefly to the *diminution* of the arterial blood-supply. Finally, as the result of stasis, edematous infiltration and distention of the interstitial connective tissue, with gradual thickening and sclerosis, are superadded.

The *albuminuria of parturition*, which has already been discussed (p. 38), should receive mention here, as it is on the boundary line between health and congestion of the kidneys. It is probably caused by a combination of the increase in the intra-abdominal pressure incident to pregnancy and the general venous stasis produced by the severe bearing-down pains, and disappears after childbirth because both causes then cease to be operative.

Pathologic Anatomy.—In recent cases, before the sequelæ referred to have had time to develop, the kidneys present a variable degree of swelling, depending on the degree of the congestion, the transverse diameter being chiefly affected; the organs are rounder, heavier than normal, of a firmer consistence, and of a darker color. The capsule is smooth, not infrequently thin, and strips readily. The surface of the kidneys is dark red, and the stellate veins are well developed and engorged. The organ bleeds profusely on section; both the cortical and the medullary substance are a darker red than normal, the color being deepest in the medullary portion, especially at the bases of the pyramids, and becoming gradually paler as the papillæ are approached. The Malpighian bodies appear as dark points and are more conspicuous than under normal conditions.

In this stage microscopic examination reveals engorgement of the interstitial veins and capillaries, and in cross-sections the uriniferous tubules are seen to be compressed. The glomeruli also are overfilled, but the engorgement is not uniform. When the *congestion is extreme*, small extravasations of blood may be found here and there in the intertubular tissue and even in Bowman's capsules; there are evidences of the excretion of albumin in the capsules, and hyaline casts are found in the uriniferous tubules of the medullary layer.

If the congestion continues for some time, the appearance of the kidneys gradually changes as the result of the above-mentioned nutritive disturbances; from the condition of "cyanotic induration" the organ, by a form of shrinking, passes into the "contracted kidney of congestion," as Bollinger has called it. The swelling of the kidneys and the dark-red discoloration gradually diminish, and if the congestion

continues for a long time the organ becomes smaller and paler than normal, the capsule slightly thickened, and in places adherent to the kidney. The surface of the organ is pitted here and there with retracted scars, some of which represent the remains of minute infarcts, while others indicate destruction of the parenchyma by the long-continued congestion.

While the Malpighian bodies and uriniferous tubules do not at first show any marked changes, if the congestion continues the epithelial cells undergo granular clouding and fatty degeneration and are cast off, the excretion of albumin into the glomeruli becomes more general and more abundant, and the tufts themselves are gradually compressed and diminished in size until they are totally destroyed, while the capsule and membrana propria of the uriniferous tubules undergo thickening. In pronounced contraction the interstitial tissue between the uriniferous tubules and the vessels, according to Schmaus and Horn,[1] is wider than normal because of the deposition of a homogeneous and fibrillar substance, all the vessels—arteries, veins, and capillaries—are greatly thickened, especially the intima of the arteries. In places round-cell infiltration is found.

Symptomatology.—The implication of the kidney in universal venous hyperemia betrays itself chiefly by the changes in the urine, which were first adequately appreciated by Traube. The urine is diminished in quantity, the color is darker than normal, the reaction is strongly acid, and the specific gravity rises to 1025 to 1030 because the watery portion diminishes more than the other urinary constituents. Owing to the diminution of the percentage of water, the urates show a tendency to precipitate as the specimen cools, and form the well-known brick-dust sediment (*sedimentum lateritium*), which is readily dissolved by heating to body temperature, by neutralizing or rendering the urine alkaline, and appears under the microscope as amorphous golden-yellow granules, which occur either isolated or collected into cylindric or irregular masses. In addition to the pigment, which gives the sediment its brick-red or pink color (uroerythrin, urinary pink), the urine may, on account of the accompanying hepatic congestion, contain bile pigment, especially urobilin, less frequently bilirubin.

Sooner or later *albumin* appears in the urine, as a rule only in small quantities, although sometimes the proportion exceeds 1 part in 1000. Hyaline, and more rarely granular, *casts* make their appearance at the same time with the albumin or soon afterward; sometimes they may be found before albuminuria develops. A few isolated *leukocytes* and an occasional *red blood-cell* may also be found.

As regards the proportion of the various constituents of the urine, the specific urinary substances—urea, uric acid, and urinary pigments—are often relatively increased because the water is reduced more than the solid constituents; the percentage of sodium chlorid, however, fluctuates within the usual limits. Neither the urea nor the uric acid

[1] *Ueber den Ausgang der cyanotischen Induration der Niere in Granularatrophie*, Wiesbaden, 1893.

is absolutely increased; on the contrary, they are rather diminished because of the interference with ingestion and assimilation and because of the presence of other disturbing factors, such as serous effusions which contain urea. When the urine contains albumin, globulin appears to predominate (v. Noorden[1]). According to A. v. Korányi,[2] the urine in renal congestion, when the kidneys are otherwise healthy, possesses a higher molecular concentration and its freezing-point Δ is lower than normal. On this account and because of the relative diminution of the sodium chlorid in the urine, the quotient $\frac{\Delta}{\text{NaCl}}$ exceeds the extreme normal limit, which v. Korányi places at 1.69.

The albuminuria represents, as our knowledge of the mechanism of urinary excretion and experiments demonstrate, the combined results of the diminution in the supply of arterial blood to the vascular tufts and of the pressure exerted by the distended veins on the uriniferous tubules. The last factor especially obstructs the flow of urine and possibly tends to increase the absorption of water in the medullary layer (C. Ludwig). As no other marked tissue changes take place until contraction supervenes, because the supply as well as the escape of blood is never quite abolished, complete restoration of function readily ensues, especially when the circulatory disturbance has lasted but a short time. For this reason no sequelæ are observed until contraction takes place; for neither the diminution in the excretion of water nor the loss of albumin, which is usually extremely insignificant, is fraught with danger to the organism. Retention of specific urinary constituents does not take place in any notable degree, and hence auto-intoxication—in other words, uremia—does not occur as in other forms of renal disease. Fever forms no part of the clinical picture of renal congestion.

When *contracted kidney* has developed as the result of congestion (see p. 259) the urine becomes pale, and this pallor, as a rule, persists even in the presence of other symptoms of congestion, such as cyanosis, dyspnea, and edema. The quantity may be small, normal, or even greater than normal, and the urine may contain albumin in minute quantities or a mere trace, as in indurative nephritis due to different causes.

In addition to the changes in the urine due directly to the renal congestion, various other symptoms are present which depend on the congestion in other vascular areas and on the primary disease. These symptoms are cyanosis, dyspnea with other signs of engorgement of the pulmonary circulation, gastric and intestinal catarrh, swelling of the liver, and jaundice, swelling of the hemorrhoidal veins, headache and stupor, and last but not least typic edema, both in its development and in its extension, beginning in the most dependent portions and gradually spreading upward.

These symptoms, generally speaking, go hand in hand with the urinary changes, although one or the other may be more prominent at times for reasons that are not always quite clear.

[1] *Path. des Stoffwechsels*, p. 328. [2] *Zeit. f. klin. med.*, xxxiv., p. 2.

Like these symptoms and their variations, the *course*, *duration*, and *prognosis* in renal congestion depend on whether the cause of the general venous stasis can be removed, and for how long a time. If, after the condition has lasted for some time, it appears that the "contracted kidney of congestion" has developed, the prognosis becomes distinctly more unfavorable.

Diagnosis.—The recognition of renal congestion in uncomplicated cases is quite easy. It is based on the above-described changes in the urine, the presence of other congestive phenomena, and the demonstration of a causal disease or condition at the bottom of the venous stasis, some affection of the heart, lungs, pleura, or the mediastinum.

Simple non-inflammatory renal congestion is distinguished from acute and chronic inflammatory conditions of the kidneys by the above-mentioned symptoms, by the smaller percentage of albumin in the urine, by the presence of urates in the sediment, by the absence of renal epithelium and granular casts, and by the insignificant number of mononuclear leukocytes, or their entire absence. From amyloid disease of the kidneys, congestion is distinguished by the absence of cyanosis, the distribution of the dropsy, the diminished quantity of the urine, the presence of a sediment, and the absence of any of the principal etiologic factors of amyloid disease. The combination of nephritis with renal congestion is difficult to recognize unless the course of the disease is known, but the differential diagnosis has little practical value. Finally, a contracted kidney due to some other cause, in which insufficiency of the heart muscle has developed, may present a perfect picture of simple renal congestion. In such a case the demonstration of hypertrophy of the left ventricle and changes in the arteries, as well as of albuminuric retinitis, would suggest the correct diagnosis even if no information in regard to antecedent symptoms of contracted kidney had been obtained.

[In some instances the true nature of the disease of the kidney is recognized only by the therapeutic test. Thus, if with rest in bed, digitalis, etc., the heart becomes competent, and if at the same time the urine becomes more plentiful, lighter in color, and of lower specific gravity, and if the albumin and casts disappear, the proof of the congestive nature of the renal lesion would seem to be clear. —Ed.]

Treatment.—When renal congestion forms part of a general venous hyperemia, it requires no special treatment; all the prophylactic and therapeutic measures indicated for the latter apply equally to the former.

In order to prevent the development of congestion in patients suffering from a disease in the course of which cardiac weakness is likely to develop, everything that throws an excessive strain on the heart muscle must be avoided—bodily and psychic overexertion and emotion of any kind, stimulating and heating food and particularly beverages, unless the latter are indicated on account of collapse. On the other hand, everything that tends to increase the force of the heart in the way of hygienic or dietetic measures—active and passive exercises,

hydrotherapeutic procedures and the like—are to be recommended. For a discussion of these the reader is referred to books on treatment of diseases of the heart. From time to time, in order to unload the vessels, mild laxatives, such as bitter waters which produce watery stools, may be given as special remedies.

When congestion has developed, its further progress should be combated by cardiac stimulants, among which digitalis still maintains the first place, notwithstanding the many remedies that have been recommended as substitutes. The necessary directions for its administration have already been discussed in connection with the treatment of dropsy; it may be added, however, that in order to spare the stomach the drug may also be given in enema, 1 to 1.5 gm. (say 15–20 ♏), or *German digitalin* may be given internally or hypodermically in the dose of 1 mm. (gr. $\frac{1}{60}$). If for any reason digitalis or digitalin is contra-indicated, some of the substitutes for digitalis in ordinary use may be employed, preferably the following, on account of their action on the heart muscle: *squills, strophanthus, caffein, spartein, convallamarin*, and in combination with these or sometimes by itself, *camphor*. If these remedies prove powerless, the other procedures and methods used for removing the edema, which is the most important symptom of congestion, must be employed either to reinforce or replace medical treatment. For details in this respect the reader is referred to p. 88.

RENAL CONGESTION DUE TO LOCAL CAUSES.

Local circumscribed congestion is produced in the following conditions:

1. Any condition in which the pressure in the abdominal cavity is raised and the escape of blood from all the abdominal organs, as well as the supply of arterial blood to the same, is obstructed; the latter is somewhat less interfered with than the venous flow on account of the great resistance to compression offered by the arteries. Such conditions are chiefly pregnancy, ascites, tumors, meteorism, and the like.

The findings in the urine in these conditions differ very little from those obtained in general venous hyperemia (see p. 151); the other symptoms of congestion are, of course, confined to the lower half of the body, and consist of edema and dilatation of the veins, which may go on to the formation of marked varices.

2. Occlusion or compression of the inferior vena cava above the renal veins. This may be caused by tumors and constricting cicatricial bands in the surrounding tissue, by thrombi that have either formed at the seat of the obstruction or have been carried from some distal point, or very rarely by inflammation of the vein itself. The effects produced on the kidneys by this occlusion of the inferior vena cava depend chiefly on the seat and extent of the obstruction, as a more or less complete collateral circulation may be established through the azygos and hemiazygos veins and through an anastomosis of the veins of the renal capsule, the suprarenal bodies, and the diaphragm, so that the congestion in the kidneys gives rise to few symptoms. But if the collateral

circulation is insufficient, the degree of congestion in the kidneys will depend on the force of the heart.

If, as in the majority of these cases, which are distinctly rare, the force of the heart for any reason is diminished, a condition practically similar to that which obtains in general venous hyperemia will develop, with the exception, however, that the congestion will be much greater in the tributary area of the occluded inferior vena cava—that is, in the peritoneal cavity and in the lower extremities. The urine presents all the characters found in renal congestion developed to the highest degree. On the other hand, when the action of the heart is good the kidneys will be engorged with blood, and thus differ from the condition in general venous hyperemia, in which the arterial supply is diminished. This engorgement of the kidneys will be limited only by the degree to which the capsule may be distended, and resembles the form of hyperemia observed after experimental ligation of the renal veins. The kidney becomes enormously enlarged, the vessels distended and filled with blood, both cortical and medullary substance, particularly the latter, contain extravasations of blood, and the microscope reveals in Bowman's capsules and uriniferous tubules coagulated albumin and numerous red blood-cells. The secretion of urine in these intense grades of hyperemia is practically abolished; at the most a few drops of bloody fluid loaded with albumin will be discharged into the ureters.[1]

Clinically, these intense grades of hyperemia are probably never observed, because death in all probability occurs before the vena cava becomes occluded; but in a few very exceptional cases a degree of obstruction, practically as complete as the writer has just described, has been observed in which the blood-supply to the kidneys was not disturbed. Such a case has been reported by C. Bartels.[2] These cases differed as regards the urinary findings from the ordinary form of congestion described under (*A*). The urine was abundant, its specific gravity was not increased but rather somewhat diminished; it contained a great deal of albumin but no urates in the sediment, which consisted of blood, epithelial tubules, and casts.

3. Obstruction or compression of one or both renal veins. In this case as in the preceding, the compression of the veins is brought about by tumors or cicatricial bands, or by thrombosis resulting from a variety of causes. Thus, the *inflammatory processes* in the kidney are especially apt to become the cause of thrombosis in the larger venous trunks, and *hemoglobinuria* in many cases is a causal factor (see p. 62).

The changes produced in the kidneys by these local forms of congestion vary with the degree of the obstruction to the blood-stream and the length of time that the obstruction continues, just as in the case of other forms of congestion. These changes have been studied chiefly through animal experimentation, as clinical cases of this kind are usually complicated by other conditions. It appears from the investiga-

[1] S. Cohnheim, *Allg. Path.*, 2d ed., ii., p. 314.

[2] "Nierenkrankheiten," in *v. Ziemssen's Handb. der spec. Path. u. Ther.*, 1876, ix., 1, p. 39.

tions of Buchwald and Litten[1] that complete occlusion of the renal vein without any impediment to the arterial blood-supply first produces the above-described conditions of engorgement, extravasation, and progressive edema, followed by cloudy swelling and fatty degeneration of the epithelium, and, beginning with the sixth day after the ligation, loss of volume going on to complete atrophy of the organ, owing to destruction and disappearance of the epithelial cells and the death of the uriniferous tubules, the vascular tufts being comparatively well preserved.

The observation first made by A. Favre[2] and later by v. Schilling,[3] that after ligation of the renal vein on one side cloudy swelling of the epithelial cells lining the uriniferous tubules takes place in the other kidney, is not without a practical bearing. Favre states that in rabbits the condition may go on to a fatal termination within from six to nine days. In explanation he assumes that when one kidney is excluded from the circulation, the other becomes flooded with metabolic products and micro-organisms or ptomaïns, which are frequently present in the blood, and the renal function is inadequate to the elimination of these substances.

There are no *clinical* cases in every respect comparable to the ligation of the vein, because in the diseases in which venous obstruction takes place the arterial blood-supply is almost always diminished as well, usually as the result of a diminution in the force of the heart. The curious observation by H. Falkenheim[4] might be compared with a case of incomplete obstruction of the renal vein without impediment to the arterial flow. This author observed that one of his patients developed albuminuria when he lay on his left side, albuminuria being due to pressure on the left renal vein exerted by a very much enlarged spleen. The quantity and other characteristics of the urine were normal. This case is in line with that of Bartels, which has just been referred to.

In most clinical cases, as has been stated, the force of the heart is reduced. Nor does the venous obstruction occur suddenly as in the experiments; it develops quite slowly and gradually and does not always go on to total occlusion of the vessel. For this reason, and on account of the varied etiology of venous occlusion, the clinical picture presents numerous variations. The disturbances that originate in the kidneys are merged in the general symptom-complex or else they make their appearance late in the disease, only a short time before the fatal termination, and therefore cannot be studied in detail. From a consideration of the results of experimental investigations, however, and a comparison with other forms of renal congestion the pathology of which is better known, it may be assumed that the urine, as a rule, is scanty, of a high specific gravity, and contains albumin and blood according to the degree of congestion, hyaline casts and, if the duration is protracted, possibly also epithelial casts.

[1] *Virchow's Archiv.* lxvi., 1876, p. 145.
[2] *Ibid.*, cxxxvii., p. 33, and cxxxix., p. 25.
[3] *Ibid.*, cxxxv., p. 470.
[4] *Deutsch. Arch. f. klin. med.*, xxxv., 1884, p. 446.

If the venous congestion affects only one kidney and the function of the other kidney remains normal, the changes in the urine are, of course, correspondingly less conspicuous.

THROMBOSIS OF THE RENAL VEINS IN CHILDREN.

This form of venous occlusion develops as the result of general cachexia, either alone or in association with thrombosis of other large venous trunks, as those of the lower extremities or the large sinuses of the brain. Like all forms of thrombosis, it was formerly, and even in Rayer's[1] time, regarded as the result of inflammation of the vessels, until Virchow fully explained the nature of thrombosis in general, and more particularly the origin of thrombosis in cachexia and marasmus—*marantic thrombosis.*

Beckmann,[2] O. Pollak,[3] and Hutinel[4] have shown that thrombosis is found oftenest in newborn and nursing infants who are in a depraved state of health from profuse diarrhea or other nutritional disturbance; it is much more frequent in the left vein, which, on account of its longer course and its crossing the aorta, is more exposed than the right. In most cases the larger branches only are occluded; more rarely the thrombosis continues into the farthest veins of the pyramids, which in longitudinal section appear to be traversed by numerous dark-brown lines.

In the majority of cases the renal substance presents the same changes as in ordinary congestion with diminished cardiac force; in other cases, as those described by Nottin,[5] Wrany,[6] and Bednar,[7] the kidney was enormously swollen, and presented hemorrhages on the surface as well as in the medullary and cortical layers. The differences may be due to differences in the extent of the thrombus formation in the renal vessels and the suddenness of the onset of the thrombosis, and, finally, to differences in the collateral circulation.

Owing to the suddenness with which death occurs on account of the wretched condition of the children, our knowledge of its *symptomatology* is very incomplete. According to Pollak, the first sign is a peculiar yellowish-green discoloration of the skin, which is said to be due to the escape of hemoglobin into the tissues of the skin and its subsequent metamorphosis. When such a piece of integument is taken from the cadaver and treated with chloroform, it yields a yellow pigment which responds to Gmelin's reaction for bilirubin. The urine, which is greatly diminished in quantity, so that only a few drops are sometimes obtainable, is turbid, dark-yellow to brown or brownish-red in color, and contains albumin and hemoglobin. In the sediment red blood-cells, renal epithelium, and casts are found. Death occurs in a few days, preceded by a fall in the temperature and acceleration of the pulse, the occurrence of cramps and unconsciousness—in other words, the symptoms described

[1] *Deutsch. Arch. f. klin. med.*, iii., p. 590.
[2] *Verhandl. der Würzburger physikal.-med. Gesellsch.*, ix., 1859, p. 201.
[3] *Wien. med. Woch.*, 1871, No. 18.
[4] *Revue mensuelle de méd.*, April, 1877.
[5] *Bull. de la soc. anat.*, 1870, p. 31.
[6] *Oesterr. Jahrb. f. Pädiatr.*, 1872, iii.
[7] *Lehrb. der Kinderkrankh.*, 1856, p. 334.

under the term "uremia" whenever a disease of the kidney is known to exist. Two of the 12 cases in which Pollak diagnosed thrombosis of the renal veins from the presence of the symptom-complex just described ended in recovery, the blood disappeared from the urine in three or four days, and the icteroid discoloration of the skin was replaced by the pallor of anemia.

The condition may be *diagnosed* with a tolerable degree of certainty when, in the case of small children in the course of a severe diarrhea with vomiting and with or without jaundice, the urine exhibits the characters described, and signs of thrombosis elsewhere in the body, as in the legs or in the cerebral sinuses, are also present.

The *prognosis*, it is needless to say, is almost absolutely unfavorable.

The *treatment* consists in improving the general condition, correcting the digestive disturbances, and strengthening the heart so as to favor the establishment of collateral circulation.

THROMBOSIS AND EMBOLISM OF THE RENAL ARTERY; HEMORRHAGIC INFARCT OF THE KIDNEY.

Occlusion of the renal artery is due either to an autochthonous *thrombosis* from local causes or to *embolism formation*.

Arterial thrombosis is extremely rare in the renal arteries, and, as in the case of other arteries, is the result of disease of the vessel wall, particularly endarteritis, arteriosclerosis, amyloid degeneration and injury to the coats, as once observed by v. Recklinghausen,[1] and as occurs in ligation. The effect on the kidneys, owing to the partial or total abolition of difference in pressure in the arterial and in the venous blood-current, is a slowing of the circulation going on to complete stagnation, similar to the stasis described in general venous hyperemia (p. 149).

The remaining changes in the renal parenchyma have not been determined by clinical observations, because, as has been said, cases of arterial thrombosis are very rarely seen, and when they do occur are complicated by other conditions. It may be concluded, however, from experimental investigations with compression and ligation of the renal arteries, that the lesion would be followed by nutritive disturbances and destruction of tissue; in fact, the identical changes described as following deficiency in the arterial blood-supply (p. 155), and better known as the results of arterial embolism, presently to be discussed. Similarly, the urinary changes may be assumed to be similar to those described as characteristic of congestion with diminution of the arterial tension.

Thrombosis of the artery may also lead to embolism of smaller branches and to the formation of an infarct; this was the case in the above-mentioned observation of v. Recklinghausen.

Arterial embolism, which is far more frequent, is due to the same causes in the case of the kidneys as elsewhere—the lodgement of clots, of inflammatory deposits from the left side of the heart or from the aorta, particles of tumors, micro- and macroparasites, particles of pigment

[1] *Virchow's Archiv*, xx., p. 205.

or of calcium that have gotten into the arterial circulation, or, finally, fat-droplets and minute bubbles of air. Not all foreign bodies that get into the renal circulation in this way lodge in the arteries; the smaller of them, and particularly micrococci, fat-droplets, and possibly also air bubbles, enter the capillaries in the glomerular tufts, which they occlude, and where under certain circumstances they produce changes that will be discussed in another place. The largest emboli, on the other hand, may be arrested in the main trunk of the renal artery, producing more or less complete stoppage of the arterial blood-supply and its effects on the circulation and nutrition of the organ, which have been described more than once.

It is in the medium-sized and smallest branches that emboli are most likely to lodge. The disturbances which follow vary according to the nature of the embolus. For while *infectious* plugs set up "metastatic" processes corresponding in their nature to the focus from which they are derived, *indifferent* emboli have only a mechanical action.

HEMORRHAGIC INFARCT.

We shall deal only with the latter variety, the *indifferent embolus* and its consequences—the hemorrhagic infarct. The foundations for the doctrine of hemorrhagic infarct were laid by Virchow,[1] and the structure was later completed with special reference to the kidneys by Beckman,[2] Blessig,[3] v. Recklinghausen,[4] Prévost and Cotards,[5] Vulpian,[6] Cohnheim,[7] Litten[8], Ribbert,[9] and others. The *causes* are the same as have just been enumerated for arterial embolism, particularly disease of the left side of the heart, which greatly predominates in frequency over all other etiologic factors.

As the larger branches of the renal artery are end-arteries, the collateral circulation established after obstruction of a branch of the renal artery is very incomplete, being formed solely by the scanty anastomosis between the renal arteries and the arteries of the capsule and of the pelvis or of the ureters.

It appears from the careful investigations of Litten, Ribbert, and others that infarct develops at the earliest twenty-four to thirty-six hours after complete occlusion of the artery has taken place. If the infarct is so large as to include both cortex and medulla, as is the case when several parallel interlobular arteries become occluded, it appears macroscopically as a grayish-white wedge surrounded by a hemorrhagic areola, the base of which corresponds to the surface of the kidney, while the apex is directed toward the hilus. Smaller infarcts that are confined

[1] Traube's *Beiträge zur exp. Path. u. Physiol.*, 1846, No. 2, p. 1; *Handb. der spec. Path. u. Ther.*, Erlangen, i., 1854, p. 156; *Ges. Abh. zur wissenschaftl. Med.*, Frankfurt a. M., 1856, p. 219.

[2] *Virchow's Archiv*, xii., xiii., and xx.

[3] *Ibid.*, xvi., p. 120.

[4] *Ibid.*, xx., 1860, p. 205.

[5] *Gaz. med.*, 1866.

[6] *Bull. de la soc. an.*, 1867, p. 611.

[7] *Untersuchungen über die embolischen Processe*, Berlin, 1872; *Allg. Path.*, 2d ed., i., 1882, p. 165.

[8] *Zeit. f. klin. Med.*, i. 1880, p. 131; *Centralbl. f. med. Wissench.*, 1879, No. 47; and *Zülzer-Oberländers' klin. Hand. der Harn. u. Sexualorgane*, Leipzig, i., 1894, p. 284.

[9] *Virchow's Archiv*, clv., p. 201.

to the cortex have a more rectangular shape and project more or less above the surface, according to their size.

The tissue in the interior of a perfectly fresh infarct is turbid, grayish white or clay-colored, and exceedingly dry; it contrasts by its pallor with the surrounding tissue, which is hemorrhagic and forms a marginal zone, receiving its blood from collateral arteries.

Microscopically, the epithelial cells of the uriniferous tubules in the portions of the infarct nearest the marginal zone, which receives a certain supply of blood and lymph from the surrounding tissue, are found during this stage in the condition of so-called coagulation necrosis; they separate from the wall, melt down, as it were, and coalesce to form casts, which fill the uriniferous tubules. The capsules of the glomeruli and the interstitial tissue are the seat of a fine granular transudate (Ribbert). The central portion of larger infarcts where the supply of blood and lymph is completely cut off contains simply necrotic tissue (Litten). In the red marginal zone, which develops later than the infarct, great hyperemia of the vessels and extravasations into the interstitial tissue and into the uriniferous tubules are found. The blood-pigment may escape from the marginal zone into the infarct, so that the latter when small may be blood-stained throughout its extent; but larger infarcts always retain the characteristic grayish-white color at the center. It follows, therefore, that the infarct is not hemorrhagic in the beginning, as Litten quite correctly pointed out, and that the hemorrhagic color is due to a secondary change.

As the condition progresses fatty degeneration of the epithelium, glomeruli, and interstitial capillaries takes place, and a variable quantity of altered blood-pigment in crystals and irregular masses accumulates in the interstitial tissue. This detritus is then absorbed, while at the same time a reactive proliferation of connective tissue takes place, and both uriniferous tubules and glomeruli are destroyed. Owing to a metamorphosis of the lining epithelium, the remains of convoluted uriniferous tubules in the developing cicatrix gradually come to resemble the straight tubules (Ribbert). Ultimately the infarct contracts more and more and becomes converted into a mass of cicatricial tissue containing a few remains of parenchyma with fatty granules, pigment, and particles of calcium. Owing to the cicatricial contraction a depressed scar remains on the surface of the kidney. If the organ contains many such infarcts, its size may be considerably diminished, the cortex narrow and full of pit-like depressions—in short, the picture of *embolic contracted kidney* results.

Symptoms referable to hemorrhagic infarction of the kidney are rarely observed unless the infarcts are unusually large or numerous, when there may be well-marked symptoms, of which sudden pain in the corresponding kidney, aggravated by pressure, and the appearance of blood and hemoglobin in the urine, are somewhat characteristic. The other urinary changes belong to the disease that has caused the infarct, or to a complication rather than to the infarct itself. Thus, symptoms of renal congestion are produced by the cardiac disease, such as endo-

carditis, myocarditis, or valvular lesion, which has usually preceded the condition, or symptoms of the accompanying inflammation or degeneration of the kidney may be present. In a case of Traube's[1] which has become celebrated, the formation of a very large infarct, almost 2 in. in length—as shown by the autopsy—which projected beyond the surface of the kidney, announced itself by a sudden acute pain in the region of the right kidney, radiating into the thigh.

For the reasons that have been mentioned the **diagnosis** can rarely be made. The condition may be surmised with some probability when, in the presence of a possible source for the formation of emboli and infarcts, sudden pain develops in the region of the kidney, and albumin, blood, or morphologic elements indicating nephritis appear in the urine.[2]

As regards the **prophylaxis** of infarct, there is little to be done; but patients who are predisposed to the accident should be kept at rest and made to avoid every form of excitement and violent movement. There is no direct *treatment* for infarct. Violent pains might, as in Traube's case, justify local bleeding, the local application of cold in the form of an ice-bag or compresses, or of heat or other analgesic remedies; severe hemorrhages would call for the administration of astringents. In most cases the basal disease and not the infarct requires treatment.

ANEMIA (ISCHEMIA) OF THE KIDNEYS.

The severest grades of anemia of the kidney occur with occlusion of the renal artery, particularly the embolic variety which has just been under discussion. In a milder form it occurs as part of a *general anemia* or as the result of *local causes* that merely impede the flow of blood to the kidneys or interrupt it altogether for an appreciable length of time.

Among conditions associated with *general anemia* are to be mentioned pernicious anemia, pulmonary phthisis, carcinomatous and other grave diseases, and senility. The *local causes* of renal anemia consist in diseases of the arterial wall, compression and constriction of the artery by tumors, exudates, connective-tissue adhesions and the like conditions in which the loss of renal function, unless the organs are also affected in some other way, is clinically quite insignificant.

We learn from physiology and experimental investigations that ischemia of the kidneys may be due to *spasm of the arteries* from direct or indirect reflex irritation of the vasomotor centers and pathways in the brain and cord or the corresponding renal nerves themselves (Cohnheim and Roy,[3] Klemensiewicz[4]). Pathologically, the most interesting forms are *ischemia from asphyxia*, *poisoning* with various drugs, such as strychnin, the *irritation of peripheral nerves*, and from *fever* (Cohnheim and W. Mendelsohn[5]).

If the ischemia is short in duration it leaves no recognizable alter-

[1] *Ueber den Zusammenhang von Herz- und Nierenkrankheiten*, Berlin, 1856, p. 77.
[2] Cited by Rud. Schmidt, *Wien. klin. Woch.*, 1901, Nos. 19 and 20.
[3] *Virchow's Archiv*, xcii., 1883, p. 424.
[4] *Wien. akad. Sitzungsb.*, 1886, xciv., iii., p. 616.
[5] *Am. Jour. Med. Sci.*, October, 1883, and *Virchow's Archiv*, c., 1885, p. 274.

ations in the affected kidney; but if the condition is protracted there develop either complete necrosis or coagulation necrosis and fatty degeneration, particularly of the epithelium of the convoluted tubules, depending on the degree of completeness of the occlusion, as has already been explained.

The only positive *symptom* produced by simple anemia or ischemia of the kidneys is *diminution in the quantity of urine*, which may go on to complete anuria. The other changes, especially the appearance of albumin, blood, casts, and cells, are in all probability caused by the tissue changes secondary to the anemia. Of these, fatty degeneration of the epithelium, unless it has gone too far, appears to be least productive of consequences.

Among the morbid conditions that are thought to be in part caused by ischemia of the kidneys is fatty degeneration of the epithelium, which generally attends chronic anemia and is regarded as the result of the slowly progressing decrease in the entire mass of the blood; *coagulation necrosis* has been found repeatedly in the kidneys of women who had died of *puerperal eclampsia*, and has been attributed in these cases to the universal arterial spasm (Schmorl,[1] Beneke[2]). The kidney changes in *cholera* and during *pregnancy* have also been interpreted as ischemic in character, although the conditions in these cases are more complicated, and other causal factors besides the diminution in the blood-supply are unquestionably at work.

On the other hand, there is much in favor of the theory that the cases of *oliguria* and *anuria* which occur in hysteric subjects (Charcot,[3] Fernet,[4] Sanquer[5]) are attributable to anemia from vascular spasm—*i. e.*, *angiospastic ischemia;* this applies particularly to cases of *reflex anuria* in one kidney occurring after intense irritation of the other kidney or its ureter; as, for instance, by a calculus.

Such cases, which are mentioned by Bonet in his *Sepulchretum* (Section XXII.), and by others among the older physicians, have been studied with some care in more recent times by Bourgeois,[6] Godlee,[7] J. Israel,[8] Kirkham,[9] A. Barth,[10] and others. [Perhaps some of the cases of anuria following operations on the kidney may be of this character, the kidney not operated upon being reflexly ischemic.—Ed.] According to an observation made by McBride and Mann,[11] severe irritation from the genital apparatus appears to be capable of producing the same effect. The anuria in these cases is readily explained by the above-mentioned experimental observations in regard to ischemia from reflex causes, a theory that is confirmed by the good therapeutic results obtained in such cases by the use of narcotic or antispasmodic remedies.

[1] *Centralbl. f. path. An. u. allg. Path.*, 1891, ii.
[2] *Klin. Handb. der Harn- u. Sexualorgane*, v. Zülzer-Oberländer, 1894, i., p. 148.
[3] *Leçons faites à la salpetrière*, 1872.
[4] "De l'oligurie et de l'anurie hystériqeues," *Union méd.*, 1873, No. 45.
[5] "Anurie," etc., *Gaz. des hôp.*, 1875, No. 51.
[6] *Union méd.*, 1855, No. 31.
[7] *Med.-Chi. Trans.*, 1887, ii., p. 237.
[8] *Deutsch. med. Woch.*, 1888, No. 1, and *Arch. f. klin. Chi.*, xlvii., 1894, 2.
[9] *Lancet*, Dec. 7, 1889.
[10] *Deutsch. med. Woch.*, 1892, No. 23.
[11] *Arch. of Med.*, i., June, 1879.

R. Caspar[1] regarded the anuria as the result of a paralysis which may be produced by a variety of causes through reflex irritation.

Except in the last-mentioned variety, which is due to reflex irritation, anemia of the kidneys and its accompanying anuria require no special *treatment.* The irritation should, of course, be removed, and if this is impossible the arterial spasm must be relieved by narcotic and antispasmodic remedies, opium, chloroform, chloral, or warm baths. If the anuria is very obstinate and becomes alarming, *nephrotomy* may be indicated. In all other cases the renal anemia is overshadowed by the general disease or by the local condition to which it owes its origin, and affords no therapeutic indications.

HYPERTROPHY AND ATROPHY OF THE KIDNEYS.

LITERATURE.—Valentin, "De functionibus nervorum cerebralium et nervi sympathici," Bern, 1839. Bekmann, *Virchow's Archiv*, xi., p. 50. Rosenstein, *ibid.*, liii., p. 141. Perl, *ibid.*, lvi., p. 305. Lancereaux in *Dechambre's Dictionn. encyclop. des sciences méd.*, article "Reins." Gudden, *Virchow's Archiv*, lxvi., p. 55. Beumer, *ibid.*, lxxii., p. 315. Grawitz and Israel, *ibid.*, lxxvii., p. 315. Ribbert, *ibid.*, lxxxviii., p. 11. O. Leichtenstern, *Berlin. klin. Woch.*, 1881, Nos. 94 and 95. Fortlage, Diss., Bonn, 1884. H. Lorenz, *Zeit. f. klin. med.*, 1886, x., p. 545. A. Barth, *Arch. f. klin. Chi.*, xlvi., 1893, p. 418.

True hypertrophy, by which is meant an increase of the normal constituents of the kidneys, particularly of the uriniferous tubules and glomeruli, in number as well as in size (numeric hypertrophy or hyperplasia), may be *partial* and represent a compensatory process which very frequently goes on in the neighborhood of diseased or atrophied parenchyma, unless it is counteracted by a depraved state of the general nutrition or by local causes interfering with the proper nutrition of the organ. An *entire* kidney may become hypertrophic if its fellow is underdeveloped or absent from congenital malformation (p. 130), or has become incapable of functionating or completely atrophied as the result of some morbid process.

But the loss of one kidney is not always followed by compensatory hypertrophy of its fellow; the second kidney may become diseased, as the above-mentioned experiments of Favre and Schilling (p. 156) go to show, and the cloudy swelling which develops may, instead of clearing up, become the starting-point of additional disturbances.[2] Age also is not without influence, for compensatory hypertrophy does not often develop after the active period of growth, the heart becoming hypertrophied instead (see p. 121). Finally, the development of hypertrophy may be prevented by acute inanition, as Sacerdotti has demonstrated.

There is a difference of opinion in regard to the more minute processes that take place in the renal tissue during the development of hypertrophy.

According to the investigations first pursued by Valentin and subsequently repeated by many others a difference is to be observed among young growing animals; and the process is different when *partial hyper-*

[1] *Wien. Klinik*, 1892, No. 3. [2] See also Schede, *Deutsch. med. Woch.*, 1889, p. 201. [3] *Virchow's Archiv.*, cxlvi.

trophy takes place in the *same* kidney to replace destroyed parenchyma from what it is when the *entire kidney* becomes hypertrophic on account of the loss of its fellow. In the latter case also it probably makes some difference whether the loss is due to congenital absence or is an acquired condition.

In *partial hypertrophy*, which represents a reparative process to replace parenchyma that has been destroyed by inflammation, injury, or some other process, such as resection in the same kidney, the epithelium of the convoluted tubules as well as the glomeruli may be considerably enlarged. It is probable that this is followed by a proliferation of cells by indirect division, which Golgi [1] observed in the epithelium of the uriniferous tubules as well as of the vascular loops and in the capsules of the Malpighian bodies. M. Wolff [2] contends that in such cases the mitosis is limited to the injured zone, especially the peripheral portion; hence the increase in size depends in the main more on hypertrophy than on hyperplasia of the glomeruli and their capsules, the tubules in the cortex, and particularly of the epithelial cells. This observation applies to young as well as to full-grown animals (dogs).

In one case Barth found in the tissue surrounding a necrotic infarct cords of cells that appeared to be newly formed straight tubules.

In *acquired compensatory hypertrophy* of one kidney the most constant alteration is an *increase in the size* of the epithelial cells in the convoluted tubules, a numeric increase being doubtful. In the majority of cases the glomeruli also, in young as well as in full-grown animals (Gudden, Grawitz, Israel, Ribbert), have been found to be enlarged. A numeric increase (hyperplasia) of the vascular tufts was found by Lorenz only in growing animals, and even then it was not as marked as the increase in size (hypertrophy). Lorenz also found a moderate enlargement of the medullary substance of the kidney, consisting in widening of the lumen of the straight and convoluted tubules without any increase in the size of their epithelial cells. Talley [3] and Sacerdotti [4] also found mitosis in the endothelium of the capillaries of the medullary substance.

Finally, in *congenital* compensatory hypertrophy Beumer, Falk, Polk, and Palma were unable to demonstrate any increase in the size of the tissue elements either in the cortex or in the medullary layer, and the enlargement must therefore be attributed to a hyperplasia. Guttmann made the same observation in 1 of 2 cases, while in the other hypertrophy of the glandular constituents, particularly of the glomeruli, was manifest, just as in cases reported by Leichtenstern and Eckardt,[5] and Pels-Leusden.[6]

Compensatory hypertrophy of the kidneys does not give rise to any characteristic symptoms. Enlargement of the organ is never sufficiently great to become appreciable to sight or touch, nor can it be demonstrated by percussion. The disturbances produced by disease or destruction of renal parenchyma are more or less neutralized, and therefore masked, by

[1] *Archivo per le science med.*, 1883, vi., and 1884, viii., p. 105.
[2] "Die Nierenresection und ihre Folgen," Berlin, 1900.
[3] Cited by Ziegler, *Festschr. f. R. Virchow*, 1891.
[4] *Loc. cit.*
[5] Regarding this see Ballowitz in *Virchow's Archiv.*, cxli.
[6] *Virchow's Archiv.*, cxlii.

the very occurrence of hypertrophy. We know from both experimental and clinical observation that after the loss of one kidney its fellow may successfully perform the excretory work previously performed by both kidneys before hypertrophy can have taken place. But this is not always the case. Aside from the possibility of previously existing disease of the remaining kidney, its function at first may be disturbed by shock and reflex anuria, or the organ may become severely diseased as the result of anesthesia or the use of antiseptics, or from being flooded with poisons (p. 156). When overcompensation occurs—as, for instance, in chronic interstitial nephritis or hydronephrosis—the condition is recognized chiefly by an increase in the quantity of urine.

Compensatory hypertrophy is to be distinguished from the *hypertrophy of both kidneys* which was assumed to take place by the older authorities as the result of a long-continued *increase in the excretion of urine;* as, for example, in diabetes mellitus and insipidus, and in the case of habitual beer drinkers. It is quite true that in such cases the kidneys are not infrequently found to be enlarged; but the enlargement, as a rule, is not due to any increase in size or number of the tissue elements, the cause being found in pathologic processes, particularly interstitial connective-tissue proliferation or fatty degeneration of the epithelium. Thus, in diabetic cases when death occurs in coma,[1] there is found fatty degeneration of the epithelial cells in the convoluted tubules and of the epithelial covering of the glomeruli, as well as of those structures themselves, and in addition Ehrlich and Frerich's[2] glycogenic degeneration of the epithelial cells in Henle's loops, which are at the same time enlarged. Fatty degeneration of the epithelium is also a common occurrence in the kidneys of beer drinkers, in addition to actual inflammatory processes.

It is not to be denied that overnutrition of the tissues, with true hypertrophy, may take place as the result of increased activity in the kidneys and the associated increase in the supply of blood and so-called "uropoietic" (harnfähigen) substances (see p. 148); but, as rule, the renal enlargement present in the above-mentioned conditions, diabetes and the like, is caused by some other alteration which may be accompanied by the presence of isolated areas of true hypertrophy. According to Hansemann's[3] description of the typical diabetic kidney the organ is enlarged, the surface smooth, and the projecting glomeruli appear as distinct large red points. The microscope reveals cloudy swelling of the tubules in the cortex, and sometimes uniform fatty metamorphosis of the epithelium, beginning in the convoluted tubules and extending down as far as Henle's loops or even the collecting tubules. After the fat has been abstracted the nuclei readily take the stain. The blood-vessels and particularly the glomeruli are engorged, but there is no interstitial proliferation. Hansemann regards the entire condition as the result of excessive excretion of a fluid containing

[1] S. Fichtner, *Virchow's Archiv*, cxiv., p. 400; Saundby, *Lancet*, Aug. 23, 1890; H. Senator *Berlin. klin. Woch.*, 1891, p. 705.

[2] Ehrlich, *Zeit. f. klin. Med.*, vi., 1883, p. 1.

[3] *Ibid.*, xxvi., p. 213.

mildly injurious substances, a functional hypertrophy with slight uniform irritation.

The question of *treatment* need not, of course, be considered in the case of compensatory hypertrophy, since the condition represents a curative process whose object is to neutralize any existing disturbance. The last-mentioned form of hypertrophy, if it were shown to be the result of the excessive indulgence in beer and other alcoholic beverages, might call for prohibition or restriction of their use, while in diabetes the treatment of the hypertrophy would be the same as that of the general disease.

Atrophy of the kidneys, applying the term to any diminution in the size of the organ, depends in the great majority of cases on contraction of the tissue elements, associated usually with proliferation of the connective tissue; or the atrophy may be the result of pressure by a tumor, or from renal congestion and other like conditions. *Simple* atrophy, on the other hand, by which is meant a decrease in the size of the normal constituents of the kidney, is extremely rare; it is either a *congenital* condition or an accompaniment of the universal involution of the organs incident to *advanced age.*

Congenital renal atrophy may be due to a defect in the "anlage" of the entire organ (Lancereaux[1]) or to congenital hypoplasia of the renal artery and consequent defective nutrition, as in the case of H. Hertz,[2] in which the atrophic as well as the other kidney was the seat of amyloid degeneration. The atrophy is generally unilateral, and the other organ presents a corresponding hypertrophy (see p. 164). Bilateral congenital atrophy occurs only in monsters incapable of life (see p. 131).

Senile atrophy of the kidneys is bilateral and, according to Ziegler[3] and Beneke,[4] due chiefly to the shrinking of the epithelial cells of the convoluted tubules, which become narrower and shorter. As a result the glomeruli are crowded together and the interstitial connective tissue adapts itself to the altered conditions. The entire process is a kind of atrophy from disuse, beginning in the glomeruli and involving the uriniferous tubules, which collapse. The vacant space is filled by the formation of dense hyaline masses from the connective tissue in the capillary walls and capsules of the glomeruli, and by proliferation of the interstitial tissue; the ultimate result is sclerosis of the kidney. Other alterations that may be present are round-cell infiltration, cicatricial retraction, and the formation of small cysts.

Atrophy in itself produces no special *symptoms.* Either the loss of glandular substance is made up by compensatory hypertrophy of the kidney itself or of the heart, or, if the compensation fails to take place, the symptoms of deficient renal function, designated uremia, develop. Hence there is no *treatment* for renal atrophy as such.

[1] *Dechembre's Dictionn. des sciences méd.*, article "Rein."
[2] *Virchow's Archiv*, 1869, xlvi., p. 233.
[3] *Deutsch. Arch. f. klin. Med.*, xxv., 1880, p. 586.
[4] Zülzer-Oberländer, *Klin. Handb. der Harn- u. Sexualorgane*, Leipzig, 1894, i., p. 121.

HEMATOGENOUS, NON-SUPPURATIVE INFLAMMATION OF THE KIDNEYS AND BRIGHT'S DISEASE.

HISTORIC INTRODUCTION AND GENERAL REMARKS.

LITERATURE.—R. Bright, *Rep. of Med. Cases*, London, i., 1827; ii., 1831. "Cases and Observations Illustrative of Renal Disease," etc., *Guy's Hosp. Rep.*, i., 1836; v., 1840. Bright and Barlow, *Ibid.*, 2d ser., 1843, i., p. 120. Christison, *Edinb. Med. Jour.*, xxxii., 1829, p. 262, and "On Granular Degeneration of the Kidney," Edinburgh, 1839. Gregory, *Edinb. Med. Jour.*, xxxvi. and xxxvii., 1831. Elliotson, *London Med. Gaz.*, vii., 1831. Copland, *A Dictionary of Practical Medicine*, i., London, 1832, article "Dropsy." J. Osborne, "On the Nature and Treatment of Dropsies," Dublin, *Jour. Med. and Chem. Sci.*, Jan., 1834; special issue, 2d ed., London, 1837. Rayer, *Traité des mal. des reins*, ii., Paris, 1840. Martin Solon, *De l'albuminurie ou hydropisie causé par une maladie des reins*, Paris, 1838. G. Johnson, *Med.-Chi. Trans.*, xxix., p. 1; xxx., p. 165; xxxiii., p. 107. The same, *Die Krankheit der Nieren*, from the English, by B. Schütze, 1854, 2d ed., 1856, pp. 68–330, and *Lectures on Bright's Disease*, New York, 1874. Reinhardt, *Charité-Ann.*, i., 1850, p. 185. Fr. Th. Frerichs, *Die Bright'sche Nierenkrankheit*, Braunschweig, 1851. R. Virchow in his *Archiv*, iv., 1852, p. 460. Toynbee, *Med.-Chi. Trans.*, xxix., 1840, p. 304. Traube, "Ueber den Zusammenhang von Herz- und Nierenkrankheiten," Berlin, 1856, *Deutsch. Klin.*, 1859, Nos. 31, 32; *Allg. Med. Ctr.-Zeitg.*, 1858, No. 65, and Feb. 29, 1860. *Deutsch. Klin.*, Jan. 17, 1863. S. Rosenstein, *Die Pathologie und Therapie der Nierenkrankheiten*, 1st ed., 1863, 4th ed., 1894. S. Wilks, *Guy's Hosp. Rep.*, 2d ser., viii., 1852. Todd, *Clinical Lectures on Certain Diseases of the Urinary Organs*, London, 1857. Dickinson, *Med.-Chi. Trans.*, xliii., 1860, and *Diseases of the Kidney*, ii., London, 1877. W. Roberts, *A Practical Treatise on Urinary and Renal Diseases*, London, 1865. Grainger Stewart, *A Practical Treatise on Bright's Diseases of the Kidney*, Edinburgh, 1st ed., 1868; 2d ed., 1871. C. Bartels in *Volkmann's Sammlung klin. Vorträge*, No. 35, 1871, and in *v. Ziemssen's Handb. der spec. Path.*, ix., 1, 1875; 2d ed., 1877. H. Senator, *Virchow's Archiv*, lxxiii., 1878; *Berlin. klin. Woch.*, 1880, No. 29. *Die Albuminurie*, Berlin, 1882, p. 105; 2d ed., 1890, p. 139. C. Weigert in *Volkmann's Sammlung klin. Vorträge*, 1879, Nos. 162 and 163. E. Leyden, *Zeits. f. klin. Med.*, ii., p. 33. Aufrecht, "Die Diffuse Nephritis," Berlin, 1879; *Deutsch. Arch. f. klin. Med.*, xxxii., p. 573; *Ibid.*, liii., p. 531; *Centralbl. f. inn. Med.*, 1895, No. 10. E. Ziegler, *Deutsch. Arch. f. klin. Med.*, 1880, xxv., p. 586. Sotnitschewski, *Virchow's Archiv*, 1880, xxxii., p. 209. Lemcke, *Deutsch. Arch. f. klin. Med.*, 1884, xxxv., p. 148. Kelsch, *Arch. de Phys. normale et path.*, 1874, vi., p. 722. Lecorché, *Traité des maladies des reins*, Paris, 1875, and Lecorché et Talamon, *Traité de l'albuminurie et du mal. de Bright*, Paris, 1888. Lancereaux in *Déchambre's Dic. des sciences méd.*, 1875, 3. p. iii., "Rein." Charcot, *Leçons sur les maladies du foie et des reins*, Paris, 1875, and *Revue de méd.*, 1882, p. 426. Cornil and Brault, *Études sur la path. des reins*, Paris, 1884. A. Brault, *Arch. gén. de méd.*, 1888, and *Traité de médecine* by Charcot, Bouchard, Brissaud, v., Paris, 1893. See also the text-books on Special Pathology.

Under the above title are included certain diseases of the kidneys caused by a defective condition of the blood, and therefore always bilateral; they are characterized by inflammatory changes in the various tissue elements, do not, however, lead to suppuration, and manifest themselves clinically in almost every case by albuminuria and frequently by dropsy. The forms in which these two symptoms—albuminuria and dropsy—occur have received the special designation *Bright's disease.*

For the history of this form of nephritis begins with R. Bright, who, as has already been stated (p. 17), demonstrated in a series of papers published between the years 1827 and 1843 that morbid changes in the kidneys are among the most frequent causes of albuminuria and

dropsy. It is true that before his time Wells,[1] J. Blackall,[2] and Alison[3] had occasionally observed the coincidence of dropsy and albuminuria with renal disease; but it is Bright's merit not only to have recognized the frequency of the renal disease, but also its causal connection with the two chief symptoms, and to have given an anatomic and clinical description of the various forms of the disease, illustrated by case histories and plates that have been accepted as models ever since.

Aside from certain rare varieties in which albuminuria was said to be slight and frequently variable, Bright distinguished three principal forms—namely: (1) One in which the kidney is about normal in size but abnormally soft, the surface presenting a yellowish, speckled appearance, which on section is found to involve the entire cortical substance, while the pyramids are pale. Later the kidney becomes harder and presents on its surface small prominences, which are lighter in color than the surrounding tissue. Bright found this form associated with the cachexia produced by phthisis or protracted diarrhea. (2) A form characterized by a granular condition of the cortical substance, the interstices of which are filled with an opaque white deposit. After the capsule has been removed the surface presents a speckled appearance, as though sprinkled with sand. As the disease progresses this speckling becomes more and more distinct, and later the kidney becomes slightly irregular on its surface and either larger or smaller than normal. The urine coagulates markedly on being heated, but dropsy may be altogether absent. (3) In the third form, finally, the entire kidney is rough and uneven from the presence of numerous granules the size of a pin-head and of a yellowish-red or purple color. The consistence of the kidney is almost as hard as that of cartilage, and the organ is frequently lobulated and contracted in all its parts. In almost all the cases of this form the urine was also found to be extremely coagulable.

As regards the nature of the changes that take place in the kidneys, Bright believed that they were due either to disturbances of the circulation in the organs, or to actual inflammatory processes caused by deleterious influences acting from the stomach or the skin. He did not commit himself definitely as to the practical identity of the three forms he described, but he was inclined to regard them as various stages of the same disease, the one gradually merging into the other, although he thought it was possible that the first form represented one disease and the second and third forms together another.

The first who unreservedly accepted Bright's teaching were Christison and Gregory in Edinburgh and Osborne in Dublin, and their writings showed that Bright's disease was frequently to be observed outside London. Christison in particular added something to the clinical of picture, pointed out the frequency of fatal coma after suppression of the

[1] *Transactions of the Society for the Improvement of Med. and Chi. Knowledge*, iii., 1812, pp. 16 and 194.

[2] *Observations on the Nature and Cure of Dropsies, and Particularly on the Presence of the Coagulable Part of the Blood in Dropsical Urine*, etc., London, 1813, 4th ed., 1804.

[3] S. Rayer, *loc. cit.*, ii., p. 543.

urine, discovered the presence of urea in the blood-serum, and distinguished an *acute* from a *chronic* form of the disease, although he was in doubt about the minute anatomic foundation for this distinction.

On the other hand, voices were raised in England as well as in France in more or less emphatic opposition to Bright's teaching. Graves[1] adopted the most extreme views in this respect; his theory was the exact reverse of Bright's, for he believed that the renal affection was the result and not the cause of albuminuria and dropsy, on the ground that an albuminous fluid was secreted in the kidney as well as in other organs in the presence of dropsy. Elliotson and Copland admitted that the renal disease might be the cause in some cases of dropsy and albuminuria, but they believed that other cases depended on disease of the heart, lungs, or liver. In France, Bouillaud[2] and Martin Solon contended that albuminuria might occur in a great variety of morbid conditions, and in itself was not a sign of Bright's disease. Martin Solon originated the term "albuminuria," which he regarded as a special nosologic group with five subvarieties.

Meanwhile Rayer, during his investigations of kidney disease pursued from the year 1830 on, had subjected Bright's statements to rigorous verification both personally and through his pupils, and the latter reported their work in a series of communications, the combined result of which Rayer embodied in his book ten years later. On account of its anatomic characteristics, the causes, the symptoms, and the treatment he regarded the renal affection in Bright's disease as inflammatory in character, but separated it from other renal inflammations, such as those caused by traumatism, poisoning or infections, gout, and rheumatism, and gave it the name "nephrite albumineuse." The characteristic features of the disease according to him are as follows: A considerable amount of albumin in the urine with or without red blood-cells, the reduction of the salts and the urea in the urine, and almost always a lowering of the specific gravity; the appearance of edema in the subcutaneous cellular tissue, and effusions into the serous sacs. He distinguished six forms of the disease, two with acute febrile course and four chronic forms, which he said were not strictly separable from one another. Rayer's chief merit is that he collected a vast amount of material and analyzed it clinically, thus adding a great deal to the knowledge of renal diseases in general and that of the various inflammatory affections in particular.

The first attempts to investigate the finer structural changes occurring in Bright's disease of the kidneys were made in Germany. Gluge[3] and Valentine,[4] who were contemporaries, had discovered certain changes that are not very characteristic, the former an engorgement of the vessels with a material which he called "inflammatory spheres," and the latter an engorgement of the convoluted tubules with a material

[1] *London Med. Gaz.*, vii., Feb., 1831, p. 585, and *Dublin Jour. Med. Sci.*, 1833, No. 16.
[2] *Clinique méd de l'hôpital de la Charité*, Paris, 1837, iii., p. 190.
[3] *Casper's Woch. f. Heilk.*, 1837, No. 38, and 1859, No. 5.
[4] *Repertorium f. Anat. u. Physiol.*, 1837, ii., p. 290.

resembling pus and molecular granules. Henle[1] gave the first detailed description of the microscopic findings in the kidneys "in the cases regarded as belonging to Bright's disease," and his statements, the following passages from which the writer quotes verbatim, must in many respects be accepted as authoritative to-day:

"The two kidneys," says Henle, "are, as a rule, uniformly enlarged or diminished in size. When a kidney is enlarged the tissue is either uniformly infiltrated or, as in the case of a small kidney, converted into new substance in places and partly at the expense of the normal secreting tissue. While the uriniferous tubules are in part atrophied and in part constricted, and here and there filled with serum, blood, drops of fibrin, granular cells, and various immature cell formations, which do not, however, so far as I know, include pus corpuscles, and the normal epithelium has disappeared, the stroma in which the tubules are embedded is either absolutely or relatively increased, poor in blood-vessels, and contains the following microscopic elements:

"1. The more or less completely developed fibers of the cicatricial tissue, covered with numerous elongated nuclei and molecules, and which, representing as they do transitional forms between fibrin and connective tissue, are found in all new formations, although they differ from the fibers of the normal stroma of the kidney only by their quantity.

"2. Fat-corpuscles of varying size, sometimes arranged in regular rows; these also are found in newly formed fibrous tissue.

"3. Granules and pigment cells, probably derivatives of extravasated blood-cells.

"4. Cysts (Simon)—spheric transparent vesicles filled with a pale fluid and of all possible dimensions, the smaller containing nuclei and resembling the ordinary cells of the renal tubules; the larger ones covered with a kind of epithelium which is not found in the largest. All these changes and the corresponding new formations are more advanced in the cortical than in the medullary substance. Johnson, Bowman and myself found no change in the glomeruli; while Simon found them compressed at the bottom of their capsules."

As the result of these investigations, Henle regarded the deposition of an inflammatory exudate from the vessels as the essential feature of the process; some of this exudate is poured into the uriniferous tubules, the rest becomes organized in the stroma and leads to an increase of the fibrous tissue. "This metamorphosis may be called *cirrhosis* of the kidney, provided the word is taken not in its old significance as describing a color, but in the sense of contraction of the organ by a new formation of contractile fibers." Henle includes certain other morbid conditions in the term Bright's degeneration of the kidneys. At the same period Rokitansky[2] described what he called the lardaceous or "*bacon*" kidney ("Speckniere"), later called the amyloid kidney, and regarded it as one of the forms of Bright's disease, of which he distinguished eight varieties.

But neither he nor Henle at first attracted much attention. On the contrary, there was a tendency to accept the doctrine put forward almost at the same time by Reinhardt and Frerichs and based on numerous investigations, which was to the effect that Bright's disease in its various forms depends on diffuse inflammation of the kidneys, characterized by three stages that cannot be sharply separated one from the other—namely: (1) Hyperemia and beginning exudation; (2) exuda-

[1] *Zeit. f. rationelle Med.*, 1841, i., p. 67, ii. p. 220, and *Handb. der rationellen Path.*, ii., 1847, p. 303.

[2] *Lehrb. der path. Anat.* ii., 1842, p. 429.

tion and beginning metamorphosis of the exudate; (3) regression and atrophy. The new formation of connective tissue which Henle regarded as a product of inflammation was absolutely denied by Reinhardt, while Frerichs admitted its occurrence only in exceptional cases.

To a certain extent this doctrine was supported by the famous treatise of Virchow, "On Parenchymatous Inflammation," which appeared shortly after, in 1852, and in which the principal stress was placed on changes in the epithelium. Virchow distinguished three degrees of inflammatory disease of the uriniferous tubules—namely: (1) "*Catarrhal inflammation*," the mildest grade, affecting preferably the straight uriniferous tubules, and characterized by an increase of the epithelial cells, which become first granular and opaque and later friable and grayish yellow; (2) "*croupous inflammation*," a severer degree of inflammation, in which the alterations of the epithelial cells are complicated by the presence of a fibrinous exudate within the uriniferous tubules; and (3) "*parenchymatous inflammation*," which occurs chiefly in the portions of the convoluted tubules nearest the Malpighian capsules, and consists in cloudy swelling of the cells and their conversion into a semi-fluid detritus or the product of fatty metamorphosis. According to Virchow, the symptom-complex of Bright's disease is produced by a combination of these three changes, and especially by the presence of parenchymatous nephritis.

Traube held exactly the opposite view in regard to inflammation of the kidney. As has been intimated (p. 116), he made a sharp distinction between *renal congestion* and *amyloid degeneration* on the one hand, and *Bright's disease* on the other. The latter he regarded as a simple inflammatory process affecting the interstitial tissue, especially that of the cortical layer. About this time A. Beer[1] demonstrated the existence of the interstitial connective tissue beyond a doubt and pointed out its significance. Traube regarded the epithelial changes as secondary and rejected the theory of a "parenchymatous nephritis"; he divided interstitial inflammation into a circumcapsular and an intertubular variety. His greatest merit is to have described the *clinical* pictures and established the diagnosis of the individual diseases which up to his time had been included under the term Bright's disease. Thus, he gave a complete and definite description of *renal congestion*, *amyloid disease*, and of the *contracted kidney*, so that practically nothing remained to be added.

Traube's conception of inflammation in general and inflammation of the kidneys in particular appeared to find support in Cohnheim's investigations on inflammation which were published soon after, and in Klebs[2] he also found an earnest advocate. The latter described Bright's disease as a primary diffuse interstitial nephritis with a stage of cellulo-lymphatic infiltration and resulting connective-tissue formation. Klebs defined *glomerulonephritis* as a special form of interstitial nephritis occurring especially after scarlet fever; but Cohnheim[3] himself, at

[1] *Die Bindesubstanz der menschlichen Niere im gesunden und kranken, Zustande*, Berlin, 1859.
[2] *Handb. der path. Anat.*, i., 1876, p. 632. [3] *Allg. Path.*, 2d ed., ii., p. 344.

least later, refused to acknowledge a formal separation of parenchymatous from interstitial nephritis, and adopted the views of C. Weigert, which will be discussed presently.

Before this time S. Rosenstein, in his *Pathology of the Diseases of the Kidneys*, published in 1863, had assumed a position midway between Virchow's and Traube's, and while accepting congested kidney and amyloid disease as described by the latter for special clinical forms, regarded Bright's disease as a "*diffuse nephritis*," in the sense that both the epithelial cells and the interstitial tissue represent the starting-point of the disease.

In England, Quain,[1] Toynbee, and G. Johnson made the earliest microscopic investigations. Toynbee, in 1846, described the thickening of the arteries and the enlargement of the intertubular spaces from cellular deposits, and Johnson, in a number of contributions, beginning in 1846, first uttered the views which he summarized in 1874 as follows: Bright's disease is not a local affection, being due to constitutional causes and probably the result of a morbid condition of the blood. The latter affects primarily and particularly the epithelial cells of the convoluted uriniferous tubules, which are destroyed or cast off—*acute* or *chronic desquamative nephritis*. In the chronic form, which corresponds to the red contracted kidney of other authors, the basement membranes of the uriniferous tubules and Malpighian capsules become thickened, so that the appearance of a newly formed mass of fibrous tissue is simulated, whereupon the muscular coat of the small arteries, the significance of which, as pointed out by Johnson, has already been referred to (p. 121), also gradually undergoes thickening. Johnson further describes as a chronic form of Bright's disease the "large white kidney," which is characterized by fatty degeneration of the epithelium and, under certain circumstances, followed by atrophy, and finally *amyloid degeneration* (lardaceous, bacon, or waxy kidney—"Speckniere"); and the *simple fatty kidney*, in which the principle change is an infiltration of the epithelium with fat.

Johnson's work is remarkable in the first place because he described a special form leading to contraction, a "chronic desquamative nephritis," believing that this condition was not secondary to other acute forms or stages, but developed independently, and, in the second place, because he described the thickening of the vessels in the kidneys. On the former point he agrees with S. Wilks, who as early as 1852 took a decided stand against Frerich's division of Bright's disease into three stages, the last being contracted kidney. He regarded the latter condition also as an independent form of kidney disease, and denied that it followed the large white kidney which Frerichs had described as the second stage. Wilks has given a very complete description of the differences between the two forms.

This conception of the duality of chronic nephritis, aside from congestion and amyloid degeneration, became the dominant doctrine in England. Todd, Roberts, Dickinson, Grainger Stewart, and others

[1] *Lancet*, November, 1845.

adopted it, but they differed with Johnson in regarding the new formation of connective tissue in (primary) contracted kidney as the primary and most important part of the morbid process. According to the current doctrine of Bright's disease in England, congestion and in part also amyloid degeneration are not included under this head, and a primary contracted kidney (cirrhosis, red granular, gouty kidney) is regarded as an independent disease and distinguished from parenchymatous tubular nephritis, which is divided into three stages similar to Frerichs' division and may also lead to contraction. In primary contracted kidney the new formation of interstitial connective tissue is the essential part of the morbid process; in parenchymatous nephritis it is the disease of the uriniferous tubules, and after the latter have been destroyed the kidney undergoes contraction by a relative increase of the connective tissue. Grainger Stewart, who was especially concerned in the elaboration of this doctrine, emphasizes the occurrence of mixed forms, and describes the transition from amyloid disease to contracted kidney.

In a sense the doctrine of the occurrence of an independent form of nephritis not presenting three stages and not leading to contraction found support in the investigations of Gull and Sutton in regard to "arteriocapillary fibrosis" as a cause of contracted kidney, which appeared in 1872, and have already been referred to (p. 120). Although they exaggerated the importance of the vascular lesions, they rendered a valuable service in bringing them more into the foreground and recognizing them as a cause of contracted kidney.

In Germany, C. Bartels was the most zealous as he was the first defender of the view that *genuine contracted kidney*, the condition which until then had been called the third stage of Bright's disease, represents an independent morbid process. He regarded it as the result of a primary proliferation of the intertubular connective tissue, leading to atrophy of the glandular substance and not preceded by swelling of the entire organ. He differentiated it sharply from "chronic parenchymatous nephritis," in which, however, he admitted the occasional occurrence of interstitial processes. The writer adopted this view in 1878 to the extent of recognizing the occurrence of genuine contracted kidney as a more frequent disease than secondary contraction, but at the same time insisted upon the difficulty or even impossibility of making a sharp distinction either clinically or anatomically between chronic parenchymatous nephritis and genuine contracted kidney, and therefore suggested that for many cases the term "chronic diffuse nephritis" would be more suitable; and, finally, that it depends entirely on the course of the disease whether the symptoms resemble one form or the other, and that parenchymatous inflammations possibly predispose to interstitial processes. In 1880 the writer, in company with Gull and Sutton, admitted the occurrence of a form of nephritis depending on a general vascular disease and terminating in contraction, differing with these authors, however, in regarding the causal vascular disease as arteriosclerotic (see p. 120). Leyden expressed a similar view except in one point. He also disapproves of the dogmatic distinction between parenchymatous

and interstitial inflammation, and accordingly also prefers the term "diffuse nephritis" to "chronic parenchymatous nephritis." He recognizes the secondary form to which it gives rise, as well as the combination of amyloid contracted kidney with genuine contracted kidney, and also believes that these processes have their starting-point in a disease of the arteries closely connected with general arteriosclerosis; but he adds a kind of cirrhosis in which the kidney does not become smaller, although the histologic changes are the same.[1]

In an authoritative treatise Weigert opposed the separation of the various forms of inflammation included under the term Bright's disease, and insisted that there is no such thing as a parenchymatous nephritis without interstitial proliferation and contraction of cellular and connective tissue, and that the differences observed in the changes in the interstitial tissue in the various forms of Bright's disease are solely quantitative. Differences in the color of the kidney—white, red, and speckled—Weigert maintained were dependent especially on variations in the quantity of blood and in the degree of fatty degeneration of the epithelium. The connective-tissue proliferation, according to Weigert, in most cases is secondary and due to the destruction of the epithelial cells of the uriniferous tubules or the glomeruli. Weigert, like the writer, insists that the various forms differ according to the course and duration, and therefore subdivides them as follows: (1) *Acute nephritis*, in which the connective tissue contains only small-cell proliferation and hemorrhages. (2) The *subchronic form* (*chronic hemorrhagic nephritis*), characterized by the new formation of connective tissue in the interstices and in the Malpighian capsules and obliterating endarteritis without diminution of the kidney as a whole. (3) *More chronic forms*, in which the contraction is more marked and can be recognized macroscopically, and in which a large part of the parenchyma is preserved. (4) *Distinctly chronic forms, granular atrophy*, with great diminution in the size of the kidney, and a small amount of intact parenchyma and communicating contraction foci. The transitional forms, anatomically speaking, do not necessarily represent successive conversions from the preceding form, as varieties similar to the transitional forms may be due to gradations and varying degrees of intensity in the course of each form. On the other hand, an acute lesion may become chronic, and a chronic affection may occasionally undergo acute exacerbation.

In Germany, Weigert's presentation of the histologic conditions in Bright's disease of the kidney and the interrelation between the various forms found many adherents, among whom Cohnheim, as has been mentioned, and E. Wagner were those who gave the most unqualified assent. Rosenstein, who from the beginning had contended for the unity of the various forms differs with Weigert only in that he does not regard the changes in the epithelium as primary to the interstitial alterations, but believes that the immigration of colorless blood-cells

[1] The case which Leyden cites as an example of this last-mentioned form does not, in the writer's opinion, belong to this category; it is a case of ascending nephritis terminating in contraction.

into the interstitial tissue occurs simultaneously and represents a primary and not a secondary process (see p. 172).

Aufrecht, on the other hand, on the strength of a number of experimental and histologic investigations, in a series of papers, denied the identity of these various forms. He divides Bright's disease into two groups—namely: (1) *Tubular nephritis* (acute and chronic parenchymatous nephritis and white contracted kidney), which begins with disease of the epithelium and later is attended by changes first of the afferent vessels of the glomeruli and then of larger arterial vascular trunks, as well as by enlargement of the interstitial tissue, and finally destruction of the Malpighian bodies; and (2) *vascular nephritis* (red contracted kidney), in which the disease begins in the afferent vessels and spreads to the glomeruli, and to which a tubular (chronic hemorrhagic) nephritis is superadded either early or late in the course of the disease.

Weigert's theory of the identity of the various forms of Bright's disease, particularly in regard to contracted kidney, was also denied by E. Ziegler, who pointed out that the epithelium does not always represent the starting-point of the disease, since an inflammation in the interstitial tissue going on to induration may develop directly under the influence of some injury. He further calls attention to the fact that arteriosclerosis is one of the most frequent causes of contracted kidney, an observation that had been made simultaneously by Leyden and the writer (see p. 173). The significance of this vascular lesion as a primary process preceding the contraction of the kidney as described by Gull and Sutton, although they offer a different interpretation for the anatomic changes, is also emphasized by Sotnitschewsky and Lemcke.

In France the doctrine of the duality or plurality of the various forms of disease included under the term Bright's disease, which had originated in England, found general acceptance, although opinions differed in regard to the interpretation of the differences between them and their mode of origin. More recently, however, a tendency to adopt Weigert's view has begun to make itself felt. Kelsch recognized the separation of a parenchymatous form, which he believed is always chronic, from interstitial nephritis or genuine contracted kidney; but he maintains that this parenchymatous form is not a true inflammation, representing as it does a degeneration of the epithelium without any interstitial process. Lancereaux distinguished "néphrite épithéliale" from "primary diffuse nephritis," in which latter form the inflammatory process begins in the interstitial tissue among the convoluted tubules and in the Malpighian corpuscles, while the epithelium of the uriniferous tubules is attacked secondarily; and this author points out also that there is a form of diffuse nephritis depending on a general arterial disease. Charcot, in his lectures, had first followed S. Wilks' classification, but later adopted Weigert's view in regard to the origin of primary interstitial nephritis and taught that the epithelial disease is the primary lesion. Cornil and Brault distinguished "*diffuse forms of nephritis*" and "*systematic forms.*" The former are subacute or chronic and involve practically all the tissue elements; while the latter first and preferably

attack only one system, either the tubules or the vascular system. The latter two subdivisions together constitute primary contracted kidney and are never secondary to diffuse nephritis. In his latest description of renal diseases, Brault abandoned this distinction, however, and dwelt chiefly on the degree of intensity with which any harmful agent (poison) acts upon the kidneys as determining the acuteness or chronicity of the clinical course. He accordingly divides all the forms of nephritis into *acute*, *subacute*, and *chronic*, and thus approaches Weigert's classification. Lecorché, who at first rigidly separated chronic parenchymatous nephritis from the form of contracted kidney designated sclerosis, abandoned this classification in the monograph which he wrote later in association with Talamon. In this paper *glomerulonephritis* is stated to be the first alteration and one that is common to all forms of Bright's disease; this may be associated from the beginning with a change in the uriniferous tubules, while the interstitial changes are secondary. The authors assume that *glomerulonephritis* is general or disseminated in acute, but only disseminated (partial) in chronic cases. All three forms, the two acute and the chronic, show a tendency to atrophy, which, however, does not develop in the two acute forms because it is prevented by the occurrence of death.

The numerous writings and investigations which, as will be seen, were chiefly, and for several decades almost exclusively, concerned with the *structural*, especially the *more minute histologic changes in the kidneys*, have been followed in recent times by investigations in regard to the *etiologic factors* of nephritis, having for their object chiefly the influence on the kidneys of various poisons, more particularly microparasites, and their metabolic products. These investigations will be mentioned in connection with the etiology of the respective morbid conditions.

It will be seen from this exposition of the evolution of the doctrine of Bright's disease that there are still differences of opinion in regard to some of the points at issue. Certain histologic questions are still in dispute, particularly the questions as to which of the constituents of the kidneys form the starting-point of the disease, and whether the starting-point is always the same in the various cases of acute and chronic disease. On the other hand, many obscure points have been nearly or quite cleared up. New facts have been discovered, and the conflict of opinions has brought out certain aspects of the question that are not without importance in the explanation of the various forms of disease known as "diffuse nephritis" and their relations to one another. The following propositions contain what to the writer's mind are the essential points bearing in the controversy:

1. The clinical differences observed in hematogenous, diffuse, non-suppurative nephritis depend chiefly on the course and duration of the disease. The course and duration in their turn depend upon the intensity of the effect produced upon the kidneys by the noxious agents in the blood (infective agents, toxins, and other poisons, defective condition of the blood in dyscrasias).

2. When the irritation is intense, either because of its specific mode

of action or its quantity, all the constituents of the kidney—epithelium, Malpighian bodies, and interstitial tissue—are attacked at once, and the acute inflammatory manifestations in the interstitial tissue, such as hyperemia, hemorrhages, and round-cell infiltration, are usually more pronounced as compared with the changes in the parenchyma.

3. When the irritation is less severe and of shorter duration, all the tissue elements are not attacked at the same time nor with a like severity, the parenchyma, which includes the epithelium of the uriniferous tubules and glomeruli, being the first to suffer. Except for a slight hyperemia, the interstitial tissue escapes altogether or does not become involved until later in the course of the disease. There is no such thing as acute interstitial nephritis without changes in the parenchyma.

On the theory that only the peculiar processes in the interstitial tissue represent true inflammatory processes and that "parenchymatous" inflammation does not exist, the changes in the parenchyma would have to be regarded as degenerative in character; but, aside from other reasons,[1] the inflammatory nature of the process is shown by the fact that the same irritant, when more severe or of longer duration, is capable of producing the phenomena of inflammation in the interstitial tissue as well. Hence the parenchymatous manifestations may be regarded as the first stage of the inflammation.

It will be readily understood, if the peculiar arrangement of the blood-supply and the function of the two secreting elements of the kidney are borne in mind, why the epithelium of the uriniferous tubules, especially that of the cortical tubules, is the first to suffer from any injurious agent contained in the blood. The cortical sections of the uriniferous tubules are supplied almost exclusively with blood that has passed through the glomerular vessels and has given up a large portion of its water—*i. e.*, has become very much concentrated. All the injurious substances contained in the blood, unless they have been carried away with the escaping serum, will be brought to the cortical tubules in a concentrated form and at a slow rate of speed peculiarly adapted to enable them to exert their full effect on the epithelium; while materials that have escaped with the serum also come in contact with the epithelium by way of the uriniferous tubules themselves, so that the latter *are greatly exposed to injury from two directions at once*, and therefore are usually the first to become diseased. In the vascular tufts, which it is true receive blood that has not become concentrated, the blood circulates under very high pressure and at a low rate of speed, conditions that permit it to exert its utmost influence. Another consideration is that anything that is not completely soluble, particularly microparasites, is very likely to be arrested in the glomerular loops and set up an inflammatory process. It is due perhaps to these circumstances, or possibly to some special property inherent in the cause of the inflammation, that in many cases (scarlet fever, for instance) the inflammation in the tufts is more pronounced and more conspicuous than the changes in the epithelium.

4. Acute nephritis is therefore either a simple parenchymatous inflammation—a tubular (badly named "parenchymatous")—nephritis or "glomerulonephritis," depending on whether the epithelium of the uriniferous tubules or the glomeruli are principally involved—or a "diffuse" nephritis in the strict sense—*i. e.*, with involvement of the interstitial as well as of the parenchymatous tissue. The latter (diffuse acute nephritis) is always the expression of a more intense inflammation which may be present from the beginning or may develop as an accompaniment of the milder form—namely, the parenchymatous disease.

[1] See v. Recklinghausen, *Allg. Path.*, 1883, p. 238.

5. When the disease is protracted, all the tissue elements of the kidneys eventually become more or less involved; when the disease first attacks the parenchyma (epithelium and glomeruli), it is regularly followed by interstitial processes (Weigert[1]). Strictly speaking, therefore, there is no chronic parenchymatous nephritis except in the sense that the parenchymatous changes may be primary and more pronounced than the interstitial changes.

It is not probable that the interstitial changes (cell infiltration and connective-tissue proliferation) are exclusively dependent upon and secondary in time to parenchymatous changes. As has been mentioned above (see p. 174), Ziegler believed that the interstitial processes may occur independently of the parenchymatous and either accompany or precede them, and that there is a primary interstitial nephritis which leads to hyperplasia of the connective tissue and induration. Nauwerk[2] also expressed the opinion that exudation and proliferation in the connective tissue may exist without disease of the specific tissue elements.

Chronic inflammation of the connective tissue is accompanied or soon followed by degeneration of the parenchyma, including both the glomeruli and the epithelium, hence the termination is the same in either case, providing the disease last long enough—induration with more or less advanced contraction of the kidneys.

6. The same thing finally occurs in another class of chronic cases, in which the disease unquestionably starts with an arteriosclerosis or aplasia of the arteries with deficient blood-supply, the first effect of which is obliteration of the glomeruli and atrophy of the uriniferous tubules, followed by an increase of the connective tissue.

7. Those forms of chronic nephritis which do not depend on sclerosis or aplasia of the arteries may be the result of an acute nephritis, or they may develop insidiously as an independent disease from the beginning.

8. In all forms of nephritis, both acute and chronic, death may occur at any time if the functional impairment due to the structural alterations in the organs exceeds a certain limit. On the other hand, the process may become arrested at any time and complete involution with recovery may take place; or, if the disease is protracted, it may terminate in relative functional recovery through the agency of compensatory processes within the kidney, which, either by themselves or in association with the cardiac hypertrophy which develops, more or less completely make up for the loss of functionating tissue. (See Hypertrophy, p. 163, and Changes in the Vascular Apparatus, p. 117.)

9. Lastly, a quiescent inflammation may be lighted up again without any recognizable provocation, or a renewed outbreak may take place in the course of a chronic inflammation, and in this way the pathologic as well as the clinical phenomena may present numerous variations.

From the above proposition the impossibility of accepting the theory of the unity of Bright's disease in the sense intended by Reinhardt and

[1] See also Burmeister in *Virchow's Archiv*, cxxxvii., 1894, p. 405.
[2] *Deutsch. med. Woch.*, 1884, Nos. 10 and 11.

Frerichs, that all the forms represent merely stages of the same morbid process, is evident; but, on the other hand, the dualistic theory advanced by S. Wilks, and practically also by Bartels, that so-called contracted kidney or chronic interstitial nephritis has nothing whatever to do with the form known as chronic parenchymatous nephritis and always develops as an independent disease from the beginning, is equally inadmissible. Each of the two theories contains a certain modicum of truth, which in itself proves that neither represents the whole truth.

It also follows that a strictly anatomic classification of the disease is impossible, because in the majority of cases several different pathologic processes are going on side by side and mutually modifying one another. Again, a comprehensive etiologic classification is impossible, not only for the reason that the causes in many cases are not known or imperfectly known, but because the same cause may under different circumstances produce different effects, as has been shown. For the present, therefore, we are forced to classify the various forms of diffuse nephritis, if not exclusively, at least chiefly from the clinical standpoint, but with some regard for the grosser anatomic differences, and this has been the general custom during the past two or three decades.

Since Traube separated *passive congestion* and *amyloid degeneration* as non-inflammatory processes from the variegated symptom-complex characterized by the two cardinal symptoms of Bright's disease (albuminuria and dropsy) and placed them on a secure clinical foundation, the symptoms belonging to Bright's disease in the narrower sense—*i. e.*, hematogenous non-suppurative inflammation of the kidney—have been divided into three groups, each of which in typical cases presents a characteristic clinical picture and corresponds roughly with one of the broad subdivisions from the gross pathologic standpoint. In this way three main groups or types have come to be almost universally accepted: (1) *Acute nephritis;* (2) *chronic nephritis without induration* (ordinary "chronic parenchymatous nephritis"); and (3) chronic indurative nephritis, which is usually called "*contracted kidney,*" although not altogether appropriately, because induration and its accompanying clinical picture may occur without true contraction or diminution in the size of the kidneys.

An attempt has been made to subdivide the various clinical pictures belonging to these three main groups in accordance with the pathologic varieties of acute as well as of chronic inflammations. This attempt is still going on. Some authorities object to any further subdivision of the main groups; others have attempted to make such a subdivision, but their methods and principles have varied. In short, there is at present no detailed subdivision that has achieved universal approval and practical acceptance; but the variations in the clinical and pathologic features of cases belonging to these main groups is so great as to call for a further subdivision, and the writer will therefore make such an attempt in the following pages, so far as it seems to him practicable and justified by the present state of our knowledge.

Every classification must be more or less artificial. This statement

is also a direct corollary to the general propositions given on the preceding pages. Such a classification is necessary for purposes of orientation and presentation, but it can never be literally and in every respect satisfactory, because in reality, as has been said, a great variety of transitional forms and combinations occur. The subdivision into *acute* and *chronic* nephritis possesses a certain advantage over other classifications, inasmuch as it takes for its basis or standard the duration of the process, thus leaving some latitude for individualization and making it possible to recognize, although tacitly, gradations in the same group, which, however, cannot be sharply divided any more than one can draw a sharp distinction between an acute and a chronic condition in general. These transitional forms may properly be designated *subacute* or *subchronic*, and thus a connecting chain may be established between the various main groups.

At best, however, the boundary lines are vague, even within the main groups, and the line which divides the entire class of hematogenous, non-suppurative diffuse forms of nephritis and Bright's disease of the kidneys from other conditions cannot be defined with any degree of accuracy. Just as acute parenchymatous inflammation cannot be strictly separated from *degenerative conditions*, so the boundary line between chronic and unquestionably inflammatory processes from other conditions that are *not inflammatory* and lead to *induration* and *sclerosis* cannot be sharply drawn. It is no wonder, therefore, that there is a difference of opinion in regard to the position that should be assigned to many clinical forms, whether among the inflammations—"nephritis"—or the various forms of "Bright's disease." Even the classification of "febrile albuminuria" is doubtful (see p. 40), and in many other affections in which the renal lesion is much more marked and in which the kidneys, in fact, are severely damaged, the same uncertainty prevails as in the case of "cholera nephritis," the "kidney of pregnancy," and "arteriosclerotic induration." To the writer's mind they appear to be more closely related in their essential nature to true inflammatory processes than to other clinical forms, and will, therefore, be described under that head.

The principles that the writer has laid down in the preceding pages lead him to propose the following classification of *hematogenous, non-suppurative inflammation of the kidneys:*

1. **Acute Nephritis.**—(*a*) Parenchymatous nephritis (tubular and glomerulonephritis). (*b*) Diffuse nephritis (additional forms: hemoglobinuric nephritis, nephritis of cholera, nephritis of pregnancy).

2. **Chronic diffuse nephritis without induration** ("chronic parenchymatous, subchronic nephritis").

3. **Chronic Indurative Nephritis** (contracted kidney).—(*a*) Secondary induration (secondary contracted kidney). (*b*) Primary indurative ("chronic interstitial") nephritis. (*c*) Arteriosclerotic induration (additional form: simple non-inflammatory atrophy of the kidneys).

As the writer has repeatedly stated, these groups do not contain all

the possible variations of renal inflammation. These variations give rise to a certain multiformity of the clinical picture, but are not constant enough to justify a greater refinement of classification.

[The question of the classification of inflammations of the kidney is an extremely complicated one. Neither clinically nor from the standpoint of etiology or morbid anatomy can the cases be grouped in a manner entirely satisfactory. Of the chronic varieties, for instance, cases are seen that are from the clinical aspect typically of the parenchymatous type and are found to be such at the autopsy; others are unquestionably of the primary chronic interstitial variety. But many cases partake of the characters of each of these two groups and are diffuse in nature. We must often be content with the diagnosis of chronic diffuse nephritis or chronic nephritis without attempting to fit the case more accurately into some particular subclass that is, after all, more or less artificial. These sensible and conservative views of Senator will, we think, be heartily applauded by both pathologists and clinicians.

It seems useless also to worry too much over the proper use of the term Bright's disease. Can it not be a term broadly, even loosely, applied to cover all the diseases called nephritis—*i. e.*, those non-suppurative forms just classified? To be sure, Bright made no such classification, but referred particularly to the types in which edema and albuminuria were striking features of the diseased condition of the kidney. Fine distinctions between acute nephritis and acute Bright's disease—the latter with edema—can be made, and successfully, too;[1] but it seems, after all, to complicate rather than simplify matters, and we prefer to speak of the condition as nephritis or as Bright's disease, using the terms interchangeably, although recognizing that some forms of "nephritis" are degenerative or atrophic in character, and not in the strict sense inflammatory, and that some cases called Bright's disease are different from anything described by Bright.—ED.]

ACUTE NEPHRITIS.

The forms included under this head correspond in general to those described by the older authors, especially Frerichs, as the first stage of Bright's disease or "acute Bright's disease," and by other authors as "acute parenchymatous" or "epithelial," "desquamative," and sometimes as "superficial and transitory nephritis."

ETIOLOGY AND PATHOGENESIS.

The origin of the disease, in so far as its causes are known, must be ascribed to sudden changes in the blood which may be described as *poisoning*, in the wider sense of the term. The conditions in which such changes occur are:

1. *The infectious diseases*, especially those *accompanied by fever*. It is probable that there is not one of this class of diseases that is not under certain circumstances capable of bringing about acute nephritis, but they

[1] See J. R. Bradford, *Lancet*, Nos. 4220 to 4223, 1904.

differ from one another as regards the frequency and intensity of the renal complication. According to the usual view, scarlet fever is the most frequent cause of acute nephritis, and the type of the disease was formerly, and is even now to some extent, thought to be shown in scarlatinal nephritis. This is undoubtedly correct so far as cases with pronounced changes in the urine, and dropsy are concerned, but it does not apply with equal justice to so-called parenchymatous nephritis, which, although it does not cause very conspicuous phenomena during life, and often remains undiscovered until the autopsy, depends on changes that occupy the boundary between inflammation and degeneration, and ultimately gradually shading into those cases which are no longer described as "nephritis," but as "febrile albuminuria." The difficulty of making a sharp distinction between these two groups of cases has already been noticed (see p. 180); but it is not a sufficient reason for excluding from the discussion all those cases which do not correspond to the type of a pronounced scarlatinal nephritis, particularly as that so-called typical form is not clearly distinguishable from other forms.

Taking the term "acute nephritis" in its broader sense, without, however, including every temporary "febrile albuminuria," we find that other febrile infectious diseases quite frequently cause nephritis, and if they do not surpass scarlet fever in this respect, at least they are very nearly on a par with this disease. This is particularly true of *influenza*, *diphtheria*, and other *infectious forms of angina*, and of *Weil's disease*. Next in order are *pneumonia*, *acute articular rheumatism*, *typhoid* and *typhus fever*, *septicopyemia*, *erysipelas*, *measles*, *beriberi*, and the like. In the very mild infectious diseases, like *varicella* and *epidemic parotitis*, nephritis is rarer than in any other disease, but still it occurs; in the former it was observed by Henoch,[1] and later by others; in the latter, by Pratalongo, Renard,[2] Henoch,[3] Croner,[4] Pognon,[5] and others. Finally, there should be mentioned *malaria*, after severe forms of which Kelsch and Kiener,[6] Th. Rosenheim,[7] G. Rem Picci,[8] and W. S. Thayer[9] observed acute nephritis, and *vaccinia* (L. Perl[10]), *tuberculosis*, and *syphilis*. (See under Pathologic Anatomy and Chronic Nephritis.)

From the fact that a *non-febrile* infectious disease may give rise to nephritis, it may be concluded that the essential and ultimate cause of this inflammation of the kidneys is not an elevation of temperature, at least not that alone, although fever is capable of exerting a certain harmful influence on the kidneys. (See Febrile Albuminuria, p. 40.) The cause, in fact, is to be sought in the *pathogenic microparasites* that produce the infections, or the poisonous metabolic products or *toxins* which they produce. The presence of microparasites in the kidneys and urine has been positively demonstrated in a number of cases, but it has not always been proved that the organisms found were identical with

[1] *Berlin. klin. Woch.*, 1884, No. 2. [2] *Arch. de méd. milit.*, 1885, vi., p. 185.
[3] *Vorlesungen über Kinderkrankh.*, 4th Ed., 1889, p. 611.
[4] *Deutsch. med. Woch.*, 1884, No. 9. [5] Thèse, Paris, 1889.
[6] *Arch. de Physiol. norm. et path.*, 1882, Nos. 2 and 3.
[7] *Deutsch. med. Woch.*, 1886, No. 42. [8] *Il Policlinico*, 1898.
[9] *Med. Rec.*, May, 1898. [10] *Berlin. klin. Woch.*, 1893, No. 28.

the specific organisms of the disease and that they were really responsible for the inflammation. On the other hand, microparasites may pass through the renal tissue, and especially through the glomeruli, and be washed away by the urine,[1] so that the absence of micro-organisms from the cadaver does not necessarily prove that they are not concerned in the production of the disease, for they may have died after producing the inflammation or may have been carried away from the kidneys in the urine. In short, it is not always possible to bring positive proof that an inflammation of the kidneys can be, and has actually been, produced by the microparasites themselves through the agency of the blood.

There is no dearth of clinical and experimental investigations, however, to prove that in many cases of nephritis the specific organisms themselves are the cause of the inflammation. In certain cases of infectious nephritis specific microbes have been found in the kidneys or in the urine or in both; this is true of the *diplococcus of pneumonia*, the *typhoid bacillus*, the *spirillum of relapsing fever*, a *streptococcus* and another *pyogenic coccus* with special properties (Mannaberg, Engel), and finally *bacilli of various kinds* in cases of *primary mycotic nephritis* (Letzerich, Litten). Here it might be objected that the kidneys were diseased to begin with, and for that reason permitted the bacteria to escape from the blood into their tissues. But it has been possible to produce infectious inflammation of the kidneys by injecting certain micro-organisms. Pernice and Scagliosi saw cases of this kind after the injection of *bacillus of anthrax*, *Bacillus pyocyaneus*, *Staphylococcus pyogenes aureus*, and *Micrococcus prodigiosus*, while the toxins obtained from those organisms, although not quite inert, were distinctly less virulent than the micro-organisms themselves. According to the description of these authors, the process in the kidneys begins with hyperemia, endarteritis, and hemorrhage, swelling of the glomerular epithelium, exudation and hemorrhage into the interior of Bowman's capsules, the formation of tube casts in the uriniferous tubules and desquamation of their epithelial cells, and is followed later by atrophy of the glomeruli and hyperplasia of the surrounding connective tissue.[2]

As for the toxins, their activity has been chiefly demonstrated in *diphtheria* and in the diphtheric form of nephritis. As Fürbringer[3] first pointed out and many others later corroborated, Löffler's bacillus, which is regarded as the cause of diphtheria, is almost always absent from the kidneys in this disease. On the other hand, Roux and Yersin,[4] as well as Spronck,[5] v. Heverden,[6] and v. Kahlden,[7] succeeded

[1] See Reissner, "Ueber die Ausscheidungen von Fremdkörpern," etc., Diss., Göttingen, 1892; R. Kraus, *Zeit. f. Heilk.*, 1896, xvii.; v. Klecki, *Arch. f. exp. Path.*, etc., xxxix.; Opitz, *Zeit. f. Hygiene*, etc., xxix.

[2] For the literature the writer refers the reader to Litten, *Zeit. f. klin. Med.*, iv., 1882, p. 191; Letzerich, *ibid.*, xiii., p. 33; Mannaberg, *ibid.*, xviii., p. 223; J. Pansini, *Riforma med*, 1893, Nos. 10 and 12; Pernice and Scagliosi, *Virchow's Archiv*, cxxxviii., 1894, p. 521; Engel, *Deutsch. Arch. f. klin. Med.*, lvi., p. 140.

[3] *Virchow's Archiv*, xci., 1883.

[4] *Ann. de l'Institut Pasteur*, 1888 and 1889.

[5] *Compt. rend.*, 1889, cix., No. 7.

[6] *Nederland. Tydschr.*, 1890, No. 12.

[7] *Ziegler's Beiträge zur path. Anat.*, ix., p. 527.

in producing nephritis by injecting diphtheria toxin. The writer has observed the same changes in the kidneys of guinea-pigs after the injection of diphtheria toxin as after injecting the bacilli themselves, and the latter could not be demonstrated in the kidneys.[1] The *poison of tetanus* has also been demonstrated in the urine.

2. "*Toxic nephritis*" represents an analogue of the renal affection produced by toxins without the direct agency of micro-organisms. Genuine toxic nephritis in the narrower sense of the term is an inflammation of the kidneys produced by soluble poisons, although it is practically or identically the same as the form of renal inflammation observed in many acute infectious diseases. The number of such poisons, which have been subjected to a great many tests in the course of experimental study of various forms of nephritis, is very large, and, like the poisons of the various infections, they differ in their action according to their special nature and the intensity and duration of the irritation; hence, all grades of inflammation, from simple changes in the parenchyma, that occupy the debatable ground between inflammation and degeneration, to the most pronounced forms of inflammation with involvement of the interstitial tissue, have been observed.

Many of these substances also have a *clinical* interest. They are those which are normally produced and excreted in the body and under abnormal conditions make their way into the blood, and those which are produced in the body only under abnormal conditions and act by virtue of *autochthonous* (or *endogenous*) *intoxication*. The latter class probably includes those toxic substances which are produced and absorbed in the intestine. The nephritis which occurs as the result of *acute* and *chronic intestinal disease* may be explained in this way. In other conditions several poisons are probably associated, as in jaundice, acute atrophy of the liver, and the like, in which the absorption of *bile* and especially of *bile acids* is an associate factor. F. Blum[2] has called attention to a special kind of *enterotoxins* that occur in thyroidectomized animals from deficient elimination and lead to nephritis. Certain urinary constituents also, such as acetone and others, may injure the renal tissue. (For urotoxins see the Experiments of Favre and Schilling, p. 156.)

A second group includes numerous substances that are used in small quantities for medicinal purposes, and which when ingested in larger doses, either accidentally or intentionally, produce *true* (*ectogenous*) *intoxication* with acute nephritis. Their number is very large, and *toxic nephritis* in the narrower sense of the term is therefore a fairly common condition. From a practical standpoint stress should be laid on the renal affections which follow the ingestion of concentrated *sulphuric* or *oxalic acid*—according to Eichhorst[3]—the ingestion of sorrel, which is very rich in oxalic acid, the inhalation of *chloroform* and *ether*, poisoning with *mercury*, *glycerin*, *turpentine*, and a number of *external antiseptics*, especially *carbolic acid*, and the *inunction with*

[1] H. Senator, *Deutsch. med. Woch.*, 1895, No. 33.
[2] *Virchow's Archiv*, vol. clxvi.
[3] *Deutsch. med. Woch.*, 1899, No. 28.

irritating substances, particularly *tar*, *naphthol*, and other drugs that have a similar effect on the skin.[1]

Highly seasoned foods and beverages, as, for example, mustard, radishes, pepper, strong alcoholic drinks, and the like, while less potent, undoubtedly have an effect similar to that of these more obvious poisons, as they are distinctly irritant to the kidneys. Excessive indulgence in such substances may, as the experiments of Pentzoldt[2] and K. Glasser[3] have shown, lead to inflammatory irritation of the kidneys, which under favoring circumstances may go on to a distinct and even intense inflammation.

A special position among poisons should be accorded to those substances which cause *hemoglobinuria* by *cythemolysis*, the hemoglobinuria with which nephritis is under certain circumstances associated, leading to the production of a form that in many respects is peculiar and may be designated *hemoglobinuric nephritis*. (See Appendix, p. 205.) The most important of these substances is potassium chlorate, although many of the above-mentioned bodies, as well as some of the causal micro-organisms of the infections and certain other toxins, may have a similar or less potent effect. Whether the separation of the hemoglobin always takes place in the general circulation to the exclusion of the kidneys themselves, as was formerly believed (see p. 64), has never been quite decided. Cases of hemoglobinuric nephritis occur and run their course without giving rise to any constitutional symptoms that would indicate injury to the blood or to the red blood-corpuscles.

It is exceedingly probable that cythemolysis and hemoglobinuria are the cause or one of the causes of the acute nephritis which follows *burns;* and it is also probable that the same cause is responsible for the nephritis in certain *chronic diseases of the skin*, as eczema and pemphigus, especially when, owing to extensive suppuration and maceration of the superficial layers of the skin, decomposition takes place with the formation and absorption of fatty acids and other substances which produce irritation and inflammation of the kidneys either by cythemolysis or in some other way. It should be mentioned, however, that acute nephritis may occur, although rarely, in the course of simple eczema.

3. *Exposure to cold* is not an altogether infrequent cause of acute nephritis. Although its influence in this as in so many other diseases was no doubt exaggerated by the older physicians, as it is even now by the laity, it cannot be altogether denied in the face of a large number of undoubted cases in which a typical inflammation of the kidneys followed immediately upon exposure to cold without any other demonstrable cause. By exposure to cold is meant sudden cooling of the body

[1] For a discussion of poisoning with sulphuric acid see E. Fränkel and Reiche in *Virchow's Archiv*, cxxxi., p. 141; with oxalic acid: A. Fränkel and *Zeit. f. klin. Med.*, ii., p. 664; with chloroform: E. Fränkel in *Virchow's Archiv*, cxxxix., p. 254; Ambrosius, *ibid.*, cxxxviii., suppl. vol., p. 197; Rindskopf in *Deutsch. med. Woch.*, 1893, No. 40; Wunderlich, *Beiträge zur klin. Chi.*, xi., 1894; with antiseptics: Senger in *Berlin. klin. Woch.*, 1888, Nos. 22 and 24.

[2] *Verhandl. des II. Cong. f. inn. Med.*, Wiesbaden, 1883, p. 226.

[3] *Deutsch. med. Woch.*, 1891, No. 43.

by a draft or drenching when the individual is fatigued and overheated. It is rather remarkable that, as others as well as the writer have observed, chilling of a part of the body only, especially the feet or back, may have a bad effect.

Just how the chilling exerts its malign influence is not known in nephritis any more than in any other disease said to be produced by cold. It was formerly believed that the functions of the skin were temporarily suppressed and excrementitious substances retained in the blood; but —not to mention other arguments—this view is contradicted by the fact that a local chilling, as of the feet or back, for example, which has just been referred to, is in itself injurious, although under any other circumstances the skin, like any other organ, is capable of compensating for the temporary functional loss of part of its tissue. According to another view, the cause is a circulatory disturbance produced reflexly by irritation of the skin. But granting the occurrence of such reflex disturbances in the kidneys, although it is far from being the case, this view fails to explain why other cutaneous stimuli do not act in the same way, nor how a circulatory disturbance, which is usually ephemeral, whether it consist in dilatation or constriction of the blood-vessels, is capable of producing inflammation, especially the intense inflammation which is almost always observed after exposure to cold.

It might be argued that the exposure to cold has a directly injurious influence on the blood. Semmola assumed that the chilling interferes with cutaneous respiration and alters the albuminous bodies in the blood in such a way that they are excreted by the kidneys as non-assimilable substances. The grounds for this theory will be discussed later in connection with chronic non-indurative nephritis. It is also possible that the red cells of the blood are destroyed by the direct influence of the cold much in the same way as has been demonstrated to be the case in periodic hemoglobinuria (see p. 59), and that this destruction of red blood-cells is accompanied by certain other insults. But in animal experiments the findings[1] after artificial chilling of the body are different from those observed in hemoglobinemia; they consist of hemorrhages into the various mucous membranes. In addition we should expect hemoglobinuria to be a constant symptom in nephritis due to cold, and that is not the case. While hemoglobinuria does occur in cases of nephritis from exposure to cold, as the writer knows from personal experience, it is by no means a constant symptom and cannot even be said to be very frequent. In this sense exposure to cold might possibly be accepted as the indirect cause of *hemoglobinuric nephritis.*

Unless that view is adopted, it seems impossible to obtain a satisfying explanation of the minute processes going on in the condition known as catching cold, and the bald fact that exposure to cold may be followed by nephritis will have to be accepted.

4. Finally *pregnancy* is responsible for a form of acute nephritis, which will be more fully discussed later. (See Appendix, p. 212.)

Whether *traumatism* other than direct injury or concussion is capable

[1] S. Neberthan, cited by Fr. Müller, *Münch. med. Woch.*, 1897, No. 47.

of producing nephritis is doubtful, and the renal symptoms that have been observed immediately after such a traumatism (hemorrhage, albuminuria, and casts) are not absolute proof of the existence of inflammation, for they may be interpreted as the effects of laceration of vessels and destruction of tissue. It is conceivable, however, that such injuries might be followed by necrosis in the kidneys and thus indirectly produce an inflammatory reaction.[1]

PATHOLOGIC ANATOMY.

The appearance and other characteristics of the kidneys vary in acute nephritis with the kind and intensity of the inflammation and the quantity of blood contained in the organs, and the vascularity, in turn, depends on a variety of conditions mostly outside of the kidneys and connected with the general circulation and the nutrition. In almost all cases except the very mildest the kidneys are large and heavy, the capsules are more tense and attenuated than under normal conditions and strip more readily unless they have become adherent to the parenchyma as the result of some previous pathologic process. The surface may be dark red or grayish red, with dark-red punctiform and linear markings that correspond to the distended radiating veins or to small hemorrhages; in some cases the organ is pale and anemic, and the color grayish red or grayish yellow. On the cut surface the tissue appears softer and more friable than normal, the cortex is more or less swollen and bulging and presents the same color changes as the surface. The medullary substance, although not so greatly swollen, is nearly always dark red or brown in color and marked by a few darker stripes, which correspond to the engorged venous trunks. The Malpighian bodies often appear as dark-red points and are more distinct than under normal conditions.

Two or three different forms of acute nephritis have been described with reference to the external appearance; thus, there is the "*hyperemic or hemorrhagic*" *kidney*, the "*pale or anemic*" *kidney*, and as a transitional form between the two, the "*speckled or many-colored*" *kidney*. But the different varieties merge one into the other by means of a succession of transitional forms.

Under the microscope the *changes in the cortical substance* first meet the eye; they may be found altogether or chiefly in the parenchyma—*i. e.*, uriniferous tubules and glomeruli, or in the interstitial tissue as well. The first set of changes represents "*parenchymatous nephritis*" in the true sense of the term, which may be subdivided, according as the uriniferous tubules or glomeruli are chiefly involved, into "*tubular*" and "*glomerulonephritis.*" If the interstitial tissue also is involved, which, as has been remarked (p. 177), is regarded by many as the characteristic sign of true inflammation, the term "*diffuse nephritis*" is used. In either case the pathologic lesions are not distributed uniformly over the entire cortical substances, but appear in irregular *foci of varying sizes* ["patchy necrosis"—Ed.].

The *epithelium of the convoluted tubules* is either the seat of cloudy

[1] S. R. Stern, *Monats. f. Unfallheilk.*, 1899, vi. 1.

swelling and granular or fatty degeneration going on to complete destruction (*plasmolysis*), or it undergoes so-called coagulation necrosis with the production of a variety of pathologic pictures. In places the cells appear as if they had been teased and nibbled or broken up into fragments, or they present in their interior pale vesicular spaces where the protoplasm has been destroyed, and in this way reticular figures are produced. These altered cells may coalesce with others and form a mass, completely obstructing the lumen of the tubules for a considerable distance. The normal cilia are usually unrecognizable, but in many cases they are quite well preserved. The investigations of K. Landsteiner[1] have shown that the essential change in the renal epithelium in *albuminous turbidity* (cloudy swelling) is the destruction of the regular rod-like structures with the appearance of granules, which, to judge from their tinctorial properties, appear to be made of different material from that which composes the rods. Various drops also are found within the cells, and other drops precisely similar in respect to their tingibility are found in the lumina of the uriniferous tubules, suggesting that hyaline casts, which take the same stain, are derived from the drops within the cells (see p. 49).

The nuclei are often seen lying free from protoplasm in the above-mentioned vacuoles. Subsequently, according to the investigations of Aufrecht[2] and the writer,[3] they break up into a number of granules capable of taking a very deep stain; these granules are at first arranged in a circular form, but later the grouping becomes irregular, the granules diminish in number and finally disappear altogether (*karyolysis*). In the cells in which the process is mildest, *karyokinetic* figures are observed, and probably indicate an effort to replace lost cells by beginning regeneration. The lumen of the uriniferous tubules presents local cylindric or sacculated dilatations from the accumulation of swollen or disintegrated epithelial cells, and in addition often contains finely granular coagulated albumin partly molded into the shape of a cylinder, and hyaline casts, fat-granules, blood-cells, and finally a few leukocytes which are usually mononuclear. In the deeper portions of the uriniferous tubules—the loops and the collecting tubules—the epithelial lining is usually normal, but the lumen of the canal is dilated and filled with hyaline casts which are not infrequently surrounded by epithelium that has been washed down from more superficially placed tubules or by the products of their disintegration.

The *Malpighian bodies* in mild cases present no alteration whatever or merely the excretion of albumin within the capsule. In severe cases, such as occur in scarlatinal influenza, typhoid fever, and the like, and are designated *glomerulonephritis*, the capillary loops are engorged and often contain masses of leukocytes; there is active proliferation of the nuclei and desquamation of cells and nuclei which more or less completely fill the capsular space, along with red blood-cells, leukocytes, and coagulated albumin which can be regarded as fibrin

[1] *Wien. klin. Woch.*, 1901, No. 41. [2] *Centralbl. f. inn. Med.*, 1895, No. 10.
[3] *Deutsch. med. Woch.*, 1895, No. 33.

when it appears thread-like. This intracapsular mass exerts pressure on the vascular loops, which may themselves be thickened and contain within their interior in places hyaline thrombi or a finely granular mass that completely blocks the lumen. As for the proliferating and in part desquamated cells in various stages of degeneration, their origin is not easy to determine and various explanations have been offered. There is no doubt that the glomerular epithelium, and sometimes the capsular epithelium also, swells, and is desquamated. According to Kiener and Kelsch,[1] Langhans and Nauwerck, proliferation of the capillary endothelium with consequent increase in the number of cells also takes place. Hansemann as well as Ribbert points out that a part, at least, of the nuclei supposed to result from the endothelial proliferation must be regarded as the nuclei of leukocytes (Cornil and Brault,[2] Renault and Hortolès,[3] Friedländer,[4] Langhans,[5] Ribbert,[6] Nauwerck,[7] Hansemann,[8] Aufrecht,[9] v. Kahlden [10]). (Compare also Chronic Non-indurative Nephritis.)

When the *interstitial tissue* is also involved in the inflammation—*i. e.*, in "diffuse nephritis"—we find it enlarged and edematous, and in addition to a more or less pronounced distention of the vessels there are accumulations of round cells in groups, usually corresponding in position to the greatest changes in the epithelium of the uriniferous tubules (Weigert), and frequently grouped around the afferent vessels of the glomeruli, and extending from there around the capsules. Various interpretations have been given for these round cells. Orth [11] regards them as derivatives of the connective-tissue cells. According to Councilmann,[12] they correspond to Unna's "plasma cells," and are found at the boundary zone of the pyramids and in the cortex beneath the capsules and around the glomeruli. He also found them in large numbers in the blood-vessels of the boundary zone, associated with lymphoid cells, but without interstitial infiltration. He believes that they escape from the vessels in the form of plasma cells or as lymphoid cells that later become converted into plasma cells.

The *blood-vessels* themselves present no distinct alterations in most cases, although Litten [13] and Fischl [14] have described hyaline degeneration of the intima or swelling of the muscularis and adventitia with the deposition of cells and the accumulation of fibrous masses, and v. Kahlden, desquamation of the endothelial cells in the nephritis of scarlet fever and diphtheria.

Associated with these changes, *hemorrhages* of variable extent also occur and have their seat in the capsules of Bowman, the uriniferous

[1] *Arch. de phys. norm. et path.*, 1882, ix. [2] *Loc. cit.*, p. 79.
[3] *Études sur les procès hist. d. néphr.*, Paris, 1881, and *Thèse* (Hortolès), Paris, 1882.
[4] *Fortschr. der Med.*, i., 1883, p. 85. [5] *Virchow's Archiv*, vols. xxvi. and cxii.
[6] "Nephritis und Albuminurie," Bonn, 1881, *Fortschr. der Med.*, 1888, No. 13, and *Biblioth. med.*, c., 1895, p. 21.
[7] *Ziegler's Beiträge zur path. Anat.*, i. 1886. [8] *Virchow's Archiv*, cx.
[9] *Deutsch. Arch. f. klin. Med.*, vol. liii., p. 555.
[10] *Ziegler's Beiträge zur path. Anat.*, xv., 1894. [11] *Lehrb. der path. Anat.*
[12] *Jour. of Exper. Med.*, 1898, iii. [13] *Charité-Ann.*, vii., 1882, p. 170.
[14] *Prager Zeit. f. Heilk.*, iv., and *Zeits. f. klin. Med.*, vii., p. 127.

tubules, or the interstitial tissue. These hemorrhages are usually more marked in the various forms of diffuse nephritis, which thus assumes a more or less hemorrhagic character, and are least marked in the tubular form of parenchymatous nephritis, which accordingly furnishes most of the cases of pale anemic kidney.

In addition to actual hemorrhages, the escape of *hemoglobin* into the kidneys takes place and produces a *hemoglobinuric renal affection* or *nephritis*, which may originate in one of two ways. Either hemoglobinuria is superadded to an already existing nephritis as the result of general blood-changes or of some local modification of the red blood-cells that occurs in the kidneys (see p. 64), or the hemoglobinuria is the primary condition, and the passage of hemoglobin through the kidneys causes secondary changes in the organs. In the latter case the kidneys are swollen, dark red or in protracted cases grayish red, and reddish-brown or grayish-red, punctiform and linear markings are to be seen under the capsule as well as on the entire cut surface, especially in the medullary substance. Microscopically a finely granular brownish-red or rust-colored coagulated mass is found in the capsules of Bowman and particularly in the uriniferous tubules, the convoluted as well as the straight; the tubules, especially the convoluted ones, contain hyaline casts and renal epithelium in process of cloudy swelling and in various stages of disintegration. Some observers assert that the epithelium of the capsules and loops also swells and is cast off. The interstitial tissue in recent cases usually presents no alterations except hemorrhages; in somewhat older cases there may be foci with small-cell infiltration (Marchand,[1] Lebedeff,[2] Forsbach,[3] Kelsch and Kiener[4]).

The inflammatory process may undergo more or less complete *involution* by absorption of the interstitial exudate, the removal of the contents of the uriniferous tubules by the urine, and partly also by absorption and regeneration of the epithelium by the formation of new elements from the remaining cells. In this way a complete or incomplete (relative) recovery—in the latter case with the loss of secreting parenchyma and scattered areas of contraction—may result.

"*Parenchymatous*" and especially "*tubular*" nephritis is the usual concomitant of most if not all the *febrile infectious processes* at the height of the fever, and is the most common form of kidney disease in cases of *poisoning* in the narrower sense (ectogenous poisons), as well as in many cases of *endogenous* (autochthonous) poisoning. (See Etiology.) In instances the changes never exceed the mildest grade of the disease, cloudy swelling and degeneration of the epithelium, and the inflammatory character of these changes, as has been repeatedly stated, is often doubtful. Such cases during life either remain latent or betray themselves merely by a "*febrile albuminuria*."[5] In other cases the changes

[1] *Virchow's Archiv*, vol. xxvi., 1879. [2] *Ibid.*, vol. xci., 1883.
[3] "Ueber Hämoglobinurie," *Diss.*, Bonn, 1883. [4] *Arch. de physiol. norm. et path.*, 1882, ix.
[5] Thus, for example, Cavazzani and Ferrarini (*La Clinica Med.*, 1899, No. 6) did not observe albuminuria in experimental nephritis produced by means of chloral hydrate or pyrogallic acid; the only changes they found concerned the epithelium of the convoluted tubules.

in the tubules are accompanied or followed by slight changes in the *glomeruli* that are more frankly inflammatory in nature and to be recognized by the escape of an exudate into the capsules; although the profound alterations of true glomerulonephritis, the proliferation of cells and of nuclei that have been described, are absent. Finally a coagulation necrosis of variable extent not infrequently becomes superadded.

The cause of these parenchymatous changes, as the writer has already remarked on page 182, is to be found partly in the *fever* itself—*i. e.*, in those processes which are present in every case of fever—and partly in the nature of the cause of the infection. In no other way can we explain the fact that parenchymatous nephritis, while it is usually more pronounced at the height of the fever, by no means bears a direct relation to the degree of temperature, and the fact that certain diseases with only moderate elevation of temperature present the same changes as others with high fever or even more profound ones.

Another proof is found in the behavior of *toxic nephritis*, the course of which in most cases is marked by very little fever or is altogether afebrile, while the parenchymatous changes may be quite marked.

Diffuse nephritis, in which the interstitial tissue is also attacked, differs from the parenchymatous form in that it occurs regularly only in very few infectious diseases, although it may also be present exceptionally in all the others. It belongs to *scarlet fever* during the stage of desquamation, as has been observed, to a much more limited extent after malaria, and is the result of exposure to cold. It is not very rare in *diphtheria*, and possibly also in *syphilis* at the beginning of the secondary stage.

As regards true so-called scarlatinal nephritis, it is to be distinguished from the parenchymatous form, which, as has been mentioned, may occur at the height of scarlet fever, and is on a par with the parenchymatous changes in the kidneys that occur in the other infectious diseases during the febrile period. True scarlatinal nephritis does not, as a rule, develop until after the febrile stage, a phenomenon explained by Leichtenstern[1] on the assumption that the scarlatinal poison, which during the efflorescent stage of the disease lodges in the skin, is later absorbed by the lymph vessels and carried to the kidneys, thus producing stasis and inflammatory edema of the skin on the one hand, and specific post-scarlatinal inflammation of the kidneys on the other hand. [In many cases of scarlatina the nephritis may be looked upon as the result of a secondary or mixed infection or, at least, as due to a streptococcus invasion, whether this organism be looked upon as the cause of the scarlet fever or not.—Ed.] In the most pronounced cases the kidney in this condition presents the picture of the hyperemic or hemorrhagic, rarely of the pale anemic kidney (p. 187), and under the microscope presents chiefly the changes described as *glomerulonephritis*, in addition to parenchymatous and interstitial inflammation of variable extent, and especially the disseminated cell accumulation described by Councilman (see p. 189).

[1] *Deutsch. med. Woch.*, 1882, Nos. 13 and 22.

In *diphtheria* the kidneys are frequently attacked, but practically only when the infection is severe and during the height of the disease. Aside from congestion, which develops as a result of the interference with the breathing when there is involvement of the larynx coupled with weakness of the heart, the kidneys present a variety of pathologic changes, ranging from the mildest grades of parenchymatous nephritis to the severe diffuse forms resembling scarlatinal nephritis.[1]

As to *syphilis*, the question whether and to what extent the disease can cause an *acute* nephritis is difficult to answer. It is true that albuminuria is frequently observed both in recent and in old cases of syphilis; but the symptom may be the expression of a previously existing renal affection or of a *chronic* nephritis (*q. v.*) that has developed during the course of and in connection with the syphilitic disease, or the albuminuria may be due to antisyphilitic treatment, particularly with mercury; in other words, it may be *toxic* in nature or it may be caused by other factors that often accompany syphilis, such as alcohol, exposure to cold, pregnancy, and the like. Finally, it may be the expression of an irritation of the kidneys, beginning in the urinary organs and spreading by continuity to the kidney—*i. e.*, an ascending nephritis (*q. v.*)—not to mention the possibility of error from the presence of a false albuminuria (albuminuria spuria, see p. 19), from gonorrhea or some other similar cause.

It is certain that an *acute* nephritis due to syphilis alone is very rare. In Germany E. Wagner[2] was the first, as he was practically the only, one who described a few cases belonging in this category, and he himself was not satisfied of the diagnosis in every instance. Other authorities, chiefly French and Italian physicians (Perroud, Horteloup, Mauriac, Tommasoli, Jaccoud, Fordyce, Allaria, and others), have expressed themselves more confidently on this subject.[3] According to them "*nephritis syphilitica præcox*" is not a curiosity in recent syphilis. In his elaborate monograph on renal syphilis, J. J. Karvonen justly excludes the majority of cases reported as renal syphilis as being doubtful, for reasons enumerated above, so far as any connection between syphilis and acute nephritis is concerned. This leaves a small number of cases that appear to argue in favor of such a causal connection: (1) because no kidney diseases had been present before the outbreak of syphilis; (2) because the symptoms of the renal affection accompanied other symptoms that were evidently syphilitic in origin; and (3)—the chief reason—because improvement or complete recovery followed the administration of mercury.

[1] Cited by F. Reiche, *Centralbl. f. inn. med.*, 1895, No. 50.

[2] *Deutsch. Arch. f. klin. Med.*, xxviii.; and "Morbus Brightii," *loc. cit.*, p. 166.

[3] J. J. Karvonen, "Die Nierensyphilis," *Dermatol. Zeit.*, vii., 1900. Since then cases have been reported by A. Stepler, *Wien. klin. Woch.*, 1900, No. 43; A. Moskowits, *Orvosi Hetilap*, 1900, No. 49; and E. Hoffmann, *Berlin. klin. Woch.*, 1902, Nos. 6 to 9. In the last-mentioned case the unheard-of quantity of 7 to 8.5 per cent. of albumin was excreted and precipitated in amorphous granules. An even higher degree of albuminuria—more than 13 per cent. in one case, with a specific gravity of 1060—in which during a period of fourteen days 420 gm. of albumin were excreted in syphilitic nephritis, was reported by Descoust, Thesis, Paris, 1878.

It appears from these cases, which must be accepted as authentic, that *nephritis syphilitica præcox* develops from two to nine months after the infection, and, like other acute inflammations of the kidney, varies in severity from a mild parenchymatous lesion to grave diffuse inflammation, like that of scarlatinal nephritis. Tommasoli states that syphilis alone is not sufficient to produce the renal affection, which requires that the kidneys shall have lost some of their resisting power through scrofula, alcoholism, exposure to cold, or some infectious disease; but these influences have not been demonstrated in every case. The diagnosis of "*nephritis syphilitica præcox*" must always be made with great caution, and if albuminuria is present and all other possible etiologic factors can be excluded, mercurial treatment should be instituted *tentatively*, and if improvement results the treatment is to be more energetically carried on.

Hereditary syphilis seems to have been the cause in a case of acute nephritis observed by Hock[1] in a child of three months. The administration of potassium iodid was followed by improvement.

For other forms of *hereditary* and *family* predisposition to nephritis see Indurative Nephritis (p. 260).

In addition to the acute nephritis other organic changes are found post mortem, which are partly attributable to the same cause as the nephritis and partly to be regarded as sequelæ of the renal affection. The second class includes principally *dropsical effusions*, *inflammation of serous membranes*, and *dilatation of the heart;* and, according to C. Friedländer[2] and F. Jäger,[3] *hypertrophy of the left ventricle* is frequently found after scarlatinal nephritis (see p. 199).

SYMPTOMATOLOGY.

(*A*) **"Acute parenchymatous nephritis"** in which only the epithelium of the urinary tubules is involved (tubular nephritis) while the glomeruli remain intact or only slightly affected is characterized in many cases by the absence of all symptoms, particularly dropsy, and in other cases by slight changes in the urine. The disease was therefore formerly overlooked, and even now it cannot always be recognized with certainty during life and is frequently only surmised.

The mildest urinary change is known as "febrile albuminuria." The epithelium is so slightly affected that, as has been mentioned, it is often doubted whether the condition really is inflammatory and whether it is the cause or, at least, the sole cause of the albuminuria, which, therefore, has frequently been called "functional" (see p. 40). The urine contains a very small amount of albumin, and in other respects presents the characteristics of febrile albuminuria—*i. e.*, it is scanty, high-colored, intensely acid, heavier than normal, and contains no sediment or only very little, in which an occasional hyaline cast is found. As the fever subsides the albuminuria disappears unless complications develop.

[1] *Wien. med. Presse*, 1895, No. 44. [2] *Fortschr. der Med.*, 1883, No. 3.
[3] *Münch. med. Abhandl.*, 1893, ii.

Between this febrile albuminuria and distinct changes in the urine, indicating beyond a doubt a more severe disease of the kidneys, "parenchymatous" (tubular) nephritis, the transitions are almost imperceptible. The urine in parenchymatous nephritis is also, as a rule, diminished in quantity, particularly when there is fever, but the quantity may be normal; the color is dark, often a brownish red, and the urine is more or less turbid from the presence of a sediment which consists chiefly of renal epithelium, justifying the name "desquamative nephritis" which has been given to this form. Some of the *epithelial cells* are well preserved and occur either singly or massed as *epithelial casts*, while others are in a state of degeneration and recognized only with difficulty. The sediment also contains *hyaline casts* in varying numbers, some of them covered with fat-droplets, and not infrequently *crystals of uric acid and calcium oxalate;* finally, depending on the character of the inflammation, *red blood-cells* in varying numbers, either singly or in the form of blood-casts, and often *hemoglobin* in granular form or in the form of little heaps and cylinders, and fine granular detritus. *Leukocytes* are rarely found in the pure tubular parenchymatous form unless, as happens in some of these cases, the deeper portions of the uriniferous tubules down to the mucous membrane of the pelvis of the kidney or even lower down become involved—that is to say, unless there is a desquamative *catarrh of the urinary passages.* In that case multinuclear leukocytes appear in considerable numbers in association with epithelial cells from the deeper uriniferous tubules.

The *percentage of albumin* in the urine, unless there is an admixture of blood, is almost always small in "parenchymatous" tubular nephritis, and is in striking contrast to the quantity of sediment, which is usually quite large. It appears from recent investigations that the greater part of this albumin consists of nucleo-albumin (see p. 21[1]).

There are practically no other symptoms in parenchymatous tubular nephritis. The patients may on inquiry state that they have a dull sensation in the region of the kidneys, but other subjective symptoms and morbid phenomena are due not to the renal affection, but to the basal process, particularly the various *acute intoxications and infections.*

(*B*) **"Diffuse nephritis,"** seen in its most typical form in scarlet fever, is generally a much more grave disease and presents a more variegated symptom-complex. The two most important phenomena are the *urinary changes* and the *dropsy.*

The *urine* with very few exceptions is diminished in quantity from the beginning, and this diminution is frequently the first symptom that attracts attention. Not more than 100 c.c. may be passed in the course of twenty-four hours, and in especially grave cases complete anuria may be present. The urine becomes dark in color, turbid, and of a high specific gravity, which may rise above 1030, and these changes are inversely proportional to the quantity excreted. In somewhat milder cases the changes are less pronounced; and in very light forms the appearance of the urine differs but little from the normal. Blood is

[1] See also Kossler in *Berlin. klin. Woch.*, 1895, Nos. 14 and 15.

nearly always found in the urine, although sometimes it can be recognized only with the microscope; when the urine contains a considerable percentage of blood, its appearance resembles that of meat juice or sometimes even blood, and in some cases complicated by hemoglobinuria the color becomes a dirty brown or brownish red, resembling chocolate.

Aside from a few exceptional cases (see Diagnosis), the urine always contains *albumin*, which is the ordinary coagulable albumin of blood-serum (serum-albumin and globulin), and if there are many cellular elements there may be some nucleo-albumin; quite frequently *albumoses* are also found. In exceptional cases the latter alone are found for a time, and this probably explains why the urine is sometimes found to be "free from albumin" by the boiling test. As a rule, the percentage of albumin is inversely proportional to the quantity of urine, and directly proportional to the number of morphologic constituents—in other words, to the mass of the sediment. The presence of blood, of course, increases the percentage of albumin; but even in the absence of blood it is quite considerable, varying from a few parts in a thousand to 1 per cent. or more.

The percentage of serum-albumin and globulin, as in all other forms of nephritis, is extremely variable; but on the whole the amount of globulin is considerable during the height of the acute nephritis, and the albumin quotient (see p. 20), therefore, is small. It is to be remembered, however, that in most of the earlier observations when globulin was said to be present, nucleo-albumin was probably present also. Cloetta[1] finds that substance constantly in acute nephritis, and the writer has been able to demonstrate its presence quite frequently, although he has occasionally missed it.

The *sediment* always contains *red blood-cells*, sometimes in a good state of preservation and sometimes more or less washed out, their quantity depending on the condition of the urine in other respects; in addition there are *leukocytes*, or, at least, *mononuclear* cells that may be regarded as leukocytes (lymphocytes), besides a few multinuclear cells (pus corpuscles) that are probably derived from the urinary passages,[2] while the mononuclear elements referred to correspond, in part at least, to the cells already described (p. 189) as being found in the renal tissue. The sediment also contains *renal epithelium*, either isolated elements or small aggregations, *casts* of various kinds, *cells in a state of fatty degeneration*, *crystals of uric acid and calcium oxalate*, and in the hemoglobinuric form *hemoglobin* in granules and in masses. (See Appendix.) Common constituents of the sediment are *micrococci*, and their presence cannot always be attributed to pollution of the specimen.

[It is now well known that in typhoid fever there is, in about one-quarter of the cases, a bacilluria especially apt to be present during or near the period of convalescence. The urine under these circumstances is at times quite normal in appearance; at other times it is slightly cloudy from the swarms of typhoid bacilli and contains a small amount of albumin. The importance of the recognition of this condition, not

[1] See also Kossler in *Berlin. klin. Woch.*, 1895, Nos. 14 and 15.
[2] H. Senator, *Virchow's Archiv*, 1893, cxxxvii.

alone for the sake of the patient, but, as well, because of the danger to others of spread of the disease by the contaminated urine, is perfectly clear. Turbidity of the urine, therefore, in typhoid with albuminuria should be regarded as possible evidence of typhoid bacilluria and should lead to the examination for the germs. It is not meant that every turbid or every albuminous urine in typhoid contains the bacilli, but that this condition of the urine should arouse such suspicion.—Ed.]

These changes in the urine, especially the diminution in the quantity and the albuminuria, are readily explained by disturbance in function of the uropoietic tissue elements brought about by the structural changes. The blood-supply, and hence the excretion of urine, is greatly interfered with by the inflammation and obstruction of the glomerular capillaries, by the pressure exerted on these capillaries by the exudate within the capsule, by the pressure on the capsules of the infiltrated and proliferated interstitial tissue, and finally by the perivascular cell proliferation, especially around the afferent vessels.

The impairment of the renal function reveals itself also in the *diminished excretion of nitrogen*. The principal representative, *urea*, is almost always diminished, not only because the quantity of nitrogen taken in with the food is diminished, and because of the loss incidental to albuminuria and to impaired assimilation in the intestine, but in all probability also as the result of a diseased condition of the epithelium lining the uriniferous tubules. The excretion of *sodium chlorid* is also diminished as well as that of *phosphoric acid*, and the diminution is only partly accounted for by the diminished ingestion of these substances, and, when fever is present, their retention within the body; for the diminished excretion of sodium chlorid is due in part to the inability on the part of the diseased kidneys to maintain a normal molecular concentration of the blood as fully and as constantly as in health (Nagelschmidt[1]). Accordingly, as A. v. Korányi[2] was the first to show, the concentration of the urine, other things being equal, is less than normal in diseased kidneys—*i. e.*, the freezing-point does not fall so low. [There are many exceptions to this. With the diminished amount of urine, concentrated and of high specific gravity, the freezing-point will often be found normal—*i. e.*, between —0.9° and —2.3° C., or even lower than this. Edema and anemia may modify this, causing the freezing-point to rise—*i. e.*, to approach 0° C.—Ed.] It is remarkable that the excretion of *uric acid*, to judge from the investigations of v. Schroeder,[3] Ackeren,[4] and Kolisch,[5] is not very much altered; while, on the other hand, the excretion of *xanthin* or *alloxuric bases* has been shown by the investigations of A. Baginsky,[6] v. Kolisch, v. Fodor,[7] and those performed in the writer's clinic by P. F. Richter, to be increased, with the exception of *ammonium*, which was normal. Nevertheless, Gumlich,[8]

[1] *Zeit. f. klin. Med.*, xlii., p. 274. [2] *Ibid.*, xxxiv.
[3] *Du Bois-Reymond's Arch. f. Physiol.*, 1880, Sup., p. 115.
[4] *Charité-Ann.*, xvii., 1892, p. 206. [5] *Wien. klin. Woch.*, 1895, Nos. 23 and 24.
[6] *Du Bois-Reymond's Arch. f. Physiol.*, 1884, p. 456, and *Zeit. f. physiol. Chem.*, 1884, viii., p. 393.
[7] *Centralbl. f. inn. Med.*, 1895, No. 36. [8] *Arch. f. exper. Path.*, etc., x., 1879, p. 206.

in an analysis which, it is true, represents the work of only a comparatively short period, found little change in the relation between urinary urea and the urea in the whole body.

According to the investigations of Jaarsveld and Stokvis,[1] confirmed by Fr. Kronecker,[2] the conversion of *benzoic acid* into *hippuric acid* is greatly diminished in acute nephritis. The excretion of various drugs and poisons (iodin, quinin, and carbolic acid) is greatly impaired in nephritis, and judging from experimental and clinical observations on cases of unilateral kidney disease, which will be mentioned later, the *excretion of sugar*, after the administration of phloridzin, may, contrary to the rule, be absent or greatly diminished.

As in the *milder* cases, all the urinary changes are but slightly pronounced, and there is nothing but albumin and a few morphologic constituents demonstrable with the microscope to indicate the presence of kidney disease, so in *severe cases with favorable course* the urine gradually returns to its normal condition. The quantity increases daily until it reaches the normal, or it may exceed the normal if, as usually happens, the dropsy diminishes. At the same time it becomes paler and clearer as the sediment diminishes, until finally the only deviation from the normal is the albuminuria, which finally disappears after complete recovery.

The second prominent symptom, the *dropsy*, presents all the characteristics of "renal dropsy" (*hydrops renalis*). It usually develops early, during the first days of the disease, coincidently with or soon after the diminution in the quantity of the urine. Its extent and severity are very variable; as a rule, cutaneous edema develops and is more marked than the various effusions into serous cavities; in rare cases the latter are demonstrable first; and in still rarer cases they exist when there is very little swelling of the skin or even when edema is entirely absent. Exceptional cases run their course without showing a trace of dropsy of any kind.

The dropsy does not always bear a definite relation to the diminution, and still less to the albumin-content or other changes in the urine; the latter may be pronounced in cases with an insignificant degree of dropsy.

According to the explanation that the writer has given, dropsy is due not so much to the renal lesion as to a *coincident* injury to the blood- and lymph vessels in the skin, and in the serous and mucous membranes, causing a greater permeability of the walls of these structures. It is therefore quite conceivable that there should be no strict relation between the dropsy and the renal disease. In scarlet fever particularly, a disease in which the skin is unquestionably in a state of irritation, the cutaneous vessels are very likely to be involved more than the kidney (see Leichtenstern, p. 191); it is even conceivable that the cutaneous vessels may have become so predisposed to the disease that they respond to the irritation more forcibly than the kidneys, and sometimes are affected to the exclusion of those organs. In this way we might explain

[1] *Arch. f. exper. Path.*, 1883, xvi., p. 344. [2] *Ibid.*

the rare cases of scarlatinal edema without renal disease, which the writer as well as others have seen.[1] (See Dropsy, p. 84.)

None of the other symptoms is constant or characteristic. *Pain* in the region of the kidneys, radiating down to the thighs, and *frequent micturition* may or may not be present, and the same inconstancy is observed in regard to the *intestinal disturbances* of various kinds. When, however, *uremia* develops or threatens to develop, nausea and vomiting are practically constant (see Uremia, pp. 95 and 98), and in these cases *nervous disturbances* are superadded, which under other conditions are rarely or never observed.

The *general state of health* is always more or less impaired. Fever is present only in severe cases with stormy course, when the temperature may reach 40° C. (104° F.), rarely higher; but the curve is not typical and the symptom frequently absent. On the other hand, the patients generally feel fatigued and somnolent; the skin is strikingly pallid, particularly where it is edematous, but elsewhere as well, and the mucous membranes are equally pale. These phenomena are probably due to the *changes in the blood*. It has been proved by older as well as by recent observers (Christison, Frerichs, Dickinson, Hammerschlag[2]) that the blood becomes attenuated, as appears from a diminution in its total weight as well as of the serum alone, although this has been demonstrated only in cases with dropsy.

[In many cases of acute diffuse nephritis there is little change in the percentage of hemoglobin and the number of red and of white corpuscles. Generally, however, the blood within a few days is of the type of a secondary anemia, the red corpuscles will be more or less reduced in number, perhaps to 3,500,000 or even less per cubic millimeter, and the hemoglobin will be correspondingly low or even more reduced than the number of corpuscles—*i. e.*, the color index

$$\left(\frac{\text{per cent. of hemoglobin}}{\text{per cent. of red blood-corpuscles}}\right)$$

will be less than 1. Often, too, there is a moderate degree of polymorphonuclear leukocytosis.—Ed.]

In other respects also the *character* of the blood, particularly its molecular concentration, which depends on the functional capacity of the kidneys, is correspondingly altered in many cases; the freezing-point in many instances exceeds—*i. e.*, is lower than the normal (56° to 57° F.). [This is particularly apt to be the case when uremia is threatening. With the development of edema the freezing-point will generally rise—*i. e.*, approach closer to 0° C.—Ed.] The *uric acid* in the blood is often increased (v. Jaksch).

Inflammations of the internal organs are frequent concomitants of acute nephritis, and, as has been stated, the *serous membranes*, pleuræ,

[1] Roberts, *On Urinary Diseases*, p. 355; Henoch, *Berlin. klin. Woch.*, 1873, No. 50; Quincke, *ibid.*, 1882, No. 27; Senator, *Albuminurie*, 2d ed., 1890, p. 144; Edwards, *Am. Jour. Med. Sci.*, October, 1898; Cassel, *Berlin. klin. Woch.*, 1900, No. 10; Herringham, *Brit. Med. Jour.*, Dec. 1, 1900.

[2] *Zeits. f. klin. Med.*, xxi., 1892, p. 491.

pericardium, seldom the peritoneum, are attacked. *Bronchitis* and *pneumonia* are also not infrequent. In addition to the peri- or endocarditis and the disturbances to which they give rise, the *strength of the heart* in severe cases is more or less impaired, and the heart, especially the right ventricle, becomes dilated. The hypertrophy of the left heart which is found in cadavers is said by S. E. Henschen [1] to be usually demonstrable immediately after the appearance of albuminuria and to disappear again after the nephritis has run its course, although it may continue in a mild degree. The writer has never been able altogether to convince himself of this fact. The tension of the pulse in many cases is abnormally high (p.116).

Finally the *visual disturbances*, which appear as a part of the uremia (see p. 97), or in rare cases independently of that condition, in the train of an acute *apoplectic retinitis* should be mentioned.

As it is impossible from a clinical as well as pathologic standpoint to draw a sharp line between parenchymatous and diffuse nephritis, there are numerous cases that do not quite correspond to either of the two clinical pictures, and accordingly represent transitional forms. In addition the clinical picture may be complicated by symptoms that are due to the disease which has caused the nephritis.

COURSE AND TERMINATIONS; PROGNOSIS.

The course of the *acute parenchymatous nephritis* which occurs as a concomitant or sequel of the acute *infectious processes* depends altogether on the latter; it is not dangerous in itself, because the diseased epithelial cells possess a great power of regeneration, which is inversely proportional to the intensity of the changes in the interstitial tissue. In rare cases the epithelial cells may undergo degeneration in such enormous numbers as to obstruct the uriniferous tubules and offer a mechanical obstacle to the excretion of urine, a condition which terminates in severe disturbances and death from uremia. In the cases due to *intoxication*, this mode of termination is somewhat more frequent; but death in those cases is due to other causes besides the disease of the epithelium, particularly the injury to the heart and circulation which results directly from the infection or intoxication. Since in protracted cases a parenchymatous disease becomes complicated by interstitial inflammatory processes, such cases present the picture of a diffuse nephritis with subacute or chronic course.

Acute diffuse nephritis in rare cases runs its course in a few days. This occurs in the severest forms, characterized by fever, a marked diminution of the urinary excretion, and termination in death from uremia. In most cases the disease has a longer duration; when the course is favorable, complete recovery takes place within a few weeks or months; more rarely the case lasts a year and over.

When the duration is long there is a proportional tendency to the development of one of the chronic forms of nephritis. How often this transition from an acute to a chronic form takes place is difficult to say,

[1] *Ueber das Herz bei Nephritis*, Jena, 1898.

as in these protracted cases the general condition usually improves or there may even have been but slight disturbance from the beginning, so that the persistence of the disease can be determined only by careful observations and repeated examinations of the urine. Many of these patients, who are usually children or adolescents, are supposed to have recovered from an acute nephritis following scarlet fever or some other infectious disease; whereas the so-called "latent" albuminuria persists and indicates the presence of an insidious nephritis; or if it is discovered is put down as a "functional," "cyclic," or even "physiologic" albuminuria, and accordingly neglected. (See p. 34 and under Chronic Nephritis.)

Although a fatal termination is rarer than recovery, death nevertheless occurs not infrequently. In the commonest of all severe forms of acute nephritis—scarlatinal nephritis—the fatal termination in a measure depends on the character of the epidemic. With the exception of the extremely malignant and fulminating cases already referred to, death does not occur earlier than a few weeks or months after the beginning of the disease, and is usually brought on by dropsy in the internal cavities of the body, pulmonary or laryngeal edema, uremia, or inflammation of the lungs or the pericardium. Sometimes, after the disease has apparently run a favorable course for a considerable period, there is a sudden violent exacerbation which terminates in death.

In view of the numerous accidents that may occur, a guarded *prognosis* should generally be given in acute diffuse nephritis, both as to life and as to complete recovery. In individual cases it depends on the severity of the symptoms, and, above all, on the condition of the urine and the presence or absence of dropsy. The scantier the urine and the greater the quantity of blood and morphologic constituents, the more grave the disease; the greater the dropsy, the more urgent is the danger to life, although recovery is not impossible in either of these cases. It is needless to say that the condition of the heart is always of the greatest significance, and that the development of other organic diseases, so-called "complications," affects the prognosis unfavorably.

DIAGNOSIS.

A physician who is thoroughly imbued with the principle that an examination of the urine for albumin is as indispensable a part of an examination as the determination of the presence of fever will never overlook a nephritis, unless it be in those exceedingly rare cases in which albuminuria is entirely absent or lasts only a very short time, and which are therefore practically unrecognizable.[1] But the presence of albumin alone is no proof of either acute or chronic nephritis. If the urine in addition contains morphologic constituents, especially renal epithelium and leukocytes, the history must decide whether the nephritis is acute or chronic or a fresh exacerbation of a chronic affection.

[1] Equally rare are the cases without albuminuria but with casts in the sediment, which may have to be obtained by centrifugation. While such a condition is not in itself diagnostic, it may be significant when combined with other symptoms.

Sudden onset and short duration, the history of an infectious fever, an acute intoxication or an exposure to severe cold, the absence of thickening of the blood-vessels and hypertrophy of the left ventricle, and the absence of an old non-hemorrhagic retinitis are in favor of the diagnosis of acute nephritis. Even when the urine contains only albumin without sediment or with only a few hyaline casts, as sometimes happens in very mild acute cases or during convalescence in severe cases, the distinction between acute and chronic nephritis will depend on the anamnestic data referred to and on the course. Other causes of albuminuria, such as congestion of the kidney and amyloid disease, must be excluded.

The distinction between nephritis with much blood in the urine (hemorrhagic nephritis) and an *acute renal hemorrhage* is sometimes quite difficult. The diagnostic factors in favor of the former are: diminution in the quantity of urine, the presence of a sediment containing renal epithelium, casts—except blood-casts—and leukocytes in numbers disproportionate to the blood-percentage, dropsy in the characteristic areas, the face and the tibiæ, and possibly fever if no other cause can be found for an elevation of temperature. Renal hemorrhage, on the other hand, is characterized chiefly by the marked variations in the amount of blood, by sudden change from bloody urine to a practically normal secretion free from blood and containing little or no albumin. The presence of a possible cause of nephritis on the one hand, and of renal hemorrhage on the other, should also receive consideration (see p. 53).

As for the differential diagnosis between acute *parenchymatous* and *diffuse* nephritis, the former is characterized by an abundance of renal epithelium in the urine with a relatively small quantity of albumin in the filtrate, and the absence of dropsy; whereas typical cases of diffuse nephritis are characterized by a higher albumin percentage and the presence of dropsy. When the symptoms are not distinctly indicative of one or the other *condition*, the physician must content himself with a diagnosis of "acute nephritis."

The behavior of "febrile albuminuria" has been described; whether it be regarded as a functional disturbance or as the expression of a very mild form of parenchymatous nephritis is of no practical importance.

[When the acute nephritis occurs in consequence of an already existing acute infectious disease, and particularly if the nephritis be unaccompanied by edema, the symptoms of the renal complication may be entirely masked by those of the primary disease. Here the recognition must depend almost entirely on the examination of the urine. Frequent urinalyses should be the rule in typhoid, pneumonia, septicemia, etc.

In the same way, after prolonged anesthesia, "toxic" nephritis (p. 184) is often to be recognized only by the urinalysis. This form is commonly transitory and has the urinary findings of the acute parenchymatous tubular nephritis. Albumin may be slight or absent, but renal epithelium and casts may be abundant.—Ed.]

TREATMENT.

Acute nephritis can often be *prevented* because the physician, in this disease more than in most others, has it in his power to ward off the possible causes or remove them in time. This is particularly true of "*toxic nephritis*" which occurs after the injudicious internal or external use of various drugs and poisons (see p. 184). In addition to the general precautionary measures which are always to be observed in the handling of poisons, it is well to bear in mind that whenever substances that irritate the kidneys are employed for therapeutic purposes, either by inunction or by some other method of introduction into the body, the urine should be examined regularly, and as soon as the slightest trace of albumin makes its appearance the remedy should be withdrawn.

For the same reason, in the treatment of the *febrile infectious diseases* such substances must be used with great caution, and measures calculated to stimulate the elimination of the infectious micro-organisms and their toxins from the body and prevent their accumulation are to be strongly recommended. In addition to other procedures, which need not be discussed here, and due attention to the bowels, therapeutic measures having for their object the thorough *flushing out of the kidneys* are indicated. For this purpose the *ingestion of large quantities of fluid*, especially in the form of alkaline carbonated waters, as Bilin, Fachinger, Giesshübler, Seltzers, etc., or of milk, and in cases of constipation buttermilk, is useful; and the same object is accomplished by ordering *lukewarm*, *cool*, or even *cold baths*, which have such a salutary effect on the circulation in general and on blood-metabolism in the kidneys in particular. Whenever, therefore, the use of baths is indicated in infections, there need be no hesitation about their employment—and on this the writer wishes to insist in opposition to many other authorities—for fear of cold and threatening nephritis, providing the application of excessive cold is avoided.

As regards the much dreaded *scarlatinal nephritis*, the deeply rooted conviction that it is due to catching cold during convalescence from scarlet fever is unquestionably exaggerated, since daily experience proves that nephritis very often develops even when, acting under this impression, the physician carries the protection of the patient against cold to extremes. It is quite true that great caution is necessary during the stage of desquamation, and the patients must not be allowed to leave their beds before the process is completed; but it is not so much on account of the danger of catching cold that the patients are likely to develop post-scarlatinal nephritis from getting up too early, as it is on account of the walking about and other muscular exertion, which, as we know, favor the occurrence of albuminuria under certain other circumstances also. The writer would not like to leave this subject without mentioning *inunctions with fat and bacon*, which have been warmly recommended by Dähne[1] and later by Schneemann,[2] as a preventive measure against dropsy after scarlet fever, not on account of the specific curative action

[1] *Beiträge zur Aetiologie und Cur des Scharlachfiebers*, Leipzig, 1810.
[2] *Die sichere Heilung der Scharlachkrankheit*, Hannover, 1848.

which has been ascribed to them, but because they diminish perspiration and increase the supply of fluid to the kidneys, thereby possibly flushing out these organs with the body juices—in other words, acting like a mild diuretic.[1]

The *treatment* of a *fully developed nephritis* may in many cases be directed with success against the causes of the condition whenever these causes are known and are amenable to therapeutic measures, and this treatment coincides with that recommended for the prevention of the disease. It is, of course, in the *toxic form* of nephritis that the causal indication can be most successfully satisfied. In recent nephritis due to *syphilis* specific mercurial treatment appears to be successful and ought to be cautiously tried (see p. 193).

The disease itself requires above all *rest in bed* even in the mildest cases, and the patient should remain in bed until an examination of the urine at *different* times of the day shows that albumin has absolutely disappeared. Even then the patient should leave his bed only for a little while at a time and never while digestion is going on; the effect of rising, on the urine, should be carefully watched on each occasion. Not until the urine remains normal, even when the patient continues out of bed and after a hearty meal, is recovery to be regarded as assured. Neglect of these precautions is not infrequently responsible for the development of a chronic nephritis, which often remains latent for a long time under the clinical picture of an intermittent (cyclic) albuminuria[2] (see p. 35).

[These directions regarding absolute rest in bed ought certainly to be followed in the more acute cases with rapid course. But in acute cases with prolonged convalescence extending over many weeks or months (see p. 199), it is not only difficult to keep the patient constantly in bed, for he often rebels against the prolonged imprisonment, but we believe it is not always necessary or even desirable so to do. Moderate exercise, fresh air, and sunlight will stimulate the appetite, help digestion, bring more refreshing sleep, improve the condition of the blood to such a degree as to warrant one in relaxing the rule as to rest in bed, and particularly as one often sees an improvement in the renal condition follow such relaxation.—Ed.]

The *diet* is a subject of considerable importance. Years ago the writer developed certain principles for the dietetic treatment of nephritis. According to these principles there is demanded a non-irritant so-called bland diet—that is to say, a diet containing all the necessary nutritive materials without any irritating constituents, such as extractives and the like. *Milk*, which is the type of such a diet, is not only a suitable food, but acts as a mild diuretic without irritating the kidneys, and is, therefore, in addition to other desirable qualities, peculiarly well adapted for flushing out the kidneys.

An exclusive milk diet, as some authorites demand, is not necessary

[1] Unna, "Ueber die insensible Perspiration der Haut," in *Trans. of Ninth Cong. of Internal Med.*, Wiesbaden, 1890, p. 230, and H. Senator in the Discussion.

[2] H. Senator, *Berlin. klin. Woch.*, 1882, No. 49.

nor can it be strictly enforced in most cases. By allowing barley broths, or, if the irritation is not very severe, thin meat broths made of meat, chicken, or squab; wheat bread, zwieback, and other carbohydrates (sugar and cocoa), and, if the digestive organs are in good condition, butter and other fats, jellies made from calves' feet, and the like, and finally the lighter vegetables, such as spinach, cauliflower, schoten,[1] and carrots, the patient can be sufficiently fed even with a moderate amount of milk without damage to the kidneys and without sacrificing the variety which is so desirable in a protracted case.

As regards the *quantity* of food to be allowed, the patient's own inclination may be accepted as a guide unless there is complete anorexia. There is little danger that the patient will take too much; and even if he takes somewhat less than the quantity required to maintain the body in good condition while he is in bed, there is no harm done, as the duration of the disease is comparatively short. Complete anorexia, unless dependent on some deep-seated cause, may be combated by appropriate remedies that do not irritate the kidneys, such as hydrochloric acid and the bitter tonics.

The best *beverages* in addition to milk and water are the above-mentioned carbonated waters or lemonade; in cases of debility wine mixed with water may be given. When there is marked edema the total quantity of fluid should be restricted as much as possible without distressing the patient. Thirst may be relieved by giving small pieces of ice and peppermint tablets, or allowing the patient to sip a cold drink.

Finally *tepid baths*, which increase the diuresis and flush out the kidneys, are to be recommended.

With this *hygienic* and *dietetic* treatment, which is based on the general principle of guarding the inflamed kidneys against irritants as well as against excessive work, most patients with acute nephritis recover completely, providing the treatment is persevered in as long as necessary, as has been explained above. If, however, the disease continues for many weeks, it may be necessary to substitute a more nourishing diet, such as would be suitable in subchronic and chronic so-called parenchymatous nephritis, and will be described more particularly in connection with that disease.

We know of no *drugs* that have a curative or even a favorable influence on inflammation of the kidneys directly, although many have been recommended and are still being recommended either as antiphlogistic, in the strict sense of the term, as astringent, or as disinfectant and antiparasitic. The favorable results observed after the use of such remedies are chiefly to be ascribed to the hygienic measures that are employed at the same time.

All authorities now agree on the inefficacy of the remedies that were formerly recommended, such as tannin and its various modifications, gallic acid, nitric acid, and secale cornutum; and the writer is not convinced of the efficacy of even the newer and most recent remedies, such as ichthyol, sodium benzoate, fuchsin, methylene-blue, and strontium lactate. Acute cases, as has been stated, so frequently terminate favorably without these remedies that they are not adapted for

[1] A vegetable resembling peas, and eaten pods and all.

testing their value; in protracted cases the writer has either failed to observe any effect from these drugs or only a mild diuretic and ephemeral effect, which was often associated with an increase of the albuminuria.

Venesection also is without effect on the inflammatory process; local bleeding by means of cups or leeches is of some value in *diminishing the pain* in the lumbar region, and may therefore be tried in the case of vigorous patients. But in parenchymatous nephritis, which is usually complicated by impaired cardiac activity, venesection should be practised with great caution; only certain special conditions, such as pulmonary edema or uremia, justify its employment in individual cases.

Among the *symptoms* that require special intervention, the most important are the *dropsy* and the *uremia*, the treatment of which has already been discussed (see pp. 88 and 112). Severe *pain in the sacral and lumbar regions* may, as has just been remarked, be relieved by local blood-letting over the kidneys, although more conservative procedures, as dry cups, a Priessnitz's compress or a hot compress, often prove equally efficacious. *If marked hematuria persists for any length of time* without the quantity of blood diminishing very much, it may be proper, in order to guard against the development of anemia, to administer secale cornutum combined with tannin (for adults: sec. corn. 0.3 gm. (5 gr.), tannic acid 0.03 gm. (½ gr.), gum arabic powder 0.5 gm. (8 gr.), every three hours), the resulting constipation being combated by appropriate measures, such as water or oil enemata, castor oil, or bitter waters (alkaline sulphates). [Chlorid of calcium (5 to 10 gr.) every four hours may be used. Adrenalin chlorid may also be tried.—Ed.]

In all other disturbances that occur in the course of a renal inflammation, the caution not to use any remedy that might irritate the kidneys is to be constantly borne in mind. Inunctions with stimulating substances containing turpentine or tar and the like; mustard plasters, and fly blisters are therefore contra-indicated.

During *convalescence* the physician's vigilance must not be relaxed for some time. The patient should wear woollen underclothing and, if the conditions permit, should spend some time in a warm climate. He should avoid highly seasoned and irritating food, such as radishes, highly spiced dishes, hot sauces, and alcoholic beverages, and abstain for some time from any form of athletic exercise that might lead to overexertion. Later he may gradually begin to *harden the skin*, and if he bears milder applications may proceed to more severe hydrotherapeutic measures. The same caution applies to bodily exercise.

APPENDIX.

Hemoglobinuric Nephritis.—It has been mentioned repeatedly in these pages (see pp. 185 and 195) that the urine in acute nephritis not infrequently contains large quantities of hemoglobin without red corpuscles, or with very few of these elements, thus presenting a deviation from the usual clinical picture, particularly as regards the urinary changes. It has also been remarked that hemoglobinuria may either develop in the course of an already existing inflammation or may

represent the primary condition, the inflammatory process occurring as a sequel (see p. 63). The latter is in all probability the sequence of events when the nephritis is caused by intoxication with *cythemolytic poisons* or by *burns* and in those forms which accompany certain severe *cutaneous affections*. In the *infectious diseases*, which may also give rise to hemoglobinuric nephritis, the mechanism is a different one; for the renal lesion and the cythemolysis in the general circulation may occur at the same time and run a parallel course, whether it be that they are both due to the causal micro-organisms or their toxins or that each condition is brought about by a special injury. The latter assumption offers an explanation why every form of nephritis is not hemoglobinuric. It is not impossible, however, that the hemoglobin is dissolved out of the red blood-cells in the kidneys themselves and not in the general circulation, there being various arguments in favor of this view (see p. 64).

Hemoglobinuric nephritis occurs occasionally in a great variety of infectious diseases; it has been observed in *typhoid fever* (Immermann [1]), in *scarlet fever* (Heubner [2]), in *malaria* (Kelsch and Kiener, Rem Picci [3]), in *yellow fever*, and in *Winckel's hemoglobinuria of the newborn*. The writer once saw the condition in a case of *infectious polymyositis*.[4]

It appears, however, that this form of nephritis may develop independently of any demonstrable intoxication or infection, perhaps from exposure to cold (see p. 64). The writer remembers 2 such cases, of one of which he possesses a careful history.

Mrs. G., fifty-two years of age, had taken several courses of treatment in Marienbad for constipation and neurasthenia, but had otherwise been in fairly good health. About the beginning of July, 1893, during one of these cures, she was seized with slight chilliness and pain in the back and noticed that the urine was dark. At the first thorough examination, which was made on the 11th of July, the writer found that the patient was strongly built, rather obese, and somewhat pale, presented no abnormalities of the thoracic or abdominal organs and only a very slight edema over the ankles. There was no fever.

The urine was apparently normal in quantity, reddish yellow, turbid, markedly acid, and had a specific gravity of 1012. The filtrate contained a fair percentage of albumin and gave a distinct hemoglobin reaction with Heller's test. The sediment, which was quite abundant, contained numerous leukocytes, renal epithelium, which was in part well preserved, hyaline and coarse granular casts, uric acid crystals, and a few isolated red blood-corpuscles.

July 15. General condition good. Urine: quantity in twenty-four hours 1400 c.c.; appearance blood-red and turbid; specific gravity 1009; reaction feebly alkaline. The filtrate contains 2 per mille with Esbach's albuminometer, and gives the hemoglobin reaction both with Heller's test and on spectroscopic examination. The sediment contains leukocytes, squamous epithelium, and numerous bacteria.

July 18. Condition good. The urine is apparently normal in quantity, but owing to the hot weather and the resulting decomposition the entire quantity for twenty-four hours was not collected; it is turbid, distinctly acid, and has a specific gravity of 1014. The filtrate contains a moderate amount of albumin, 0.5 per mille, and a large percentage of hemoglobin. The sediment contains hyaline casts, casts covered with hemoglobin granules, hemoglobin in granular masses, a few isolated red blood-cells, and squamous epithelium.

[1] *Deutsch. Arch. f. klin. Med.*, xii., p. 502. [2] *Ibid.*, xxiii., p. 288.
[3] *Arch. de Phys. norm. et path.*, 1882; and *Il Policlinico*, 1898.
[4] *Deutsch. med. Woch.*, 1893, No. 39.

July 20. The urine is brownish-red, turbid, acid, and has a specific gravity of 1010; the albumin content is higher than before—1.5 per mille—and there is hemoglobin. The sediment contains finely granular casts, some of them of unusual length and very thin; hemoglobin granules, leukocytes, and squamous epithelium. There is no trace of edema.

July 27. The urine is abundant, of a pale-yellow color like white wine, acid, has a specific gravity of 1013, and contains small amounts of albumin and hemoglobin. In the sediment hyaline casts, leukocytes, squamous epithelium, and detritus consisting of hemoglobin are found.

August 1. The urine is almost clear, acid, and has a specific gravity of 1012. The filtrate contains 0.3 per mille of albumin and a little hemoglobin. The sediment the same as at the last examination.

After this time the percentage of albumin steadily diminished, the hemoglobin disappeared altogether, the sediment became less abundant and consisted of hyaline and pigmented granular casts, uric-acid crystals, and squamous epithelium. Occasionally the examiner succeeded in finding a red blood-cell. By the beginning of September the urine had become quite free from albumin, and remained so after the patient left her bed.

Recovery was complete and permanent, as the writer had the opportunity to determine a year later.

The patient attributed the disease to the drinking of ice-cold water.

The second case occurred in a boy about fifteen years of age. All the writer remembers about it is that it was also supposed to have followed exposure to cold, was attended by slight febrile movements and sacral pain, was without edema, that the blood contained hemoglobin and albumin as well as casts and renal epithelium in the sediment, and after a number of weeks returned to its normal condition. The general health in this case was also very little impaired.

The sole characteristic feature of this form of nephritis is the occurrence in the urine of free hemoglobin, not combined with red blood-cells. It is distinguished from simple hemoglobinuria by the fact that the urine contains a larger amount of albumin and that the sediment is richer in morphologic constituents, casts, leukocytes, and renal epithelium, indicating that the renal parenchyma is involved in the process, and by the appearance of uric-acid crystals, which are so common in acute nephritis.

The structural changes in the kidneys in this condition have been described on p. 190.

When this form of nephritis is a concomitant of a general infection or intoxication, its course depends altogether on that of the general disease; when it assumes the character of an independent disease, the writer believes from his experience with the 2 cases that have come under his observation that it runs a benign course with proper management and terminates in complete recovery.

The *treatment* is the same as that of acute parenchymatous nephritis—that is to say, chiefly hygienic and dietetic.

Cholera Nephritis.—Among those forms of renal disease which occur in the course of infectious diseases, that which accompanies *Asiatic cholera* and, although more rarely, severe cases of *cholera nostras*, in many respects occupies a unique position.

The peculiar behavior of the urine in cholera, particularly the diminution in quantity to almost complete suppression, could not escape the notice of even the earlier observers; the presence of albumin in the urine was first demonstrated by Hermann, in Moscow in 1830, and

later by Fr. Simon, in 1832. Reinhardt and Leubuscher,[1] Virchow,[2] and others were the first, however, to make careful microscopic examinations of the kidney structure during the epidemic of the year 1848. These investigations were followed by numerous others during later epidemics by such men as L. Meyer,[3] Buhl,[4] Lebert,[5] Kelsch,[6] Straus,[7] and in the last Hamburg epidemic by Klebs,[8] Eugen Fränkel[9] in association with Simonds and Rumpf,[10] Leyden,[11] Schuster,[12] Aufrecht,[13] and others. Broadly speaking, these investigations during various epidemics agree in the pathologic changes found, and present only some minor points of differences.

The *condition of the kidneys* varies with the stage of the disease during which death occurs.

In cases terminating fatally between four and nine hours after the onset of the disease, the kidneys, according to Fränkel and Rumpf, present nothing remarkable *macroscopically;* the color particularly gives no hint of any ischemic condition. The volume is practically normal or very slightly diminished; the color is a grayish-red; on section the cortex is not found to be increased in width, while the renal labyrinth and the medullary radiation are distinct. *Microscopically,* a *degeneration of the epithelium* in the convoluted tubules is found throughout the entire organ. The cells are greatly swollen, particularly on the side toward the lumen; they are cribriform and in a partial state of fusion. Some of the cells present a nuclear necrosis, which in exceptional cases may be found by itself without any marked changes in the protoplasm.

When death occurs somewhat later—*i. e.*, after several days—the kidneys are distinctly swollen and of a dark bluish-red color; the capsule can be readily stripped; and on the cut surface, which appears sticky, the boundary zone is intensely hyperemic, while the cortex is greatly increased in width and of a grayish-red and later yellowish color, the medullary rays being paler and of a more grayish-yellow tint. A milky fluid consisting of desquamated epithelial cells, casts, and detritus can be expressed from the papillæ. Microscopic examination shows great distention of the glomeruli as well as of the interstitial *capillaries,* so that they appear ready to burst, more intense swelling of the *epithelium* of the uriniferous tubules with fragmentation, going on to complete disintegration into finely granular detritus. According to Klebs, the *nuclei of the cells* are usually necrotic and have lost their power of taking the stain; while Fränkel and Rumpf as well as Simmonds only found coagulation necrosis in exceptional cases during the Hamburg epidemic. The *uriniferous tubules* in the cortex and the medullary substance are greatly distended and contain, in addition to the

[1] *Virchow's Archiv,* ii., 1849, p. 467, and *Charité-Ann.,* i., 1850, p. 223.
[2] *Ibid.,* iv., 1852.
[3] *Ibid.,* vi., 1854, p. 471.
[4] *Buhl, Henle und Pfeufer's Zeits. f. rationelle Med.,* vi., 1855, p. 1.
[5] *Lehrb. der praktischen Med.,* 1859, i., p. 212.
[6] *Progrès méd.,* 1874, Nos. 33 and 34.
[7] *Ibid.,* 1884, p. 481, and 1885, p. 10.
[8] *Allg. Path.,* i., p. 376.
[9] *Centralbl. f. klin. Med.,* 1852, No. 50, and *Deutsch. med. Woch.,* 1892, Nos. 51 and 52.
[10] *Deutsch. Arch. f. klin. Med.,* lii., 1894, p. 20.
[11] *Zeits. f. klin. Med.,* xxii., 1893, p. 1.
[12] *Deutsch. med. Woch.,* 1893, No. 27.
[13] *Centralbl. f. klin. Med.,* 1892, No. 45.

detritus derived from the disintegration of the epithelial cells, numerous hyaline and coarse granular casts. Aufrecht states that the distention and obstruction with detritus and epithelial casts take place first and chiefly in the uriniferous tubules of the medullary substance, all other changes (in the cortex) being the result of this obstruction; but his observations have not been confirmed. True fatty degeneration of the epithelium is observed only in protracted cases, and then only exceptionally. When death occurs during the third or fourth week of the disease, the only additional findings are the remains of disintegrated tissue and isolated hyaline casts within the convoluted tubules, the epithelial lining of which is found to have already been restored.

The only change found by the majority of investigators in the *Malpighian bodies* is an increase in the quantity of blood; Straus was the only one who found in every case desquamation in the loops and capsules and an albuminous transudate within the capsules. Leyden found the same thing in 2 cases and Rosenstein in 1.

The *interstitial tissue* remains quite free from cellular infiltration. Straus reports that it becomes distended with edematous fluid. Finally, there are found not infrequently *wedge-shaped infarcts* similar to embolic infarcts, which Litten[1] does not, however, believe to be embolic in origin, but to be in some way connected with changes in the veins. The *pelvis of the kidney* and the *ureters* contain thick mucoid masses (desquamated epithelium), and the mucous membrane is swollen and frequently the seat of small hemorrhages.

It appears, therefore, that the disease is a simple *parenchymatous nephritis in which the tubular lesions predominate.* This is in the main borne out by the findings in the urine, except that the quantity is diminished to a much greater degree than in parenchymatous nephritis generally, and it is well known that in severe cases there may be anuria lasting several days. If the anuria continues longer than five to seven days, the secretion is not re-established and the patient dies. When the disease is less severe and there is not complete suppression, the urine shows a high percentage of salt on account of the great loss of water, precipitates a sediment of urates, and usually contains albumin, the percentage of which is *relatively* higher than in parenchymatous nephritis from other causes, in which the loss of water is not so great. The first urine evacuated after the attack or after the period of complete anuria is usually still quite scanty, the specific gravity is slightly below normal (1012 to 1216), although not infrequently it is higher and may even exceed 1033 (Wyss[2]). The urine is dark, turbid, almost always albuminous, very rarely blood-tinged, and the sediment contains hyaline and granular casts, renal epithelium in various stages of disintegration, red blood-cells, leukocytes, and crystals of uric acid and calcium oxalate. With beginning convalescence and during its progress the quantity of urine gradually increases, while the sediment and albumin diminish in quantity.

A peculiar feature of the urine in cholera is a high percentage of

[1] *Zeits. f. klin. Med.*, 1893, xxii., p. 190. [2] *Arch. der Heilk.*, 1868, ix.

indican and ethereal sulphates (G. Hoppe-Seyler, v. Terray, Vas and Gara), owing to absorption of the products of intestinal decomposition. *Diacetic acid* also is frequently present in large quantities, and the excretion of *ammonia* is greatly increased (G. Hoppe-Seyler[1]).

As regards the *quantitative* composition of the urine, that which is evacuated first is very poor in urea and sodium chlorid, a finding that is readily explained by the state of inanition to which such patients are reduced. Vas v. Terray and Gara,[2] however, do not believe that the diminution of urea or of phosphoric acid is very great, while calcium and magnesium are greatly diminished in quantity, and both kinds of sulphuric acid, the preformed as well as the combined, are increased in the urine of cholera patients. During the stage of reaction all the constituents increase in quantity, the ethereal sulphuric acid at first more in proportion to the others, although later the normal relations are restored.

Dropsy is rare in the nephritis of cholera, as it is in other forms of parenchymatous nephritis; on the contrary, dropsical effusions have been seen to disappear rapidly in cholera patients from the concentration of the blood.

Two theories have been advanced to explain the changes found in the kidneys and their functional disturbance during cholera; one of them lays the greatest stress on the *circulatory disturbances*, while the other favors a specific *toxic action*.

In regard to the former theory, Griesinger[3] was the first to show the effect of the circulatory disturbances on the kidneys in cholera. Referring to the well-known investigations of C. Ludwig and Goll in regard to the interdependence of urinary secretions and the condition of the circulation, he regarded the cessation of urinary secretion and the pathologic changes in the kidneys as the results of a marked venous congestion coupled with diminished tension in the arterial system, a condition that exists also in cases of heart disease with disturbed compensation, except that the onset is much more sudden in cholera and is possibly modified and reinforced by the concentration of the blood. This interpretation Bartels professes to adopt in all its details, although he disagrees with Griesinger in regarding the interference with the blood-supply to the kidneys without accompanying engorgement of the venous system—that is to say, an "ischemia" of the kidneys—as the cause of the pathologic changes. Cohnheim,[4] Rosenstein, and particularly Leyden and Litten,[5] have adopted this view of Bartels, and appeal to the older experiments on the effect of interrupting the blood-supply to the kidneys, cited by Bartels, and to the painstaking investigations of Litten in regard to the changes produced in the kidneys by ligating the renal arteries—particularly coagulation necrosis, which they regard as identical with the changes found in cholera.

In this connection it is to be remembered that the changes in the

[1] *Berlin. klin. Woch.*, 1892, No. 43. [2] *Ibid*, 1893, Nos. 12 and 15.
[3] *Virchow's Handb. der spec. Path.*, ii., 2, 1864, p. 412. [4] *Allg. Path.* ii., p. 370.
[5] *Zeits. f. klin. Med.*, xxii., p. 182.

renal epithelium produced by cholera have been differently described by different observers, and especially that, according to the careful investigations made during the last Hamburg epidemic, coagulation necrosis is exceptional (see p. 208). In regard to the Malpighian bodies also, the effect of ligating the artery differs from the changes produced by cholera.

Litten has shown that after the ligature has been removed, Bowman's capsule regularly becomes filled with an albuminous transudate; while the majority of observers found no changes of any kind in the Malpighian bodies. Finally, it has been urged against the theory that all the phenomena, and particularly the structural changes, are to be ascribed to ischemia, that the kidneys do not show any signs of an ischemic condition (Klebs), and that in other diseases of the kidney accompanied by a marked loss of water the changes characteristic of cholera are absent, just as conversely these changes may be found in cases in which there has been no notable loss of water in the first place, and in which the loss had been compensated by the introduction of large quantities of fluid into the circulation (Rumpf and Fränkel).

The theory that the kidney changes in cholera depend on a *toxic action* has been defended by Klebs as well as by Rumpf and Fränkel, who regarded these changes as analogous to those observed in other infectious and toxic conditions. As there is no doubt that a toxin is developed in cholera, this view appears entirely justifiable; but the significance of the circulatory disturbances should not on that account be overlooked, for although the changes in the kidneys are practically the same in cholera as in other infections and intoxications, it is only in exceptional cases that an equal diminution of the excretion is observed, because the circulation is never disturbed to the same degree. The pulselessness, which has given the disease its distinctive name "asphyctic," the cyanosis, the coldness of the entire body surface, the weakening of the cardiac impulse and heart sounds going on to total disappearance, abundantly indicate how low the tension in the entire arterial system has fallen and how great the venous congestion, since the two conditions go hand in hand. It is the highest grade of cardiac insufficiency, the same process, as Griesinger has correctly remarked, as failure of compensation in valvular disease, but in its acutest and highest development—a condition to which "ischemia," in the ordinary acceptation of the word, should not be applied.[1]

The *loss of water* is of secondary importance. It leads to concentration of the blood and other body fluids, and thereby impedes their onward flow, but in itself—*i. e.*, without impairment of the force of the heart—it cannot do much harm. This is proved by the effect of diaphoretic measures in which the abstraction of water is not less than in many severe cases of cholera; it is also proved by an observation of Rumpf and Fränkel that, when the water is restored by the introduction of fluid, the functional disturbance of the kidneys and the structural changes take place just the same.

[1] Virchow, who introduced the word "ischemia" into pathology, uses it to designate a local want of blood or partial anemia (*Hand. der spec. Path.*, i., 1854, p. 122).

It is the writer's opinion, therefore, that the nephritis, and incidentally the changes in other organs as well, that occur during cholera represent the combined effects of a toxin and extreme cardiomuscular insufficiency, a view that has been similarly expressed by Rosenstein[1] and Fürbringer.[2]

The *toxin* acts injuriously upon the heart muscle, on the blood-vessels, and through them on the general circulation, the nutrition and function of the renal epithelium being the first to be affected; but in addition the toxin directly affects the renal parenchyma, and its action is not only intensified but also prolonged locally by the stagnation of the blood-current. The changes in the kidneys and in the urine are attributable in part to the general venous stasis of the highest degree, such as is produced by a diminution in the force of the heart (see p. 149), and in part to the infectious or toxic nephritis (see p. 191), and these changes are in many cases intensified by the abstraction of water and desiccation of the tissues.[3]

The *coma* during the stage of reaction is not *uremic* in character, at least not always, as was formerly supposed. It is not necessarily associated with a diminution of the nitrogen in the urine—*i. e.*, the insufficiency of renal action is not great enough to produce uremia. The coma must therefore be regarded as the effect of a special toxin.

From a *practical standpoint* cholera nephritis, which is recognized without any difficulty, has a certain bearing on the prognosis, the diminution of urinary secretion being a valuable although not absolutely trustworthy criterion of the severity of the disease and the danger to life. The longer the anuria lasts, the more unfavorable in the main is the prospect of recovery. The longest duration of anuria compatible with recovery was formerly given as four to six days, but Rumpf and Fränkel in the Hamburg epidemic not infrequently saw cases recover after an anuria of three to seven, and in exceptional cases twelve to fifteen days. It is possible, therefore, that recent methods of treatment are not without influence on this change which has come about in the prognosis.

The nephritis in cholera requires no special *treatment*.

Kidney of Pregnancy.—This term is used to describe a peculiar acute affection of the kidneys caused solely by pregnancy. Its inflammatory nature is not admitted by all authorities, and there is a great divergence of opinion in regard to its nature and etiology. It is needless to say that those cases in which pregnancy develops during an already existing renal affection, or, conversely, in which a pregnant woman is overtaken by an ordinary nephritis as the result of exposure to cold, infection, or intoxication,[4] do not belong to this class. Nor does it include the renal congestion which sometimes develops during pregnancy, the symptomatology of which differs in many respects from that

[1] *Nierenkrankh.*, 4th ed., 1894, p. 120. [2] *Deutsch. med. Woch.*, 1894, No. 2.

[3] See "Ueber die Wirkung der Wasserentziehungg," A. Czerny, *Arch. f. exper. Path.*, xxxiv., 1894, as also Pernice and Scagliosi in *Virchow's Archiv*, cxxxix., 1895, p. 155.

[4] The writer has repeatedly seen attacks of acute nephritis in pregnant women which could only be attributed to the use of purgatives.

of the kidney of pregnancy. If these two renal conditions are excluded, the remaining cases of nephritis occurring during pregnancy may with some show of reason be attributed to that condition and regarded as specific; but the number of such cases must be small and probably includes cases of various kinds, for the descriptions given by authors of the "kidney of pregnancy" and its symptoms are anything but uniform.

Etiology and Pathogenesis.—The disease develops most frequently during the second half—never before the third month—of the first pregnancy. Youth and a twin pregnancy are said to be special predisposing factors. Sometimes the disease recurs during a subsequent pregnancy.

Rayer, the first observer to point out the coincidence of pregnancy and nephritis,[1] believed that the pressure exerted on the pelvic organs by the enlarged uterus was in part responsible for the production of the disease, which he called "*nephritis simplex*," while the form which he distinguished as "*nephritis albuminosa*," and which is much rarer in pregnant women, he regarded as the result of exposure to cold. He evidently does not attribute any specific influence to *pregnancy* as such. Not long after him Lever[2] called attention to the frequent occurrence of *eclampsia* in pregnant women whose urine contained albumin, without, however, expressing any opinion in regard to the special nature of this albuminuria or of the renal affection which produces it. Since that time eclampsia has come to be recognized as the *result of albuminuria or of kidney disease*, and the question of the connection between the two conditions became the subject of lively discussion, until it was recognized that eclampsia can occur without albuminuria and, conversely, that the latter may be the *effect of eclampsia*. Devillier and Reynauld,[3] who wrote an elaborate treatise on the albuminuria of pregnant women, which is frequently accompanied by dropsy, also refer to the constant occurrence of eclampsia, but they remain in doubt whether the changes that they found correspond to Rayer's "*nephritis albuminosa*" (Bright's disease). They are inclined to regard as the cause of the disease not a venous stasis in the kidneys, but an *abnormal condition of the blood*, which they say is frequently present during pregnancy. On the other hand, Frerichs[4] who regarded it as proved that these cases are the same as Bright's disease, laid great stress on the *stasis in addition to the changes in the blood*. He regarded the eclampsia of pregnant and puerperal women as uremic. Virchow[5] also regarded the renal changes in pregnancy as in the main inflammatory, and compared them to the parenchymatous inflammations of other organs, especially the liver and possibly also the spleen, which are also caused by pregnancy. He did not admit that eclampsia had been proved to be constantly uremic in character. Bartels,[6] in the main, adopted this view. Later Virchow[7] called attention to the frequency of fat emboli in the glomerular capil-

[1] *Loc. cit.*, i., p. 507, and ii.
[2] *Guy's. Hosp. Rep.*, April, 1843.
[3] *Arch. gén. de méd.*, 4th Ser., xvii., 1848, p. 48.
[4] *Loc. cit.*, p. 219.
[5] *Gesammelte. Abhandl.* Frankfurt a. M., 1856, p. 778.
[6] *Loc. cit.*, p. 272.
[7] *Berlin. klin. Woch.*, 1886, No. 30; Jürgens, *ibid.*

laries and in the pulmonary vessels during the puerperium, whether eclampsia was present or not. Jürgens believed that these emboli were formed from the fat in the abdominal walls and in the liver, which suffered compression during the eclamptic convulsions. According to Rosenstein,[1] the most important factor in the production of "the albuminuria of pregnancy and the associated renal affection" is the increased pressure within the abdomen, which chiefly affects the pelvic veins and ureters. He regards eclampsia in many cases as the result of changes in the circulatory conditions in the brain and acute anemia with or without edema, and as to the production of the latter adopts the same view as Traube proposed for that of uremia (see p. 102). But aside from the objections to this theory already referred to, it should be pointed out that M. Stumpf[2] usually found the blood-pressure diminished during eclampsia. Finally, Leyden[3] differs with earlier authors inasmuch as he rejects both the theory of renal congestion and that of acute nephritis, and believes that eclampsia is a peculiar process produced by arterial anemia and developing as the result of anemia of the kidneys with fatty degeneration. Whether the anemia is produced by swelling of the cortex or by the stagnation of the secretion in the ureters still remains to be decided. But it is difficult to understand how the fatty change, which he expressly says is not a fatty *degeneration* but a fatty *infiltration*, can be produced by anemia.

A *parasitic* origin for the kidney of pregnancy has been assumed by a number of authors, Doléris,[4] Blanc,[5] A. Favre,[6] Gerdes,[7] Hergott,[8] and refuted by F. Hofmeister,[9] Haegler,[10] Fehling,[11] Döderlein.[12] Nevertheless Favre recently again put forward the opinion that bacteria play the principal part in the production of the kidney of pregnancy, which he regards as a "parenchymatous nephritis," and that the development of these micro-organisms is favored by deficient renal function as the result of compression of the ureters, of the renal veins or arteries, or the kidneys themselves. Puerperal eclampsia, according to Favre, is the result of ptomainemia—that is, an accumulation of products of bacterial decomposition. Other observers have pointed out that toxic metabolic products are retained in the body during pregnancy as the result of the deficient renal function—that is to say, that there is a *toxemia* which manifests itself by diminished toxicity of the urine, as contended by Bouchard (see p. 105). Chambrelent,[13] E. P. Davis,[14] Ludwig and Savor and A. Gönner[15] also adopted this view, which finds

[1] *Berlin. klin. Woch.*, 1886, No. 30; Jürgens, *ibid.*, p. 101.
[2] *Münch. med. Woch.*, August, 1887.
[3] *Zeits. f. klin. Med.* ix., p. 126, xi., p. 133; *Charité-Ann.*, 1889, xiv., p. 129.
[4] *Comptes rend. de la soc. de Biol.*, 1883, p. 504, and *Progrès med.*, 1883.
[5] *Contribution á l'etude de la pathogénie de l'albuminurie*, etc., Lyon, 1889.
[6] *Virchow's Archiv.*, cxxiv., cxxvii., cxxix., cxli.
[7] *Deutsch. med. Woch.*, 1892, No. 26.
[8] *Progrès méd.*, 1892, No. 27.
[9] *Fortsch. der Med.*, 1892, Nos. 22 and 23.
[10] *Centralbl. f. Gynäk.*, 1892, No. 51.
[11] *Ibid.*, No. 10.
[12] *Ibid.*, 1893, No. 1.
[13] *Semaine méd.*, 1892, Nos. 9 and 10, and *Arch. de Gynécol.*, November, 1893.
[14] *Am. Jour. Med. Sci.*, 1894, p. 147.
[15] *Monats f. Geburtshülfe u. Gynäk.*, 1895, 5; and *Centralbl. f. Gynäk.*, 1901, No. 29.

some corroboration in the observations of Th. H. Van de Velde, who found that the blood—but the urine as well—of pregnant rabbits was more toxic than that of non-pregnant rabbits.[1]

Schmorl [2] advanced the theory that eclampsia is due to embolism by the propulsion of placental giant cells into the organs, particularly the lungs. Lubarsch,[3] Pels-Leusden,[4] Maximow,[5] and K. Winkler [6] have confirmed the frequent finding of these cells, but offer a different interpretation, regarding them as the result of the labor-pains and not as characteristic of eclampsia. J. Veit asserts that during pregnancy cells make their way from the periphery of the ovum into the blood, and this marked increase of albumin in the blood leads to albuminuria or the kidney of pregnancy.[7]

The divergence of opinion is not to be wondered at when the difficulties of determining in the first place what is the "kidney of pregnancy," and in the second place what circumstances peculiar to pregnancy have any influence on its production, are borne in mind. It is always difficult in a given case, without an accurate knowledge of the former medical history, to exclude the existence of some renal affection not dependent on pregnancy. On the other hand, a combination of symptoms that really is dependent upon pregnancy and parturition may develop and strongly suggest the diagnosis of the kidney of pregnancy, even when such a condition is not present. Suppose, for instance, a perfectly healthy woman a short time before her delivery develops edema of the legs from abdominal stasis, as so frequently happens, and as the result of the labor-pains albuminuria is superadded, or, if the urine already contained albumin from stasis, possibly casts in the urine (see p. 46), and during labor eclamptic convulsions make their appearance, which as we know might have occurred without any albuminuria (see p. 216—Ingerslev). Now, if all these symptoms should be present, we should have before us a symptom-complex which would seem to justify the diagnosis of "kidney of pregnancy," although as a matter of fact the condition is a combination of *stasis*, due it is true to the pregnancy, and certain changes in the *central nervous system* produced by labor-pains, and all the symptoms may subside at once after delivery, even after a few hours. There is no doubt in the writer's mind that a number of cases described as "kidney of pregnancy," which disappear so rapidly that they arouse the astonishment of observers, should be interpreted in this way.

Those cases which appear to have a better claim to the diagnosis of "kidney or nephritis of pregnancy" are probably due to a variety of causes, which explains why their pathologic and clinical features have been described in so many different ways.

The purely *local conditions*, the increased intra-abdominal pressure

[1] *Wien. klin. Rundschau*, 1896, No. 50.
[2] "Pathol.-anat. Untersuchungen über Puerperaleklampssie," Leipsig, 1893.
[3] Lubarsch, *Fortschr. der Med.*, 1893, Nos. 20 and 21.
[4] *Virchow's Archiv*, 1895, cxlii., p. 1.
[5] *Ibid*, cli.
[6] *Ibid*, cliv., and *Festschr. f. Ponfick*, Breslau, 1899.
[7] *Berlin. klin. Woch.*, 1902, Nos. 22 and 23.

acting chiefly on the kidneys, are not sufficient as an explanation, for identical or similar increase of pressure in conditions other than pregnancy, as tumors or ascites, cause a different set of alterations from those that are ascribed to the "kidney of pregnancy." For this reason the stagnation of the urine by the pressure of the enlarged uterus on the ureters, on which so much stress has been laid by Halbertsma,[1] cannot be accepted as the chief etiologic factor, although it may have a contributory significance.

When it is remembered that the kidneys of a pregnant women have to work for two organisms—that of the mother and that of the child—it will be readily understood how an apparently slight obstacle may lead to great disturbances, particularly as the conditions are rendered still more unfavorable by the lack of room. It is not necessary that a marked dilatation of one or both ureters be found, although as a matter of fact such a condition has been reported, since that would be the expression of a very high degree of urinary stagnation; under the conditions that obtain during pregnancy, the renal function may become insufficient without any gross mechanical obstacle being visible to the naked eye. Another consideration is that more toxic products are probably formed during pregnancy than in the normal metabolism of a non-gravid woman, because there are really two organisms living in one.

That the poison in the body is not carried off by the kidneys in pregnant women as thoroughly as under ordinary conditions may be inferred directly from the above-mentioned investigations in regard to the increased toxicity of the blood and the diminished toxicity of the urine, and in view of what has just been said, we can readily understand that the blood might become overloaded with excretory products which normally ought to be carried off by the kidneys—in other words, that a toxemia, in the widest sense of the term, might take place. The exact nature of these noxious bodies, whether they are the products of microparasites ("fungi" according to Favre) or some other poison, has not been determined. There are cases that have been carefully investigated without anything having been found to justify the assumption that the eclampsia had a bacterial origin (Pels-Leusden),[2] although bacteria have been found in other cases, so that it does not appear that every case of eclampsia is due to the same cause. The writer is inclined to regard the "kidney of pregnancy" as the result of a "toxemia" due to insufficient renal function.

This theory of a toxemia produced in this way also appears to be more plausible in the explanation of *eclampsia*. In those cases in which insufficiency of the kidneys betrays itself by pronounced symptoms of nephritis or which present nothing but albuminuria without any other abnormalities in the urine, one will be forced to follow the traditions of the fathers and regard the intoxication as uremic in character. But the kidneys may fail to act even when there is no pronounced nephritis, or when there is no albuminuria; Ingerslev[3] succeeded in collecting 106

[1] *Centralbl. f. die med. Wissenschaft*, 1871, No. 27. [2] *Virchow's Archiv*, 1895, cxlii., p. 1.
[3] *Zeits. f. Geburtshülfe u. Gynäk.*, vi., p. 171.

cases of eclampsia without albuminuria, in which the kidneys at the autopsy were found to be healthy.

Hence, as the writer would like to emphasize once more, albuminuria in a pregnant woman is not necessarily a sign of true *nephritis*, and, conversely, the toxemia alone suffices to produce eclampsia, and may in addition give rise to a (toxic) nephritis.

It is probable that, owing to the changed condition of the blood during pregnancy, the nervous centers are *more irritable*, and there are animal experiments by Blumreich and L. Zuntz[1] that would seem to confirm this theory. That being the case, any stimulus, be it feeble or strong, will suffice to bring on an eclamptic attack. In most cases the stimulus is supplied by the labor-pains (see Uremia, p. 111), particularly in primiparæ.

Pathologic Anatomy.—Even after the exclusion of cases in which alterations of some standing are found in the kidneys, or the signs of a recent exacerbation of an older process or changes caused by the acute febrile infection which carries the patient off during pregnancy, the statements of authors in regard to the conditions found in the "kidney of pregnancy" present many divergencies, as may be shown by the following: Bartels asserts that the condition of the kidneys found in the cadaver is quite as variable as in other forms of acute nephritis, and that the hemorrhagic form is exceptional, because in pregnancy the renal disease seldom or never runs a fulminant course, as in scarlet fever, typhoid fever, and other infections. Grainger Stewart also includes the "kidney of pregnancy" among the acute inflammatory forms. Rosenstein describes the kidney as "more or less hyperemic, quite frequently pale, and somewhat enlarged and swollen"; E. Wagner, on the other hand, says that it is "oftener anemic than hyperemic, slightly yellowish, somewhat softer and usually somewhat larger than normal"; and, finally, Leyden and Hiller[2] describe it as enlarged, pale, and of a grayish-yellow or brownish-yellow color. All the observers agree that the *microscopic* changes are strictly confined to the parenchyma, and that the interstitial tissue remains absolutely intact; Mayor[3] is the only one who found the connective tissue edematous and thickened and containing numerous minute fat-granules which were heaped up chiefly around the blood-vessels.

The changes in the parenchyma, according to Rosenstein, consist of swelling (edema), and changes in the quantity of blood, with its logical consequence. The Malpighian bodies he describes as usually normal and rarely diminished in size; Leyden, on the contrary, found the glomeruli intact in only 1 case, except for the presence of deposits of fat-granules here and there on the coils. Three other cases were characterized by fatty change, affecting chiefly the epithelial lining of the vascular loops. Hiller made the same observation in his case. As the writer has already mentioned, Virchow does not regard this as a fatty change, but looks upon the fat as embolic in origin (see p. 213).

[1] *Deutsch. med. Woch.*, 1902, No. 2, p. 12. [2] *Zeits. f. klin. Med.*, ii., p. 685.
[3] "Lesions des reins chez les femmes en couches," *Thèse*, Paris, 1880.

Obstruction of the glomerular loops with parenchyma cells is regarded by many as characteristic of the eclampsia of pregnant and parturient women.

Most authors agree in describing the *epithelial cells of the uriniferous tubules*, particularly of the convoluted ones, as being in a state of more or less pronounced fatty degeneration; but here again Leyden, in a case characterized by marked fatty degeneration of the glomeruli, found the epithelium but little changed. Mayor, after treating the renal tissue with osmic acid, found the condition described by Cornil as vacuolated or vesicular degeneration of the epithelium, and also found red blood-cells in the uriniferous tubules. The tubules in the medullary substance occasionally contain hyaline casts.

The fatty change in the glomeruli as well as in the epithelial cells must be due to *fatty infiltration* and not to *fatty degeneration*, as Leyden and Hiller have repeatedly insisted, because, after the fat has been removed with turpentine and alcohol, the cells practically regain their normal appearance.

According to the writer's own experience, which includes a few indubitable cases of "kidney of pregnancy," there is in addition to the marked pallor of the parenchyma, chiefly fatty degeneration of the epithelium in the convoluted tubules as well as in the glomerular coils.

Among other pathologic findings may be mentioned more or less extensive edema and, somewhat more rarely, effusions into serous cavities. When death occurs during pregnancy the enlarged uterus is found to contain the product of conception and presents the corresponding changes; when death occurs after delivery, the organ presents the signs of that condition, and very frequently, if death has been preceded by eclampsia, there are changes in various organs, such as edema, emboli, hemorrhage in the brain, hemorrhage and necrosis in the liver, and edema and emboli, particularly emboli, consisting of hepatic cells in the lungs, which are regarded by some as the cause and by others as the effects of eclampsia (see p. 214),

Symptoms, Course, and Termination.—Unlike other acute, especially inflammatory, conditions of the kidneys, the disease develops imperceptibly, and at first gives rise to but slight disturbances not essentially different from many of the symptoms that often occur during pregnancy, and therefore receive little attention because they are attributed to that condition alone. Such symptoms are sacral pain, frequent micturition, slight swelling of the feet, and a variety of others that are not in the least characteristic.

The only important sign is the change that takes place in the urine; and here again the statements are as various as those in regard to the condition of the kidneys themselves. The only points that are conceded are that the *quantity* is diminished, the *specific gravity* increased, and that the *urine* usually contains *albumin*. But even in regard to these fundamental changes there are certain differences of opinion. Thus, for example, in one of the cases reported by Leyden[1] as typical

[1] *Zeits. f. klin. Med.*, ii., p. 186, Case 3.

"kidney of pregnancy," the specific gravity at the height of the disease was 1005, while the total daily quantity was 500 c.c., and later, as the quantity increased, the specific gravity rose to 1006–1012. The coloring-matter is said to be diminished—in other words, the urine is said to be paler by Rosenstein, E. Wagner, P. Fürbringer,[1] and Prior;[2] on the other hand, the color is described as remarkably *dark*, brownish-red, and muddy by Leyden and Hiller.

Judging from the writer's own observations, which, if he includes only those cases in which the diagnosis is absolutely certain, are not very extensive, the urine is pale, the percentage of albumin is high, and the rather scanty sediment contains morphologic elements.

The sediment, which is always present, but according to the writer's observations is usually scanty in amount, is said by Bartels to be exactly the same as in the other forms of acute nephritis, except that it is rare to find any great admixture of blood. Leyden, who has devoted special attention to these conditions, states that the urinary sediment presents so many variations that it is not possible to draw definite conclusions. Personally the writer has only found a few hyaline casts and leukocytes. Sometimes, in spite of albuminuria, no sediment is found during the entire course of the disease. Occasionally, but not frequently, and only when the quantity is very small, the urine may be very bloody, the sediment is often very abundant, and consists of hyaline casts and lymphoid cells, and frequently a greater or less abundance of blood-corpuscles. Sometimes, but not by any means always, it presents a variegated appearance, as in Hiller's case, in which *hematoidin crystals* in great abundance were found both free in the fluid and seated upon the casts. In other cases granular and even distinctly degenerated fatty epithelial cells (fatty granule cells) were found. Hiller asserts that *hematoidin crystals* had been found in all the cases up to his time, and always in relatively large numbers; but his statement is contradicted by most of the cases reported by Leyden and others as well as by the writer's own experience.

In a case of eclamptic coma H. Cramer[3] found turbid milky urine, the turbidity being due not to fat but to finely divided albumin.

Edema is said to develop slowly and to spread from below upward; sometimes the face and the upper extremities also become swollen. [The editor would question the correctness of the statement that the edema always begins below and spreads upward. He believes he has seen instances in which, with the "kidney of pregnancy," edema has been noticed in the face and hands as soon as in the lower extremities.—Ed.] Of the effusions into serous cavities, hydrothorax is mentioned most frequently.

A somewhat more infrequent symptom is *albuminuric retinitis*. P. Silex[4] remarks that the visual disturbance develops slowly in the course

[1] "*Die Krankheiten der Harn- u. Geschlechtsorgane*," Braunschweig, 1884, p. 47.

[2] "*Klin. Handb. der Harn- u. Sexualorgane*," by Zülzer-Oberländer, Leipzig, 1894, p. 381.

[3] *Deutsch. med. Woch.*, Feb. 6, 1902.

[4] *Berlin. klin. Woch.*, 1895, No. 18.

of weeks or months, usually in primiparæ, and reaches its full development in the second half of pregnancy. The condition has a tendency to recur in subsequent pregnancies, and renders the prognosis more unfavorable each time. On the whole, the prognosis is not so bad in the albuminuric retinitis of pregnancy as in the form which accompanies acute and chronic "Bright's disease."

If uremia develops, amaurosis may appear as in the ordinary form of nephritis.

The symptoms all become intensified as pregnancy progresses, but disappear rapidly after delivery unless some accident occurs; within a few days, and according to some even after a few hours, or more rarely after weeks, the condition clears up entirely. The quantity of urine becomes increased, the percentage of albumin as well as the sediment diminishes, and the dropsy subsides at the same time. The outlook, so far as the retinitis also is concerned, improves the more promptly pregnancy is terminated.

There is danger to life in about 25 per cent. of all pregnant women on account of the epileptiform attacks known as *eclampsia of pregnancy and parturition*, which occur shortly before or during delivery, or very rarely after labor is completely terminated. [If we understand this statement aright—viz., that 25 per cent. of all pregnant women are subjected to danger from eclamptic seizures—we must say that the percentage seems unusually high. Surely not 25 per cent. of pregnant women have eclampsia. We fear a misprint or a misunderstanding on our part. Perhaps 25 per cent. of cases of eclampsia are fatal.—Ed.] The writer will not enter into a description of these attacks, which do not differ from epileptiform convulsions, and like them are heralded by various kinds of premonitory signs and an aura; they also resemble the acute uremic attacks which have already been described (see p. 95). The various explanations that have been offered for this eclampsia have already been discussed, and it was also mentioned in that connection, although it does no harm to emphasize the statement once more, that the complication may develop in pregnant or parturient women who up to that time have had *no albuminuria*, showing that there was no renal congestion or any form of nephritis. Under the influence of labor, whether it be accompanied by eclampsia or not, a temporary albuminuria may develop (see pp. 38 and 150); and, on the other hand, eclampsia may lead to albuminuria. The "kidney of pregnancy" is, therefore, not a necessary condition for the occurrence of eclampsia. It may, however, be simulated, and there is no doubt that it has frequently been diagnosticated in cases in which, although there was no nephritis, albuminuria and tube casts were present as the result of pregnancy or in consequence of labor and eclampsia.

The termination of eclampsia in a large proportion of the cases is death. The percentage of mortality is variously given; the older statements make it somewhat higher—more than 30 per cent.—than the more recent ones, the difference being possibly due to improved methods of treatment. To what extent true "nephritis of pregnancy" is con-

cerned in the production of the attacks cannot be decided, because, as has just been remarked, it is difficult to eliminate the cases of eclampsia accompanied by albuminuria due to other causes than nephritis. The cases that are not attended by eclampsia usually end in recovery after the woman has been delivered; the development of chronic nephritis secondarily is rare, although it has sometimes been observed (Leyden and Weinbaum [1]).

The effect of eclampsia on the product of conception is even more baneful than on the mother. More than half the children born of eclamptic mothers die, and those that live frequently present albuminuria and other signs of nephritis. The subsequent course of the disease in such infants is not known.[2]

Diagnosis.—In order to make a diagnosis of "nephritis of pregnancy," it is necessary first to demonstrate the existence of a nephritis or, at least, of an affection differing from simple renal congestion, and, in the second place, that the affection did not exist before the beginning of pregnancy, but developed during that condition without the operation of any other known cause. It is obviously difficult to demonstrate these facts, and therefore a positive diagnosis cannot always be made.

Above all, the mere finding of albumin or casts or both together must not be accepted as a proof of "nephritis"; for it cannot be repeated too often that albumin and casts may be produced by simple congestion from distention of the abdomen, and the contraction of labor-pains or eclamptic convulsions, without a true inflammation of the kidneys being present.

The urinary findings in themselves are not decisive; for identical conditions, particularly so far as the sediment is concerned, occur in acute as well as in chronic forms of Bright's disease. It is to be remembered that a urine which is characteristic of *a chronic form of Bright's disease* may lose these typical qualities so far as color, quantity, specific gravity, and sediment are concerned, on account of the congestion, which is unquestionably a contributory etiologic factor during pregnancy and in a higher degree during labor. In such cases the history and the demonstration of cardiac hypertrophy or of an *old* (not a recent) retinitis may clear up any doubt that may exist in the physician's mind.

In order to exclude an *acute nephritis not caused by pregnancy*, a painstaking inquiry into every part of the history is necessary, and in many cases the diagnosis is even then impossible. If the condition clears up rapidly after delivery, it argues in favor of a nephritis of pregnancy in doubtful cases. From *renal congestion* the kidney of pregnancy is distinguished by the pale color of the urine, the low specific gravity, the demonstration of leukocytes not derived from the urinary passages or the parturient canal—*i. e.*, especially mononuclear leukocytes in considerable abundance—and renal epithelium presenting

[1] *Berlin. klin. Woch.*, 1895, No. 18.

[2] See Fr. M. Jochkewitch, "Contribution à l'étude de l'allaitement chez les albuminuriques," *Thèse*, Paris, 1899.

some degree of fatty change; while, on the other hand, in renal congestion the urine presents the characteristics that have already been described, and signs of congestion, such as varicose veins, are frequently found in other parts of the body.

Prognosis.—Eclampsia is the only serious factor in the prognosis, and as it does not develop until shortly before or during delivery or immediately after the termination of labor, and can never be forseen, the prognosis should always be given with great caution. [While it is true that eclampsia cannot be foreseen with certainty, it must be said that one may often with reasonable certainty predict its onset by certain symptoms that may without impropriety be called premonitory. Among these are epigastric pain, nausea and vomiting, headache, unusual dizziness, and flashes of light. In any pregnant woman who is beyond the fifth month, one should regard headaches of increasing frequency and severity, epigastric pain not clearly due to dietetic error, unaccountable vomiting, puffiness of the hands and face, as symptoms that portend eclampsia, and that should lead to immediate examination of the urine, which will commonly be found heavy with albumin.—Ed.] The prognosis cannot be said to be absolutely favorable until all danger of eclampsia has passed—*i. e.*, in most cases three days after the termination of labor, or after the eclampsia has been successfully overcome. The development of secondary chronic nephritis after "kidney of pregnancy" is rare, and such an event can probably be prevented in most cases by judicious management.

Treatment.—As a *prophylactic measure*, women who have once suffered from nephritis of pregnancy may be advised to guard against another pregnancy. [This is undoubtedly the safest advice to give. But many wives are anxious to become mothers, and when the dangers are clearly set before them, the risk is not as great as during the first pregnancy, because the "kidney of pregnancy" is less frequently met with in multiparæ, and because the woman and physician will now be on the watch, and not only will undue effort be made to secure a hygienic mode of life, but frequent urinalyses will be made and the approach of danger generally discovered in this way. It is, of course, assumed that some time has elapsed since the first pregnancy, and that by careful examination of the urine, the heart and retina, the physician is satisfied that no chronic nephritis is present.—Ed.]

The *treatment of the renal disease* itself is concerned chiefly with hygiene and diet, as in other forms of acute nephritis, and has already been discussed in a former section (p. 202). The writer will merely insist once more on the beneficial effect of rest and the horizontal position on the hypostatic congestion in the lower half of the body and in the kidneys.

As everything depends on preventing the occurrence of eclampsia, which is assumed to rest on a toxemia caused by deficient renal action, it is important, as soon as the earlier signs of failing kidney action, particularly edema, have made their appearance, to stimulate the renal, intestinal, and cutaneous excretion without, of course, doing anything

to irritate the kidneys. Mild laxatives, warm baths, and so-called refrigerant diuretics are indicated, as has been mentioned in connection with the treatment of dropsy (see p. 88). To combat the actual attacks of eclampsia, the remedies which *diminish the excitability of the nervous centers* have been found most useful: *chloral hydrate* in the dose of 2 gm. (30 gr.), given in the form of an enema on account of the inability to swallow, *morphin* hypodermically, and *chloroform* by inhalation. These drugs should be given whenever a violent attack comes on, and their administration continued until profound narcosis is achieved, with due regard, of course, to the behavior of the heart, the respiration, and the pupillary reaction. Unfortunately, the administration of narcotics has an unfavorable effect on the life of the fetus. *Venesection*, which was formerly practised, is not much used now, perhaps too little, as the withdrawal of blood at the same time removes from the body a part of the toxins which cause the disease. It is, of course, admissible only in the case of vigorous, full-blooded individuals with good heart action. *Infusion* or *transfusion* of physiologic salt solution, human blood or serum, with or without venesection, may also be employed to wash the poison out of the body and thus exert a favorable influence on the eclampsia.

The *congestion in the head*, which develops progressively during the convulsions, is best combated by means of an ice-bag or cold compresses, or in appropriate cases and depending on circumstances by means of wet or dry cups applied to the nape of the neck, or by leeches applied behind the ears. [Some attempts have been made to relieve symptoms of eclamptic coma—supposed cerebral edema and pressure—by lumbar puncture, but so far with very uncertain and indifferent success.—Ed.]

Since the eclampsia usually subsides after the uterus has discharged its contents, labor, if it is in progress, should be terminated as speedily as possible. Whether labor should be induced artifically, and at what period such interference is indicated, is an obstetric question which has been answered in different ways and which does not fall within the present discussion. Experience shows that the nearer the normal term of pregnancy, the more favorable is the result of the artificial induction of labor to both mother and child. [The question of induction of premature labor is, as said, an obstetric one, but our own views may be hinted at when we say that we have several times in the case of the kidney of pregnancy regretted not having induced labor; we have never regretted having induced it prematurely when the complexus of albuminuria, edema, nausea, headache, and epigastric pain was present. Temporizing measures seem under these circumstances hazardous.—Ed.]

The question whether a *woman with albuminuria shall be allowed to nurse her child* is of great practical importance. The writer says advisedly a woman with albuminuria and not with nephritis, because, as he has already explained, the diagnosis cannot always be made positively immediately after labor when the antecedent history is

unknown. The question cannot, therefore, always be decided at once. It is needless to say that the first requisite is that the mother shall be well nourished and vigorous; these two conditions being granted, the causes of the albuminuria must be weighed. (1) The albuminuria of passive congestion is not a contra-indication. (2) True nephritis of pregnancy, in the strict sense of the term, is not a contra-indication. (3) Any other form of nephritis due to infection or intoxication bars the woman from nursing her child on account of the danger of transmitting the disease. (4) In chronic non-indurative parenchymatous nephritis the woman should not be advised to nurse her child. (5) In chronic indurative nephritis the children do not appear to suffer, but the mother's health is, on the other hand, unfavorably affected. (See Jochkewitch, foot-note, page 245 of text.)

CHRONIC DIFFUSE NON-INDURATIVE NEPHRITIS (CHRONIC PARENCHYMATOUS NEPHRITIS).

ETIOLOGY AND PATHOGENESIS.

In its purest form this variety of nephritis, which corresponds to Weigert's "subchronic" and to some extent his "chronic" form, is very rare. Only a fraction of those cases which are still frequently described as the "second stage of Bright's disease" after Frerichs, Grainger Stewart, and others, as the "large white kidney" after S. Wilks, and as "chronic parenchymatous nephritis" after Bartels, belong to this group; the remaining majority represents a *combination of inflammatory processes with amyloid degeneration*, which formerly was either unknown or overlooked.

The impossibility of separating this form from the indurative forms of chronic nephritis on the one hand, and from acute nephritis on the other hand, cannot be emphasized often enough. Acute nephritis is connected with chronic nephritis by numerous intermediate cases characterized by a subacute or subchronic course, and this transition becomes most evident when *a chronic nephritis develops directly from an acute attack* (see p. 199). The process can only be followed in a small minority of the cases, and it is usually acute *diffuse nephritis* that, as has already been mentioned, not infrequently terminates in a chronic form; in rare cases the "*kidney of pregnancy*" may also lead to such a result. As the writer has repeatedly stated, the cases are somewhat more frequent in which a previous acute renal affection creates a *predisposition* to the chronic form of the disease, although the transition is not immediate. On careful questioning, it is often learned that the patient has had an acute nephritis at some previous time, usually after scarlet fever, diphtheria, or some other infectious angina, influenza, and the like, and then for a time presented no signs of kidney disease (particularly albuminuria). The assumption appears to be justifiable that in such cases the kidneys have lost part of their resisting power and become a "locus minoris resistentiæ."

In many cases—whether in the majority, as is frequently stated, cannot be determined, because the histories are often untrustworthy or

otherwise defective—no direct or indirect connection with an acute attack of nephritis can be demonstrated. The disease develops without apparent cause, insidiously and imperceptibly, so that the exact moment of its inception escapes observation. For this reason it is more difficult than in the case of an acute nephritis to give the cause of the disease with any degree of assurance. It is usually called "spontaneous" by the laity because it begins without any obvious and recognizable cause.

The difficulty is enhanced by the impossibility of sharply separating the various forms of nephritis one from the other; nor is it easy to estimate the influence of existing etiologic factors on the production of any special form of nephritis, in this case the non-indurative form. The matter is still further complicated by the fact that this variety was frequently confounded with *amyloid disease*, and in reality an association of the two conditions is not infrequent, making it doubtful in many cases which of the two developed first, and what, therefore, is the causal connection between the two.

On general pathologic grounds it may be assumed from the analogy with acute and subacute forms of nephritis, from which the chronic forms may undoubtedly develop, that the ultimate cause of chronic diffuse nephritis is also to be found in an alteration of the blood, developing more slowly and with less intense irritation of the kidney than in the acute cases. Whether the one or the other form of chronic nephritis—that is to say, with or without induration—develops appears to depend on the rapidity with which the noxious agent exerts its influence. The slower and more insidious the irritation, the more likely is the indurative form to develop (see p. 176). Weigert's division into chronic and subchronic cases correctly represents the condition of affairs in this respect, and implies that the same or similar causes are met in the various forms of chronic nephritis with and without induration.

The following specific causes are usually given for the non-indurative (so-called "parenchymatous") chronic nephritis when not secondary to acute nephritis.

1. So-called "*chronic colds*"—*i. e.*, long-continued or repeated action of dampness or cold—as, for example, a protracted residence in a damp dwelling-house, working in water or moist earth or in changeable weather. The significance of this etiologic factor was pointed out by Christison, and almost all the authors have followed him, with the exception of Bartels and E. Wagner, who neither accept nor contradict this view. Although one can readily understand their reserve in the face of the difficulties surrounding the etiology to which the writer has referred, he is nevertheless impelled by his personal experience with the occurrence of chronic nephritis to agree with the great majority of authors, who believe that exposure to dampness and cold is an etiologic factor, without altogether denying that other unfavorable conditions, such as bad food, the abuse of alcohol, and the like, may have been operative in cases of that character.

2. Various *chronic constitutional diseases*, especially those which lead to anemia and cachexia. The difficulty of determining the etiology

is enhanced because many of these cases represent a combination of chronic inflammation with amyloid disease, which escaped the notice of the older writers. This is true of chronic nephritis following *tuberculosis* and *pulmonary phthisis*, and of that which follows *syphilis* and *malaria*. For this reason the figures of v. Bamberger,[1] which are based on a large clinical material, cannot be utilized in studying the pure uncomplicated form of nephritis. Among his 805 cases of secondary "chronic (non-atrophic) Bright's disease"—that is, caused by an antecedent illness—205, or more than 25 per cent., are stated to have followed tuberculosis, phthisis, and scrofulosis; but, as he himself says, amyloid degeneration of the kidneys and other organs was a fairly frequent complication in these cases.

There is no doubt, however, that chronic nephritis not of an amyloid character does develop in consequence of pulmonary tuberculosis. The writer has a number of cases that have been carefully analyzed with special reference to this point, and believes that, in Berlin at least, of all chronic diseases tuberculosis must be regarded as the most frequent cause of this form of nephritis.

Acquired syphilis as a cause of chronic ("parenchymatous") nephritis other than amyloid in character must be extremely rare, and v. Bamberger's 29 cases (3.7 per cent.) must again be rejected on account of the complication with amyloid degeneration. E. Wagner found among 9000 autopsies only 4 cases of "subacute or chronic Bright's disease," which, however, were not examined microscopically, for which reason he believes that some of them probably belonged to amyloid degeneration.

In *congenital syphilis*, on the other hand, the kidneys are regularly diseased. R. Hecker[2] found in *premature, stillborn fetuses* small-cell infiltration in the walls and in the immediate neighborhood of the smallest cortical vessels, and sometimes of the larger vessels in the medullary substance, and more rarely leukocytes within the capsules, and proliferation of the capsular endothelium.

In infants born *at full term* with hereditary syphilis, more pronounced degenerative changes in the epithelium of the uriniferous tubules only are found. If the infant lives a certain length of time atrophy, cloudy swelling, granular and fatty disintegration and desquamation of the cells with resulting dilation of the uriniferous tubules, which contain hyaline and granular casts, are observed. Leukocytes within the capsular space, desquamation and proliferation of the capsular endothelium, atrophy, disintegration, and fatty degeneration of the vascular coils are also found.

Finally, "gummatous" growths, which will be discussed on p. 403, sometimes occur.

In regard to the influence of *malaria* we find diverging statements, not only because the cases complicated by amyloid disease are not always properly separated from the others, but also, it would appear,

[1] Volkmann's *Sammlung klin. Vorträge*, Leipzig, No. 173.
[2] *Deutsch. Arch. f. klin. Med.*, lxi.

on account of endemic variations, and possibly also on account of differences in the character of individual epidemics. Thus, while Frerichs very frequently observed dropsy after intermittent fever in Friesland, on the shores of the North Sea, without seeing a single case in which the kidneys were diseased, Bartels found that in the low marshy land of Schleswig-Holstein "chronic parenchymatous nephritis" was distinctly frequent after malaria. In Dantzig, on the shores of the Baltic, Rosenstein[1] found that 23 per cent. of all the cases of Bright's disease were undoubtedly secondary to intermittent fever; while in northern Holland, a fever province *par excellence*, the relation was very rare. He also cites Heidenhain's experience in Marienwerden, where the latter failed to observe either dropsy or kidney disease in a series of intermittent fever epidemics with the exception of the last, during which almost every case was complicated by nephritis. In Algiers, so Kiener and Kelsch[2] report, both acute and chronic ("parenchymatous") nephritis are not infrequent after malaria, and the same is said by Rem Picci[3] to be true of Rome. Along the marshy banks of the Danube, Soldatow[4] says, chronic nephritis ending in contracted kidney is quite common as the result of malaria; and Zakrzecky[5] makes the same statement in regard to the Caucasus. In America, C. S. Wood[6] regards malaria as an important cause of nephritis, although many of his countrymen disagree with him. Busey,[7] in Washington, places special stress on malaria as a cause of nephritis in children. [Thayer,[8] who studied the cases of malaria treated at the Johns Hopkins Hospital in Baltimore, finds that albuminuria occurs in nearly half of these patients, being most frequent (58.3 per cent.) in the æstivo-autumnal form of fever. Acute nephritis was found in 4.7 per cent. of all the cases of æstivo-autumnal fever treated in the hospital wards—*i. e.*, excluding the ambulatory patients. In the tertian and quartan infections there was a much smaller percentage of cases of acute nephritis. He is inclined to believe that malarial infection, especially in tropical countries, may play an appreciable part in the etiology of chronic renal disease. I myself have seen a case of acute nephritis follow hard upon an acute malaria contracted in the South.—Ed.] In Leipzig, at a time when intermittent fever was epidemic, E. Wagner was never able to demonstrate any causal connection with Bright's disease, and the writer has seen a number of cases of chronic nephritis in Berlin in persons who had suffered from intermittent fever some time before, but was only able in one case to convince himself of any direct connection between the two conditions.

A rather infrequent cause which, according to E. Wagner, should be mentioned in this connection, is the *hemorrhagic diathesis*, in the course of which he twice observed a chronic hemorrhagic nephritis in youthful

[1] *Virchow's Archiv*, xiv., p. 110, and *Path. u. Therap. der Nierenkrankh.*, 4th ed., 1894, p. 329.
[2] *Loc. cit.*
[3] *Petersburg. med. Woch.*, 1878, No. 42.
[5] *Jour. f. Militärärzte*, 1870, cited in Virchow-Hirsch, *Jahresb.*, 1870, p. 214.
[6] *N. Y. Med. Rec.*, 1888, No. 24, with Discussion.
[7] *Am. Med. Assoc.*, 1880.
[8] *Trans. Assoc. Am. Phys.*, 1898.

individuals. The writer himself has made this observation on several occasions.

3. *Diseases of the heart*, especially endocarditic processes, in the writer's opinion, undoubtedly cause chronic nephritis, although not very frequently; nor should we include the cases of cyanotic induration and contracted kidney which result from renal congestion (p. 150). In v. Bamberger's statistics, 117 of the 805 cases, or 14.5 per cent., of "secondary chronic Bright's disease" were complicated by valvular lesions, but this fact cannot be utilized to prove this etiologic relationship under discussion; for, in the first place, as the writer has frequently remarked, the cases of amyloid disease were included in these statistics, and in the second place, the fact was lost sight of that endocarditic processes and valvular lesions may also be secondary to chronic nephritis. Judging from the writer's own experience, however, he believes that simple nephritis without amyloid disease sometimes occurs as a sequel or concomitant of valvular disease of the left side of the heart. Rosenstein has made similar observations, and correctly calls attention to the fact that both affections—heart disease and nephritis—ought possibly to be ascribed to the same cause.

4. Among the *chronic intoxications* the abuse of *alcoholic liquors* has been regarded as the most fruitful cause of chronic nephritis by the early observers, such as Bright and Christison, as well as by most of the later authors, but the various forms have not always been differentiated with sufficient exactness in this respect. According to more recent investigations, indulgence in alcohol is most concerned in the production of the indurative form (contracted kidney), and more will be said about it in that connection.

Wells [1] and Blackall [2] believed that the protracted use of *mercury* also had some influence on the production of nephritis; but judging from later observations that metal plays a rather insignificant part; in fact, Rayer and others regard every case of renal disease occurring in the course of mercurial treatment to be due to the accompanying syphilis, but this is probably an exaggeration in the other direction. For since acute mercurial poisoning is undoubtedly capable of producing nephritis (p. 184), the possibility of chronic nephritis developing after protracted, excessive, and improper use of mercury, or of an originally acute nephritis changing to the chronic form, cannot be denied. It is true that neither of these events seems to be at all frequent, and in most of the reported cases the influence of the syphilis, which was the original reason for applying mercurial treatment, is difficult to measure.

However imperfect our knowledge of the *exciting* causes may be, it is clearly shown that the disease is most common among youthful individuals who live and work amid unfavorable hygienic surroundings, and that childhood and the female sex are therefore least exposed to chronic diffuse ("parenchymatous") nephritis. All observers are agreed that

[1] *Trans. of a Society for Improvement of Med. and Chi. Knowledge*, iii., 1812, cited after Frerichs.

[2] *Observations on the Nature and Cure of Dropsies*, London, 1813, 4th ed.., 1824.

the greatest contingent is furnished by young and middle-aged males belonging to the laboring classes. Whenever it occurs in childhood, it is usually the result of a former acute nephritis which not infrequently is overlooked or neglected (see p. 200).

Hereditary and *family predisposition* is also of some importance, principally, however, for the production of the indurative form, under which head these factors will be discussed.

According to universal and well-founded belief all the causes, whatever may be their nature, act through the blood—*i. e.*, by causing some morbid change in that tissue—thus bringing about a condition of disease or, more specifically, setting up an insidious and inflammatory process in the kidneys. Albuminuria is regarded as the expression and the result of inflammation of the kidneys, which is also attended by certain other less constant changes in the urine. The *change in the blood* which is the *direct cause* of the disease is unknown in the great majority of cases, probably because it is different for every case, although its effect on the kidneys is always the same. The writer has already sufficiently explained the sensitiveness of these organs to any change in the blood that passes through them (see p. 177).

More than fifty years ago Semmola[1] advanced an entirely different theory in regard to the pathogenesis of chronic nephritis and Bright's disease in general, and has since maintained its correctness in the face of many objections. He believes that the cause of the *excretion of albumin in Bright's disease* does not reside in a primary disease of the kidneys, but in a changed power of diffusion of the albumin of the blood, causing it to pass through the kidneys unaltered, like injected egg albumin. If this excretion of albumin, which at first is purely functional, continues for any length of time, there results a morbid condition of the kidneys, which may be either a simple hyperemia and extravasation or may go on to diffuse nephritis analogous to Bright's disease ("large white kidney, chronic parenchymatous nephritis"). The cause of this change in the albuminous bodies of the blood, rendering them more diffusible and less assimilable, is found by Semmola in a disturbance of the function of the skin; as, for example, in scarlet fever and other cutaneous affections, or the effect of cold on the skin. (See Acute nephritis.)

This theory at first sight appears to be supported by an observation of E. Freund,[2] that the blood-serum of patients with Bright's disease usually contains more diffusible albumin than the blood-serum obtained from normal individuals or such as are suffering from albuminuria due

[1] *Compte rend. de l'Acad. méd.-chi. de Naples*, 1850, i. 3. *Gaz. des hôp.*, 1861, No. 101. *Revue mensuelle de méd. et de chi.*, 1880, iv. *Arch. de Phys.*, etc., 1881, i., p. 59; 1884, i., p. 287. "*Nouvelles recherches expérimentales pour démontrer l'origine hématogène de l'albuminurie Brightique*," Naples, 1884. "Neue Untersuchungen über die Pathologie und Therapie des Morbus Brightii" in *Wien. med. Blätt.*, 1886, Nos. 45 and 49. "Nouvelles contributions à la Pathologie et au Traitement de la Mal. de Bright," *Bull. de l'Acad. de méd. de Paris*, Sept. 7, 1886. See also *Deutsch. med. Woch.*, 1888, Nos. 21 and 23. *Bull. de l'Acad. de méd.*, Paris, July 29, 1890. *Internat. klin. Rundschau*, Wien, 1891, Nos. 30 and 32. *Wien. klin. Rundschau*, 1895, No. 4.

[2] *Wien. klin. Rundschau*, 1895, No. 4.

to some other cause. As a matter of fact, however, this observation proves nothing unless it is established in a given case that the blood-changes preceded all other symptoms, or, at least, the albuminuria; in other words, represent the *primary condition* and not, as is quite possible, the effect of the disease. This skepticism appears to be fully justified, since injections of blood, urine, and transudates derived from kidney patients fail to produce albuminuria in animals, according to the investigations of Stokvis,[1] Riva,[2] and Tizzoni,[3] although on Semmola's theory they ought to do so. Hayem[4] also was unable to induce albuminuria by injecting the blood of a dog suffering from nephritis into another dog.

Semmola's other statement, that a disease similar to Bright's disease can be produced by the continued injection of egg albumin, is not fully confirmed by the numerous experiments that have been made for the purpose of testing it, although it is not altogether unsupported, since on various occasions the investigators succeeded in producing inflammatory changes in the kidneys by means of such injections; but none ever succeeded in producing a large white kidney (Kuipers,[5] Sosath,[6] Riva,[7] Brancaccio,[8] Lecorché, and Talamon[9]). Dropsy was found by Prior[10] in some of the animals which he had injected subcutaneously with egg albumin for a number of weeks, but he regarded it as the result of the continuous, although slight, destruction of red blood-cells by the egg albumin and of the loss of albumin from the blood, for the changes in the kidneys were quite insignificant.

And, finally, the clinical course in acute Bright's disease, in which the succession of the phenomena can be traced from the beginning, differs radically from the process as explained by Semmola, according to which albumin appears first in the urine, and the signs of the so-called secondary nephritis, such as leukocytes, red blood-cells, renal epithelium and casts, do not make their appearance until the albuminuria has lasted several days. But it is well known that these changes may occur at the very beginning and at the same time as the albumin.

Semmola's clever theory therefore lacks foundation in fact, and the current view that the albuminuria is the result of the inflammation in Bright's disease still maintains its ground.

PATHOLOGIC ANATOMY.

Chronic diffuse nephritis occupies a position intermediary between acute nephritis and chronic indurative nephritis, the gap being bridged by numerous transitional forms, and owing to this close relation it is not to be wondered at that the anatomic line of separation is no more

[1] "Recherches experimentales sur les conditions pathologéniques de l'albuminurie," Brussels, 1867.
[2] *Arch. ital. de Biol.*, 1884, vi., p. 398.
[3] *Ibid.*, p. 345.
[4] *Gaz. hebdom.*, 1888, No. 12.
[5] Diss., Amsterdam, 1880.
[6] Diss., Würzburg, 1880.
[7] *Loc. cit.* and *Gaz. degli ospidali*, 1885, No. 8.
[8] *Rivista internat. di med. e. chi.*, 1888, No. 3.
[9] *Traité de l'albuminurie*, etc., Paris, 1888, p. 445.
[10] *Zeits. f. klin. Med.*, xviii., pp. 88 and 89.

sharply drawn than the clinical, and that the pathologic picture presented by the kidneys is anything but uniform. Hence, the changes observed belong partly to the acute and partly to the chronic indurative forms, or may combine the characteristics of both. In chronic non-indurative nephritis the only constant change observed with the naked eye, even when the appearances differ in every other respect, is that the kidneys are never perceptibly diminished in size, but, on the contrary, are quite frequently enlarged. Beyond this the kidneys often present practically nothing remarkable on macroscopic examination; but in certain cases, which are not at all infrequent, marked changes in size, color, consistence, and other relations are observed, which have led to a division into numerous forms and subvarieties, such as the "pale," "many-colored," "spotted," and "speckled" kidney. On microscopic examination it is found, however, that these differences in appearance depend solely on quantitative variations in the pathologic changes of the individual tissue elements.

These changes affect almost exclusively the *cortical substance*, particularly the *epithelium* of the convoluted tubules and, to a less extent, that of the straight collecting tubules. The epithelium is found in various stages of degeneration from cloudy swelling to complete fatty metamorphosis. In places the cells are fragmented and in the act of breaking down, and there is more or less general desquamation. As in the case of acute nephritis, the areas in which the process is most recent contain epithelial cells in a better state of preservation which may present *mitoses*.

As a result of this disintegration, the *uriniferous tubules* are in places greatly distended by the swollen epithelial cells or their remains, while in other places they have lost their epithelium and are collapsed. It is not uncommon to find in the lumen, along with the remains of cells or nuclei, leukocytes, free fat-granules, red blood-cells or granules of pigment, and hyaline or granular coagula, which are not infrequently carried down by the current into deeper portions of the otherwise intact uriniferous tubules. The *stroma* always participates, although in a variable degree, in the inflammatory process. The tissue is always distended with edematous fluid. In less advanced cases and after recent exacerbations the stroma is the seat of cellular infiltration as in acute nephritis, and contains a variable quantity of blood and fatty granular cells or free fat-droplets. Finally, in more advanced cases, it is converted into connective tissue which is thickened and well supplied with cells except in the oldest portions, where the cells are few, and which in part takes the place of obliterated uriniferous tubules.

Although the *Malpighian bodies* never escape altogether, their share in the morbid process is extremely variable. As a rule, they exhibit the pathologic changes of acute *glomerulonephritis*, particularly fatty change and desquamation of the epithelium of the coils and Bowman's capsules, the interior of the latter being filled with these cells and an albuminous exudate which compresses the capillaries. The latter are frequently covered with fat-droplets, and their lumen is not rarely

obstructed by swelling and desquamation of the endothelium. In more pronounced cases the proliferation of connective tissue may be so great as completely to obliterate the coils and cause thickening of the capsules, thus presenting a transition form between this variety of nephritis and the indurative variety. According to H. Engel,[1] the vascular tufts and the capsules are first glued together by the "fibrin" retained in the capsular space, and later the adhesions are converted into connective tissue and bind the tissues firmly together. As the coagulation of fibrin is the result of the death of epithelial cells, it follows that the epithelial disease represents the primary change in *adhesive glomerulitis*.

In cases of this kind changes are also found in the *smaller arteries* that are absent in less advanced cases. (See also Indurative and Acute Nephritis.)

The tissue changes are never distributed uniformly over the entire cortical substance, but occur in streaks and spots, forming larger or smaller foci which show a tendency to confluence. The differences in the macroscopic appearance which have led to a division into the above-mentioned subvarieties depend on differences in the extent of these foci, the different degrees in which the individual tissues are affected by the disease, the more or less advanced stage of fatty degeneration, the loss of tissue and contraction in individual portions of the organ, and, finally, differences in the quantity of blood contained in the kidney.

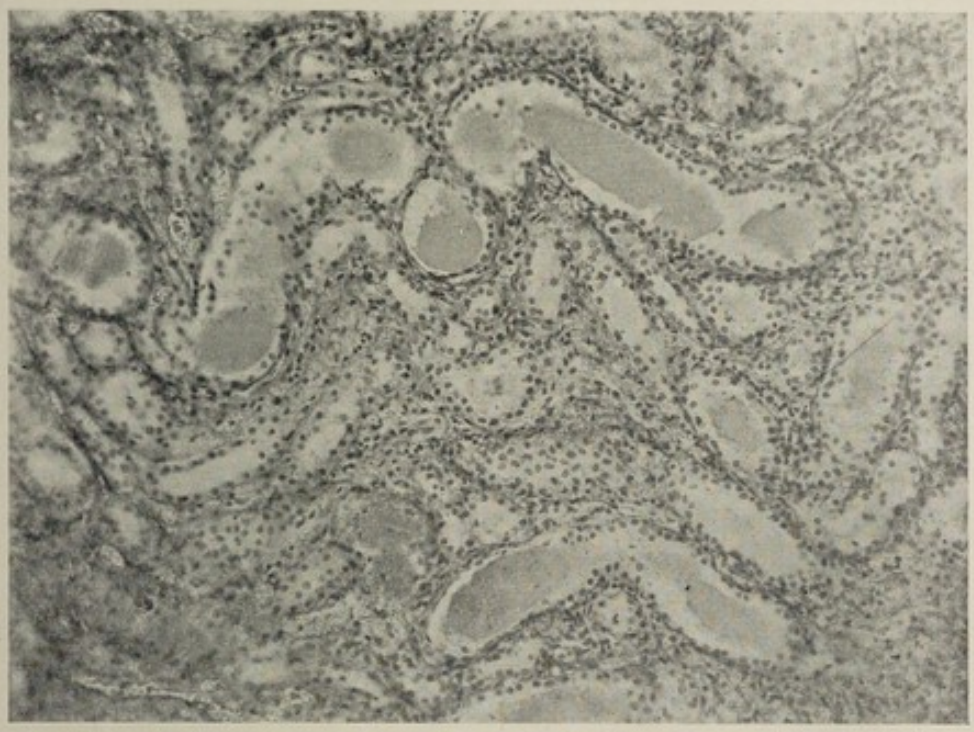
The *large white kidney* was formerly regarded as the commonest form, and therefore the type of chronic non-indurative ("parenchymatous") nephritis; but we now know that this is incorrect, because many of the cases included in that category represented a *combination of inflammation with amyloid degeneration*, whereas the simple inflammatory form without amyloid disease is quite rare. The mistake is due to the fact that the macroscopic appearance of the kidneys is almost, if not quite, identical in the two conditions. The organs are larger and heavier than normal, of a doughy consistence, and dull-white or pale-yellowish color, the uniformity of the surface being interrupted here and there by darker, grayish-red macular and linear markings and an occasional venous radiation as well as by minute hemorrhages. The capsule is thin and strips readily. When the kidney is cut, it appears that the increase in volume and the pale coloration exclusively affect the cortex, which is swollen and thickened and shows in marked contrast with the pyramidal substance, which may be of a normal red color or hyperemic.

The most prominent feature of the large white kidney is the widespread *fatty degeneration of the uriniferous tubules*, and to a lesser extent of the glomeruli and of the stroma, the signs of recent inflammatory interstitial changes, such as cellular infiltration, with hyperemia and hemorrhages, being comparatively unimportant. The fatty degeneration and anemia suffice to explain the naked-eye appearance.

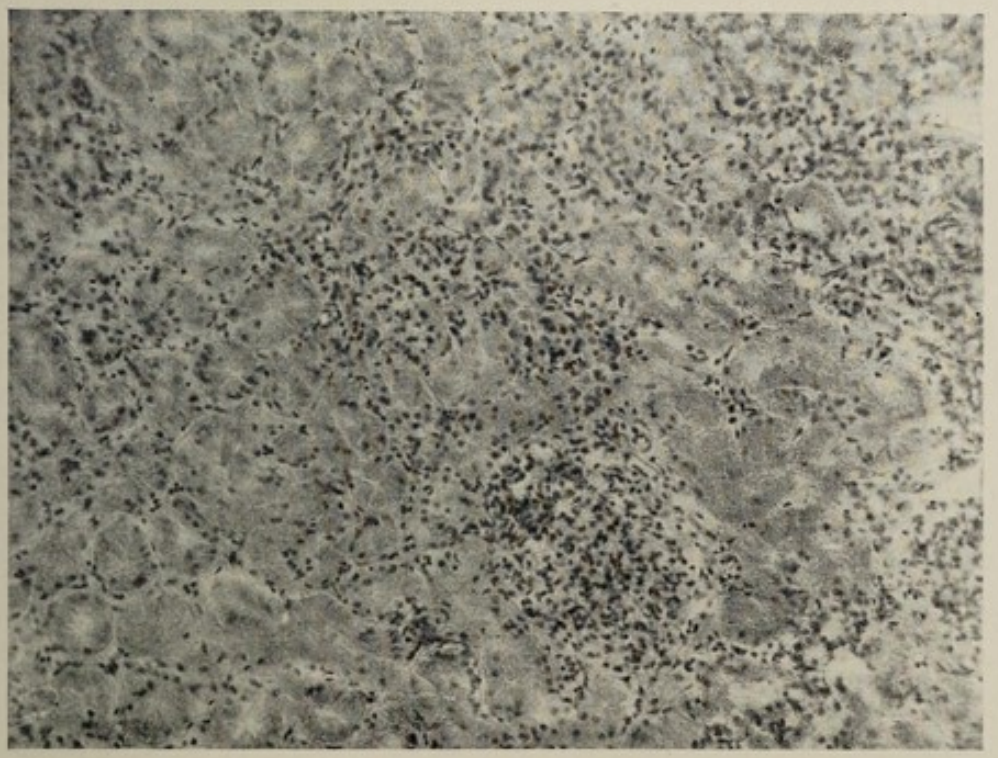
The (large) "*many-colored kidney*" in appearance closely resembles that of acute diffuse nephritis, and is distinguished from the latter by its greater firmness. The variegated appearance is due to the alterna-

[1] *Virchow's Archiv*, clxiii.

PLATE IV.



CHRONIC DIFFUSE NEPHRITIS WITH CASTS IN THE TUBULES. (Specimen loaned by E. R. Le Count.)



DEGENERATIVE NEPHRITIS, "PATCH NECROSIS."

From a case dying of general miliary tuberculosis. Kidney small; many white pin-point-size areas visible externally. The illustration shows patches of necrosis affecting the working epithelium. (Specimen loaned by E. R. Le Count.)

tion of yellowish or grayish-yellow patches with violet or dark-red areas, which lends to the outer surface as well as the cut surface a macular appearance. The capsule is thin and slightly adherent to the surface in places; the cortical substance is also increased in width and swollen, and in places marked by small hemorrhages; the glomeruli appear as prominent red dots.

This form derives its peculiar appearance from the numerous and extensive hemorrhages and general plethora of the organ and the comparative want of fatty changes; on the other hand, interstitial changes are more marked. But these features are subject to so much variation that the dividing line between this form and the large white kidney is very indistinct. Both exhibit, although in varying extent, contraction by the obliteration of glomeruli, and destruction of uriniferous tubules, which are replaced by a more or less cellular connective tissue.

As the disease progresses, in protracted cases the contraction increases, and the paler—*i. e.*, the fatty—areas diminish in extent. The capsule in places becomes thickened and more closely adherent to the cortex, while the surface presents slight irregularities, due to small yellowish prominences corresponding to the uriniferous tubules, which are full of fat, and project above the reddish-gray interstitial portions. We then have the picture of the "*spotted*" or "*speckled*" kidney. The organ is firm, of practically normal size or very slightly contracted, though frequently even larger than normal; the cortex is not contracted and may even be wider than normal, and the cut surface presents an alternating arrangement of grayish-white or yellowish and red stripes. This variety forms the transition to the indurative (so-called contracted) kidney, the transition taking place by numerous gradations without any sharp dividing line.

The morbid process may come to a *standstill* for a time, and may even undergo *resolution*, to judge from clinical as well as pathologic observation; but the improvement is never as great as in the case of acute nephritis, because large portions of the secreting parenchyma have been destroyed and replaced by connective tissue. It is not uncommon to find at the autopsy kidneys of normal, or larger than normal, size in which the remains of a former inflammatory process are discovered with the microscope, although the patient for some time before death had presented no signs of kidney disease, particularly no albuminuria.

For the pathologic changes observed in congenital syphilis, the reader is referred to p. 226.

As for the other *postmortem findings*, it may be said that external and internal dropsy are almost always present, and in the majority of cases enlargement of the heart, frequently associated with inflammatory or degenerative changes in the myocardium, and with endo- and pericarditis of varying severity. In addition there are found signs of one or another of the numerous diseased conditions to which chronic nephritis predisposes, and which may have brought on death or existed as a so-called complication at the time of death; of these the most frequent is pulmonary edema.

Rabinowicz[1] is authority for the statement that the marrow of the long bones is the seat of a lymphoid degeneration in chronic parenchymatous nephritis.

SYMPTOMATOLOGY.

As in the case of acute diffuse nephritis, so in the closely related chronic non-indurative form, the clinical picture presents two dominant features—the *urinary changes* and the *dropsy*. Owing to the insidious onset of the disease, the changes in the urine are usually overlooked or neglected; in rare cases the patient's attention will be directed to his condition by the evacuation of a frothy, usually turbid, dark urine, or the presence of indefinite symptoms, such as anorexia, headache, or a feeling of fatigue; or the urine may be examined for some other reason, such as an application for life insurance, and the disease thus be accidently discovered before the advent of dropsy. But in most of the other cases dropsy is the first sign that the patient observes and that is brought to the physician's knowledge.

At first the edema is slight and confined to the well-known seats of predilection of "renal dropsy"—the eyelids, ankles, and shins—disappears in the morning after a night's rest, returns during the day, and progressively increases. But sometimes in a few days, more frequently in the course of weeks or months, *dropsy* of the most pronounced form that is ever observed develops with all the phenomena and sequels that have already been described (p. 80). As the writer has stated in that place, the patients are usually extremely pale, in striking contrast to the cyanosis observed in cases of dropsy caused by venous congestion. The skin is usually dry, and sometimes scaly in places.

If the anasarca persists long enough, *sclerema* of the skin, which sometimes leads to a condition like that of true scleroderma, not infrequently develops.

The *cutaneous exhalations* are reduced in quantity and perspiration is infrequent; but if improvement takes place and the edema diminishes, the sweating becomes more profuse.

According to E. Wagner, *dropsy may be absent* during the entire course of the disease in some cases of chronic hemorrhagic nephritis.

Urinary Changes.—The quantity is always diminished, and usually, although not without exception, it is inversely proportional to the extent of the dropsical effusions. Rarely, and, as a rule, only shortly before death, the suppression attains the same degree as in acute nephritis; but at the height of the disease a daily quantity of only ¼ to ½ liter (say 8 to 16 oz.) is not so very rare, while during periods of improvement it may attain 1 to 2 liters (quarts), and temporarily, if the dropsical fluid is rapidly absorbed, the quantity may exceed the normal. In cases of "spotted or speckled kidney," which represent the transition to the indurative form, the quantity of urine is greater, and in its other characteristics the urine resembles that of the indurative form.

The *specific gravity* presents similar variations. Generally speaking,

[1] *Wratsch*, 1898, No. 14, cited in *Monat. f. Harn.- u. Sexualorgane*, 1898, p. 495.

it is inversely proportional to the daily quantity of urine—*i. e.*, it rises when the secretion is scanty and falls after a copious evacuation; on the average, however, it is slightly above the normal, and may be considerably higher than the normal at times when the secretion of urine is greatly reduced. Under such circumstances Bartels and Rosenstein have obtained a specific gravity of 1040 or more.

The *reaction* is usually faintly acid, and if the specimen stands any length of time rapidly changes into neutral or alkaline. Rosenstein asserts that he observed an alkaline reaction in one case from the beginning of the disease.

The *appearance* of the urine in other respects varies, unless it contains a large admixture of blood, which is rare, according to the quantity from pale-yellow with a suggestion of green to reddish brown or, if there is much blood, to the color of meat juice. As a rule, the urine is cloudy, the turbidity being inversely proportional to the quantity, and very frothy, on account of the large quantity of albumin it contains, the froth persisting for a long time after it has formed.

Albumin is a constituent that is rarely absent in this form of nephritis, and it is usually present in the urine in larger quantities than is the case in the indurative forms, and even in the majority of cases of acute nephritis. There is an approximate relation between the quantity of albumin and the specific gravity, and consequently an inverse relation between the amount of albumin and the quantity of urine; but the albuminuria as a rule bears no relation to the dropsy. In typical cases —the white or many-colored kidney—the albumin on the average amounts to several tenths of a per cent. or even to 1 per cent. of the entire weight. In many cases a high percentage is observed during the entire disease, while in others the percentage of albumin is quite moderate. When the disease is protracted—*i. e.*, lasts many months—the average daily loss of albumin ranges, as a rule, between 4 and 8 gm., but does not reach 10 gm.

The greater the tendency to indurative processes, when the disease is protracted, as in the "speckled" kidney, the smaller the percentage of albumin.

The highest percentage of albumin that the writer has ever observed in chronic cases is 2.8 per cent., determined by weight; it was obtained in the case of a patient who, during the course of his illness, which lasted six to seven months, always passed more than 1 per cent. of albumin in the urine. The greatest daily quantity the writer has ever found, which was in the same patient, is 22.4 gm. Snyers[1] obtained from 30 to 35 gm. daily for several days in succession in the case of one of his patients. Bartels observed unusually high percentages of albumin in a few cases, 4, 5, and even more than 6 per cent.; an even greater percentage has been found in a few instances in subacute *nephritis syphilitica præcox*, as has been mentioned on page 192.

As in most cases of albuminuria, the albumin consists of *serin* (serum-albumin) and *globulin*. The relation between the two, known as the "albumin quotient," is extremely variable, and depends on other factors besides their relative quantities in the blood (see p. 20). Csatáry's[2] painstaking investigations show that in "parenchymatous" nephritis the percentage of globulin is relatively small—*i. e.*,

[1] *Wratsch*, 1898, No. 14, cited in *Monat. f. Harn.- u. Sexualorgane*, 1898, p. 208.
[2] *Deutsch. Arch. f. klin. Med.*, 1891, xlvii., p. 159, and xlviii., p. 358.

the "albumin quotient" is large. In 6 cases of this variety of the disease he found on the average a maximum of 5.48 and a minimum of 2.09 per cent.

Nucleo-albumin, which until recently has received little attention, the writer has always found to be either present in extremely small quantities or altogether absent, unless there happened to be an acute exacerbation of the inflammatory process.

Albumoses in the urine are also found occasionally, either in association with albumin or by themselves. Their significance is quite unknown. It is possible that they are formed from albumin when digestive ferments are present in the urine. Putrefaction may act in a similar manner.

Normal Urinary Constituents.—The excretion of *urea* in this form of chronic nephritis is in general proportionate to the diminished excretion of urine—that is, it is less than normal, especially when large effusions are present in the body. The quantity of urea is, however, subject to many variations, which may depend in part on the varying condition of the renal parenchyma itself, in part on changes in the quantity of albuminous food ingested and absorbed, on the loss of nitrogen with the urinary albumin, and, finally, on the retention of variable quantities of urea within the body.[1] *Uric acid*, on the other hand, to judge from Van Ackeren's[2] investigations, is more constant and, as in the case of acute nephritis, the quantity is within the normal limits. The excretion of *ammonium* in Gumlich's[3] investigations did not show any notable change. The so-called *extractives*—creatinin and xanthin bodies—appear, from the results of the investigations made in the writer's clinic by P. F. Richter, to behave in the opposite manner from urea—*i. e.*, their quantity increases and diminishes directly as the dropsy increases and diminishes. This is in accord with the result of Gumlich's investigations, which show that the proportion between the nitrogen excreted as urea to the entire quantity of nitrogen in the urine is, generally speaking, normal (83 to 87 per cent.); but in a few cases characterized by rapidly increasing dropsy there was found a difference in their proportion in favor of the residual or "extractive" nitrogen, which was increased to 14 to 23 per cent. of the entire quantity of nitrogen.

Contradictory statements are found in regard to the behavior of the *mineral acids* (chlorids, sulphates, and phosphates). This discrepancy may be explained by the fact that investigators have failed to take sufficient account of the quantity ingested, principally of sodium chlorid, and in part by the failure to distinguish the individual forms of the disease or the impossibility of classifying the cases investigated in any one definite class. The excretion of the mineral acids, especially of hydrochloric acid, often runs parallel with the excretion of urea. Judging from the writer's own investigations, the excretion of hydrochloric acid frequently falls short of the ingestion in chronic non-indurative nephritis.

The *sediment*, which is almost regularly present and is often quite heavy, contains on the whole the same constituents that are found in

[1] Regarding this see v. Noorden, *Lehrb. der Path. des Stoffwechsels*, Berlin, 1893, p. 369.

[2] *Charité-Ann.* xvii., 1892, p. 206. [3] *Zeits. f. phys. Chem.*, xvii., 1892, p. 10.

acute diffuse nephritis (see p. 195), from the sediment of which it is usually distinguished, however, by the predominance of fatty epithelial cells, cells and casts with fine fat-granules upon them, and free fat-droplets, while the red blood-corpuscles are rather less numerous, unless there is a special tendency to hemorrhage, as in "hemorrhagic nephritis" in the narrower sense of the word, or the patient happens to be going through an acute inflammatory exacerbation.

The differences in the urine peculiar to the individual forms, especially the "*white*" and "*many-colored*" kidney, are not sufficiently constant to deserve recognition as characteristic features of one or the other of these forms. It might be said that the larger percentage of blood or a greater tendency to bloody urine is rather characteristic of the "many-colored" than of the "white" kidney, while the sediment of the latter, on the other hand, contains more of the elements of fatty degeneration. The urine of the *spotted* ("*speckled*") kidney, as has been mentioned, shows more of the characteristics of the indurative form (contracted kidney).

Disturbances of Function.—In this respect also chronic diffuse nephritis resembles the acute form; but, in agreement with the less fulgurant course, the different conditions of the kidney and of the entire organism, the functional disturbances are not always so marked, and compensation may at times be practically complete. The frequent changes observed in the excretory functions of the organ may find an explanation in the tendency for the parenchyma to be attacked in successive instalments, so to speak, and the great compensatory activity of that portion which is still intact, or possibly also the regeneration of the parts that had been attacked by the disease. Accordingly, the *molecular concentration* of the urine, which is an index of the functional power of the kidneys, is almost always lessened. [The molecular concentration of the urine in chronic parenchymatous nephritis is very variable, depending not a little on the degree of edema and the amount of urine passed. In general it is between —1° and —2°.—Ed.] In addition the excretion of *water and urea*, as has been mentioned, is on the whole impaired; a deficiency which becomes more marked when rapid changes are made in the quantity of nitrogen ingested (F. Hirschfeld,[1] Kornblum,[2] and Mann[3]).

The functional disturbance of the kidneys, as in the case of acute nephritis, also reveals itself in the lessened ability of the kidneys to produce *hippuric acid* synthetically from benzoic acid and glycol, as well as to excrete certain substances, such as *drugs*, *pigments*, and *poisons;* but in this respect also a lack of uniformity is observed in different cases and in the various phases of the disease. This is particularly true of the power of the kidneys to excrete certain substances that are readily recognized in the urine, such as iodin and methylene-blue, and which some seem to regard as an index of the severity of the renal disease. But even under normal conditions the earliest appear-

[1] *Grundzüge der Krankenernährung*, Berlin, 1892, p. 47.
[2] *Virchow's Archiv*, 1892, cxxvii., p. 409. [3] *Zeits. f. klin. Med.*, xx., p. 107.

ance of the substance in the urine and the length of time during which it is excreted are subject to great variations, which again are different for each substance. This difference probably depends in part on the fact that different substances require different lengths of time for their absorption, and in part on some elective property of the kidneys, by virtue of which they behave differently to different pigments; and, finally, the power of excretion in a diseased kidney must depend on the extent of the still intact parenchyma and the compensatory power retained by such healthy tissue.

A better criterion is found in the excretion of sugar after the administration of *phloridzin*.[1]

Digestive disturbances make their appearance quite early and are the most frequent among the remaining symptoms. The disturbance consists in more or less anorexia or distaste for special foods, especially meat, and this may in the course of the disease go on to actual nausea and vomiting. Irregularity of the bowels and diarrhea are quite common. The causes of all these disturbances are ordinary gastro-intestinal catarrh, edematous infiltration of the gastric and intestinal mucous membrane, and the flooding of the intestinal canal with retained urinary constituents or the products of their decomposition—in other words, manifestations of uremic intoxication (see p. 98). In numerous instances of chronic nephritis the secretions of the alimentary canal from the mouth to the large intestine have been found to contain urea and uric acid and particularly ammonium (also trimethylamin?), and the irritation due to the latter is no doubt responsible for many of the disturbances. The variability in the composition of these secretions also serves to explain the constant fluctuations in the patient's condition. The saliva is sometimes quite normal, at others it contains a relatively large quantity of urea. Similarly, the gastric juice and gastric digestion present qualitative and quantitative variations, and the vomitus may be acid, neutral, or alkaline. There is no change that can be regarded as typically characteristic.[2]

Nervous Symptoms.—Unless there is an acute uremic intoxication, the nervous symptoms are neither constant nor characteristic. The patients frequently complain of headache and insomnia and are peevish, not so much at the beginning as during the subsequent course of the disease. These symptoms may be partially explained by the prolonged rest in bed to which the patients are condemned on account of the edema, and the deprivation of bodily exercise and fresh air, as well as of many other accustomed sources of stimulation and diversion; in part they may be uremic in origin. Organic disease of the central organs is rare, especially as compared to its frequency in the indurative form; *cerebral hemorrhage*, however, does occur; according to v. Bam-

[1] For literature regarding excretion of pigments, consult Achard and Castaigne, *Gaz. hebdom.*, 1897, No. 37; Lépine, *Lyon méd.*, 1898, Nos. 8 and 17; Devoto, *Clin. Med. Italiana*, 1898, No. 37; Fr. Müller, *Deutsch. Arch. f. klin. Med.*, lxv.; H. Strauss, "Die chronischen Nierenentzündungen," *loc. cit.*, p. 97.

[2] See v. Noorden, *loc. cit.*, p. 362.

berger's statistics, in 29 out of 357 cases of his "primary chronic Bright's disease." Inflammatory and softening processes are even more infrequent.

Albuminuric Retinitis.—Albuminuric retinitis is rare in the beginning but fairly common during the latter course of the disease; Litten[1] observed it 6 times among 33 cases of chronic parenchymatous nephritis—*i. e.*, in 18 per cent. The visual disturbance to which the condition gives rise is sometimes the first symptom for which the physician is consulted; it does not, however, attain so high a degree in this form as in induration of the kidneys, and responds somewhat more readily to treatment. A much more uncommon condition is inflammation confined to one of the optic nerves, or *papillitis;* in such cases either the inflammation, for certain reasons, is confined to the head of the optic nerve, or the condition is a so-called congestive neuritis and dropsy of the optic sheaths.[2]

Finally there may be visual disturbances and complete blindness either as symptoms or as sequelæ of *uremia* (see p. 97). It is difficult to say how often uremia occurs in so-called "parenchymatous" nephritis, because the various forms of chronic inflammation of the kidneys are not sufficiently differentiated in the statistical collections. It is certain, however, that uremia is decidedly more rare in "parenchymatous" nephritis than in the distinctly indurative forms, at least so far as typical *acute* uremia is concerned; certain individual phenomena which might possibly be attributed to *chronic* uremic intoxication, such as certain forms of digestive disturbances, headache, and other nervous symptoms, are, as has been mentioned, frequently observed in parenchymatous nephritis.

Alterations in the Circulatory Apparatus.—*Enlargement of the heart* is a frequent and most important condition. Referring to what the writer has said before (p. 116) about the behavior of the heart in diseases of the kidney, he will merely remark here that, contrary to the older views, (1) true *hypertrophy* and not only simple dilatation is quite frequent, (2) that *hypertrophy of the left ventricle in this form of renal disease also is much greater than that of the right*, and (3) that *hypertrophy of the heart* in the great majority of cases is associated with dilatation—*i. e.*, it is a so-called *eccentric* hypertrophy, and differs in this respect from the form which occurs in indurative nephritis or contracted kidney. The older, erroneous views are in part explained by the fact that many or most of the cases that were classified under chronic "parenchymatous" nephritis (or the "second stage of Bright's disease") were complicated with amyloid disease and were not simple inflammatory cases.

The different mode of development of cardiac hypertrophy in nephritis complicated with amyloid disease and simple non-amyloid chronic (parenchymatous) nephritis is clearly shown in v. Bamberger's large collection of cases.[3] Among the 1623 cases of his "secondary" Bright's disease with and without atrophy—

[1] *Charite-Ann.*, 1819, iv., p. 168.

[2] See Leber, "Die Krankheiten der Netzhaut," in *Graefe-Sämisch's Handb. der Augenheilk.*, 1877, v., p. 583.

[3] *Loc. cit.*

i. e., secondary to all kinds of diseases, such as phthisis, valvular heart disease, alcoholism, carcinoma, typhoid fever, syphilis, etc.—only 54, or 3.3 per cent., presented cardiac "enlargement," while the percentage among the 807 cases of "primary" Bright's disease after exposure to cold or other unknown causes was 42.6 per cent. In the first group amyloid degeneration was much more common than in the second; this is what was to have been expected, and has already been pointed out in this volume. As regards the chronic "parenchymatous" form without atrophy, there is no way to determine the frequency of cardiac enlargement among the 805 cases of "secondary" Bright's disease belonging under that head, because v. Bamberger does not state how often enlargement of the heart was present in the individual forms. But even if we assume the *improbable*—namely, that the entire number of cases of "secondary" Bright's disease with cardiac enlargement (3.3 per cent., equal to 54 cases) occurred among the 805 cases of chronic ("parenchymatous") nephritis without atrophy—we should have a percentage of only 6.3 computed on 805 cases. Over against these we have 367 cases of "primary," mostly non-amyloid, chronic ("parenchymatous") nephritis with 122 cases of cardiac enlargement—*i. e.*, 33.9 per cent., or, if we deduct 6 cases of simple dilatation, 32.2 per cent. of *true cardiac hypertrophy*. In addition, the 6.3 per cent. which represent the cases of cardiac enlargement belonging to the first category include simple dilatation, which is unquestionably much more frequent in secondary Bright's disease than in primary Bright's disease. But even without this reservation the difference is quite manifest.

The relation existing between hypertrophy with and hypertrophy without dilatation (eccentric and simple hypertrophy) is illustrated by the following figures from v. Bamberger's statistics: Among the 357 cases of the chronic ("parenchymatous") form of primary Bright's disease, eccentric hypertrophy, either of the entire heart or of the left ventricle, was found 89 times, or in 25.5 per cent., and simple hypertrophy 27 times, or in 7.6 per cent. of the cases.

Clinically, cardiac hypertrophy can be recognized only in a small proportion of the cases. In the first place, the actual demonstration of enlargement is often difficult on account of the edema of the soft parts or the presence of a pericardial effusion, and the same factors make it difficult to recognize accentuation of the heart sounds; in the second place, the force of the heart itself, notwithstanding the hypertrophy, is frequently very much reduced on account of the general impairment of nutrition or on account of disease of the myocardium. The result is *weakness* and *syncopal attacks*, to which such patients are subject, congestive catarrh, thrombosis and inflammatory conditions of the respiratory organs.

Not until the indurative process becomes marked, the effusions disappear, and the patient's strength is somewhat restored, as in the "speckled" kidney or the so-called secondary contracted kidney, do the signs of hypertrophy become more distinct.

Blood-vessels.—The blood-vessels are generally normal except in those cases which represent the transition to induration or contracted kidney, in which the changes peculiar to that condition begin to take place (see p. 120). The behavior of the *pulse* is closely related to these vascular conditions. In the great majority of cases it is not characteristic. At the height of the disease and when edema is very pronounced the pulse is more apt to be weak than vigorous unless the tension is temporarily raised on account of great dyspnea. During the later stages, as the induration of the kidneys progresses, the pulse changes and begins to assume the qualities characteristic of that condition.

Blood.—The blood-changes, on the other hand, are usually quite

pronounced in non-indurative chronic ("parenchymatous") nephritis and attracted the attention of the earliest investigators (Bostok, Christison, and Gregory); these changes have since been repeatedly investigated and are regarded as characteristic of "Bright's disease." The *watery quality of the blood* and the turbid, milky appearance of the serum are often quite evident on simple inspection; the changes in the serum, according to Christison, Blackall, and Rayer, are caused by an increased percentage of fat, and, according to Frerichs, by fat or by molecules of albumin. The *specific gravity* of the blood and its *albumin content* are almost regularly diminished, the serum being chiefly affected by this reduction. Hammerschlag,[1] like the older investigators, found that the specific gravity of the *serum* at the height of the disease and when dropsy was present varied between 1019 and 1029, and mostly was not far from 1023; in health it is 1029 to 1032, usually 1030. The specific gravity of the *blood* as a whole, according to the studies of Hammerschlag, Devoto,[2] Schmaltz,[3] and Jahn,[4] ranges between 1026 and 1062; and these variations, aside from the differences in the methods of determination employed, probably depend on the different conditions of the patients and the looseness of the term "chronic nephritis." Askanazy[5] found that the *percentage of water in the blood as a whole* was increased in the presence of dropsy, sometimes above 85 and 86 per cent., and that of *serum* alone more than 94 per cent. Bruner[6] found only 13 to 20 per cent. of solid constituents, instead of 21.5 to 22.5 per cent., in the blood. The hydremia is inversely proportional to the specific gravity of the blood (Dzieballa and Kétly[7]) and to its albumin content (v. Jaksch[8]).

According to v. Limbeck and Pick,[9] the serum always becomes impoverished when there is an escape of albuminous fluids, and when the effusion of fluid is great, serin and globulin are affected about equally by the reduction; whereas, when there is only a small effusion, the serin appears to be diminished more than the globulin. Lecorché and Talamon[10] assert that they found more globulin than serin in various cases belonging to different forms of chronic nephritis, which is abnormal—*i. e.*, an albumin quotient of 0.54 to 0.82, and once 1.16.

The *molecular concentration* of the serum is not increased in typical cases without uremia. [And it is apt to be lessened when edema or marked anemia develop.—Ed.]

The serum often appears *turbid, whey-like* or *slightly milky*, and the same appearance is sometimes noticed in the transudates, particularly in the fluid of ascites. This peculiar appearance seems to depend on the presence of finely divided particles of albumin. [Minute fat-globules may also at times be the cause of the milky or chyliform appearance. This I have seen in 1 case, at least.—Ed.]

[1] *Zeit. f. klin. Med.*, 1892, xxi., p. 491.
[2] *Prager Zeit. f. Heilk.*, 1890, xi., p. 176.
[3] *Deutsch. med. Woch.*, 1891, No. 16.
[4] Diss., Greifswald, 1891.
[5] *Deutsch. Arch. f. klin. Med.*, lix.
[6] *Centralbl. f. inn. Med.*, 1898, No. 18.
[7] *Deutsch. Arch. f. klin. Med.*, lxi.
[8] *Verhandl. des Cong. f. inn. Med.*, 1893, xii., p. 236.
[9] *Prager med. Woch.*, 1893, Nos. 3 and 12.
[10] *Loc cit.*, p. 534.

Conflicting statements are given in regard to the *alkalinity* of the blood, which is not surprising, however, as the methods of determination are most unreliable.

The number of *red blood-cells* is usually diminished, according to both the older and more recent authorities; but perfectly normal figures are at other examinations encountered in the same patient, as the writer has learned by personal experience, without any special changes in the general condition being demonstrable. The same is true of the *leukocytes*. The *percentage of hemoglobin* in the blood undergoes various degrees of diminution, as Leichtenstern[1] and Quinquand[2] have shown.

The quantity of *urea* contained in the blood was found by the older investigators to be increased, especially when there was uremia (see p. 103), and also when uremia was not present. The increase may represent 10 to 20 times the quantity regarded as normal. The highest figure (1.5 per cent.) was obtained by Babington[3] in the case of a woman who had died in a uremic attack, although she presented a contracted kidney; it was the same percentage as in the urine. But some of these observations were made by means of inadequate methods.

Uric acid in abnormally large quantities has been found by Garrod,[4] v. Jaksch,[5] G. Klemperer,[6] and Magnus-Levy.[7] The percentage of *chlorin* in the blood, as well as that of *sodium*, which varies in the same way, was found by Biernacki[8] to be increased; while on the other hand *potassium*, *iron*, and *phosphorus* are diminished, as always in the hydremic blood of any form of anemia.

For some other changes in the blood, the reader is referred to the section on uremia, p. 100.

In addition to the changes enumerated so far, which are more or less constant and belong to the nature of the disease, there occur in the course of the illness, particularly when it is protracted and in proportion as the powers of resistance diminish, a series of *complications, mostly of an inflammatory nature*, which are in part due to the deterioration of the blood. The serous membranes, the lungs, and the heart are most exposed to these complications. During the later stage of the disease particularly, *pleurisy* and *pericarditis*, inflammatory and degenerative conditions of the *myocardium*, indolent *pneumonia* and bronchopneumonia are quite common and hasten the fatal termination. The *skin*, in addition to the itching, which is particularly frequent in uremic conditions (see p. 100), is often the seat of obstinate eczema, furuncles, and urticaria. Severe *inflammation of the intestines*, diphtheric inflammation of the colon, representing an exaggerated form of the simple catarrh, not infrequently make their appearance during the last stage.

These as well as other rarer complications may sometimes produce *fever*. Otherwise the disease usually runs an afebrile course, and the body temperature only rises above the normal temporarily during inter-

[1] *Untersuchungen über den Hämoglobingehalt des Blutes*, Leipzig, 1878, p. 99.
[2] *Chimie path.*, Paris, 1880, p. 110.
[3] *Guy's Hosp. Rep.*, 1836, p. 368.
[4] *Med.-Chi. Trans.*, 1848, xxxi.
[5] *Prager Festschr.*, 1890, p. 79.
[6] *Deutsch. med. Woch.*, 1895, No. 40.
[7] *Zeit. f. klin. Med.*, xxxvi.
[8] *Arch. f. klin. Med.*, 1894, xxiv., p. 475.

current exacerbations with renewed inflammation and during acute uremic attacks. Chronic uremia is more likely to be attended by subnormal temperature, as the writer has already stated.

COURSE, DURATION, AND TERMINATION.

Chronic "parenchymatous" nephritis presents during the greater part of its course, unless uremia or some special accident intervenes, a certain uniformity, varied only by the fluctuations in the dropsy and in the urinary excretion. These fluctuations, however, are not the same in all cases, and so the clinical course of the disease presents many variations.

In one class of cases the dropsy, which is usually the first symptom noticed by the patient, rapidly attains a very high degree. Within a short time, sometimes only a few days, the edema, primarily localized, changes to universal anasarca, the serous cavities become filled, and this condition persists with only slight variations, defying all remedial measures, until death. The urinary excretion obstinately remains below the normal, although considerable variations in the daily quantity take place, which, however, exert no appreciable influence on the dropsy. Cases of this kind usually have the shortest duration; they almost all terminate fatally a few months or possibly a year after the first appearance of the dropsy, either from pulmonary edema or with the symptoms of acute or chronic uremia. The *large white kidney* appears to be particularly associated with the clinical course that has just been described. Very rarely, if ever, does the patient live through this first stage; if he does, the dropsy disappears and the disease progresses at a more moderate pace.

In other more numerous cases, those which generally correspond to the "*many-colored*" *kidney*, the course is more changeable, the dropsy develops more slowly and is less obstinate and rises and falls inversely with the fluctuations in the urinary secretion; it may disappear altogether for a time, although the urine never quite regains its normal character, the albuminuria and excretion of morphologic elements in varying numbers persisting and showing that the renal disease unquestionably still exists. Such intervals, during which the patient feels practically well, may last weeks or even months, and several such periods may alternate with intervals of equal length during which the patient is worse. Eventually, in the majority of cases, the condition becomes permanently worse and resists all the remedies which before had proved effective; and the patient dies, either in the same way as in the first form or of one of the above-mentioned complications, usually one or two years after the approximate beginning of the disease, rarely later. Recovery is a rare exception, but has nevertheless been observed beyond a doubt. The writer's experience leads him to agree with Rosenstein, that this occurs only in cases which begin acutely after some infectious disease or exposure to cold, become chronic, and ultimately, after eighteen months or two years, end in complete recovery, the urine even completely regaining its normal character. In such cases, how-

ever, a complete *restitutio ad integrum* never takes place in the kidneys, as the writer has already explained (see Pathologic Anatomy); but such return to the normal is not necessarily included in the idea of "recovery."

[The editor has seen one case of nephritis in a child of about six years, where there were edema, scanty urine, albumin and casts in abundance, lasting over a period of two years or more. It seemed a typical case of chronic parenchymatous nephritis. Gradual improvement and what seems to be complete recovery have taken place and the patient is now a robust, apparently healthy young women, twenty years of age. Richard Cabot,[1] in 1899, made a collective investigation tending to show that in chronic nephritis of the type under consideration recovery occasionally occurs, as described by Senator.—ED.]

Improvement or *incomplete recovery* is a rather more common termination. The dropsy and all the other symptoms gradually diminish, the urine flows more freely, but continues to show the presence of albumin, until gradually the signs of advanced induration (contraction) become evident.

In a final category of cases the course is even slower; the disease extends over a number of years, and the symptoms are even less pronounced. There are at first indefinite complaints, most frequently of a slight headache or a moderate degree of edema of the face or of the lower extremities, and when the urine is examined an abundance of albumin with a scanty supply of morphologic constituents, especially casts and leukocytes, but also a few renal epithelial cells in process of fatty degeneration, is found, without any great diminution in the quantity of the urine. For months the patients feel tolerably well, and at the worst their peace of mind is disturbed by the occasional appearance of a moderate degree of edema; then follows a period during which all the symptoms become aggravated, and the clinical picture is more like that of one of the above-mentioned varieties, while the urine shows the same changes, and finally the patient dies during one of these periods; or the picture of contracted kidney may develop and also show considerable fluctuation. These cases belong usually to the "*spotted*" or "*speckled*" kidney, and just as the latter pathologically represents the transitional form to indurative nephritis, so the cases cannot be sharply separated clinically from those belonging to the latter variety of nephritis. The only points of distinction between it and typical contracted kidney are the somewhat shorter duration, ending in death, and the occurrence of episodes during which the picture of true "parenchymatous" nephritis predominates.

The clinical course may at any time be interrupted by renewed inflammatory outbreaks, which run the course of an acute diffuse nephritis and may terminate directly in death.

DIAGNOSIS.

The fully developed form of chronic non-indurative nephritis is so well characterized by "renal dropsy," with its characteristic localiza-

[1] R. C. Cabot and F. W. White, *Trans. Mass. Med. Soc.*, 1899.

tion, the remarkable pallor of the patients, and the attendant urinary changes which have been described, that it cannot be overlooked. It might possibly be confounded with *acute diffuse nephritis* or with *amyloid kidney*. From the former it is readily distinguished by the history and a few other points which have already been mentioned (see p. 201). Even an *acute exacerbation* of a chronic nephritis may usually be recognized if these same factors receive due attention.

The distinction from *amyloid kidney* is more difficult and cannot always be made with absolute certainty, especially as the combination of inflammation and amyloid degeneration is quite frequent, as has been mentioned before. The *absence* of the causes which usually lead to amyloid degeneration (*q. v.*) is, of course, against the assumption of that disease; but their *presence* does not necessarily argue against the diagnosis of nephritis, as the two diseases in part have the same etiology. It is more important to demonstrate (amyloid) enlargement of other organs, as the liver and spleen, and the absence of cardiac hypertrophy, and to examine the urine. (See Amyloid Disease). Quite frequently the symptoms are so grouped as to justify the diagnosis of "amyloid nephritis."

Renal congestion and pronounced forms of *contracted kidney* can usually be distinguished without any difficulty from chronic parenchymatous nephritis; the former by the presence of a cause for the congestion, such as a heart lesion, emphysema, and the like, by the cyanosis, by the different distribution of the edema, and by the differences in the urinary findings, especially the absence of fatty epithelial cells, balls of fatty granules, leukocytes, etc.; the latter by the absence of edema, the increase in the quantity, and differences in the general appearance of the urine and the presence of circulatory symptoms. Difficulties may arise in cases in which congestion becomes superadded to chronic nephritis from weakness of the heart. The history and the findings in the urinary sediment may in such cases assist in clearing up the diagnosis.

[The therapeutic test is often of value in clearing up the question of how much of the condition is due to congestion. Rest in bed, cardiac stimulants, etc., will in most cases of congestion be followed by a prompt improvement in the urinary findings, as well as in the edema, enlargement of the liver, etc., and thus make it plainer that passive congestion is responsible for many, at least, of the renal symptoms. Acute exacerbations of a chronic indurative nephritis that may closely resemble the chronic parenchymatous form may rapidly clear up under the therapeutic test of rest, and leave the contracted kidney clearly revealed as the underlying primary disease.—Ed.]

The *individual forms of chronic "parenchymatous" nephritis* (white, many-colored, spotted and speckled, and hemorrhagic kidney) can be distinguished with some degree of certainty only when the differences in the composition of the urine and in the clinical course, which have been described, are very distinct. In most cases one has to be content with the diagnosis of "chronic non-indurative or parenchymatous"

nephritis, and in the cases which occupy the boundary between indurative and non-indurative nephritis, such as cases of speckled kidney, it is not possible to particularize further than the diagnosis of "chronic nephritis."

An attempt has frequently been made to *localize the morbid process in the kidneys themselves* and to determine what individual tissue elements are involved. Traube[1] distinguished an intertubular and a circumcapsular form; the former he believed to be characterized by scantiness of the urine, with profuse and persistent admixture of blood, and by rapid course ending in death after a few months; the latter by urinary findings approximately like those of contracted kidney and by a longer duration. For his part, the writer does not think this distinction is correct, and believes that the differences depend on the different degrees of chronicity.

Some authorities have attempted to distinguish between involvement of the glomeruli, on the one hand, and of the urinary tubules on the other hand—*glomerulonephritis* and *tubular* nephritis—by means of the urinary findings. According to Fr. Fede,[2] the diagnostic points of glomerulonephritis are the absence of any form of renal epithelium and epithelial casts and the presence of leukocytes and hyaline casts. Theoretically, this appears to be correct enough,[3] but the facts are different, because an isolated glomerulonephritis without any affection of the uriniferous tubules is hardly conceivable. Even if under the influence of a special injury the glomeruli alone should become diseased at the very beginning of the attack, the inevitable effects on the circulation would implicate the epithelial cells in the process. In the type of glomerulonephritis which occurs during scarlet fever, the urine does not show the peculiarities demanded by Fede (see p. 194). All that one is justified in saying is that the proportion of renal epithelium or its débris and of casts is an indication of the extent to which the uriniferous tubules are involved.

PROGNOSIS.

Chronic "parenchymatous" nephritis is always a grave disease, and its prognosis can never be regarded as favorable; at best it may be considered doubtful, especially as regards recovery. For although, as has been remarked, complete restoration of health and functional recovery may take place in very exceptional cases, one is never justified in counting on such a result. As regards the duration of life, the outlook is not quite so bad, and in this respect the prognosis in the main is more favorable in proportion as the course is slow. Much depends, therefore, on early recognition and appropriate treatment of the disease.

Among the individual symptoms extensive and obstinate edema and persistent diminution in the quantity of the urine are to be regarded as

[1] *Deutsch. Klin.*, Jan. 17, 1863.

[2] *Contribuzione allo studio della malattia del Bright, 1880, und Giornale della assoc. dei naturalisti e medici di Napoli*, i., 1889, p. 93.

[3] It is to be observed, however, that, according to the writer's opinion, even hyaline casts cannot be formed without the renal epithelium being involved.

unfavorable, while a diminution of the edema and increase of the urinary excretion indicate an improvement, which may unfortunately be only temporary. The prognosis is affected also by copious and persistent or repeated admixture of blood in the urine. It is needless to say that the occurrence of any complication and the appearance of uremia render the prognosis much worse. Those cases which from the beginning or in their subsequent course resemble indurative nephritis may last a long time, and like the latter may cause comparatively little discomfort.

TREATMENT.[1]

The development of chronic nephritis may be prevented in many cases of acute inflammation of the kidneys by persevering with the hygienic and dietetic measures, laid down in a previous section (see p. 202), in the end-stage of the acute nephritis and during convalescence. In those cases which do not develop after an acute nephritis, the general directions in regard to the care of the health, with special regard for the kidneys, should be supplemented by a caution against the use of any food or condiment, such as alcohol, radishes, spices, and the like, calculated to irritate the organ, in practically the same way as for the prevention of acute inflammations.

It is needless to add that any disease that may be more or less correctly regarded as a possible cause of chronic nephritis should be combated with all the means at our command so long as chronic nephritis has not developed; but this would have to be done in any case, even if there were no fear of nephritis.

The treatment of the *causal* disease, however, is somewhat different when nephritis has already developed, even leaving out of consideration the numerous cases in which the cause is not known and cannot be determined. When there is a *syphilitic* taint the writer regards the use of mercury in chronic forms of nephritis as ineffective and, if used in large doses, positively harmful. Even potassium iodid, according to the writer's experience, is of doubtful utility in the treatment of chronic "parenchymatous" nephritis following syphilis. [In one case in particular the editor was convinced of the efficacy of potassium iodid and mercury, each in small doses, in cleaning up the nephritis. The case from the time-point of view might perhaps be classed as a subacute or subchronic rather than a chronic parenchymatous nephritis.—Ed.] In the same way the value of quinin in *chronic* nephritis after *malaria* appears to the writer very doubtful, although, of course, he does not question its efficacy against any malarial element remaining in the disease. It appears, therefore, that in the treatment of chronic parenchymatous nephritis little on the whole can be done to satisfy the *causal indication*. In fact, the etiologic factor in the treatment of renal disease may be largely disregarded, except that in the treatment all those measures and remedies which are believed to be capable of causing nephritis or of irritating the kidneys are to be avoided

[1] See H. Senator and v. Ziemssen in *Verhandl. des IX. Cong. f. inn. Med.*, 1890, p. 142; W. Leube in *Hand. der spec. Therap. inn. Krankh.*, Jena, 1895, vi.

unless more important indications, such as urgent danger to life, make their employment indispensable.

The *indicatio morbi* is somewhat less difficult to fulfil. Chronic parenchymatous nephritis is essentially an *insidious inflammation with successive exacerbations of varying intensity*, and accordingly requires anti-inflammatory treatment suited to these constant exacerbations and variations in the intensity of the process. But the ordinary so-called "antiphlogistic" procedures are even more useless in chronic than in acute nephritis. *Venesection* and *cold* appear to be quite powerless to combat the insidious inflammation and probably do more harm than good; *derivation* and *counter-irritation*, as well as *drugs*, are equally unreliable. Not one of these remedies, which have also been recommended for acute nephritis, and have already been enumerated on page 204, have proved to be of any value.

Although the writer has used *organotherapy* in a few cases, he has never seen any good results therefrom. Obolenski,[1] it is true, reports good results from the administration of lambs' or pigs' kidneys; he was most successful when he injected 400 gm. (12½ oz.) of the substance with 800 gm. (25 oz.) of physiologic salt solution subcutaneously, or in the form of an enema, 30 gm. (1 oz.) of substance with 50 to 60 gm. (1½ to 2 oz.) of physiologic salt solution.

Only those procedures which in acute nephritis yield the best results and are based on the principle of *sparing* and *relieving* the inflamed organs are moderately successful in chronic parenchymatous nephritis, with certain modifications adapted to the insidious character of the inflammation. They may arrest the progress of the inflammatory process and bring the disease to a standstill; if not permanently, at least for a variable length of time.

The kidneys may be relieved by diminishing the quantity of work required of them, or by removing any mechanical obstruction to the secretion of urine, such as is present in so-called parenchymatous nephritis in the form of compression or plugging of the uriniferous tubules, and at the same time by improving the circulatory conditions in the glomeruli. The second mode of relieving the kidneys is accomplished by vigorous *flushing of the organs* to wash out the masses of exudates, the swollen epithelial cells and their débris and the casts, and to dissolve out and carry off the stagnating excrementitious substances.

These indications are met chiefly by regulating or rather restricting the muscular activity and by a suitable diet.

As regards the former, it has been found by experience that *rest in the horizontal position* relieves the kidneys. The results of numerous observations show not only that bodily exercise almost always increases analready existing albuminuria, but also that severe and fatiguing work, especially work that involves the muscles of the thigh and pelvis, may produce even in perfectly healthy persons signs of renal irritation, such as albuminuria and the appearance of casts and leukocytes in the urine.

[1] *Wratsch*, 1899, No. 27, cited by Casper and Lohnstein, *Monatsber. über die Krankh. des Harn- u. Sexualapparats*, iv., 1899, p. 632.

(See Albuminuria, pp. 32 and 34, and Acute Nephritis, p. 203.) Conditions are more unfavorable for the kidneys when the body is in the erect posture; for, other things being equal, standing and walking are more injurious than muscular work performed in the horizontal position, even if it requires a greater expenditure of force. The explanation of these phenomena is naturally sought in the changes in the circulation.

In every case of chronic parenchymatous nephritis a strict watch must be kept on muscular exercise, remembering that an amount of work which would be mere play to a healthy man means great exertion and fatigue to such a patient. Under all circumstances excessive muscular exercise and every form of sport involving much use of the muscles must be prohibited. How much more bodily exercise is to be restricted will depend on the course of the disease and the severity of the symptoms, especially the urinary findings, as well as on the degree of dropsy that may be present. The latter alone may form a more or less considerable obstacle to movement of any kind.

So long as the urine is scanty and the dropsy is increasing or at its height, absolute rest in bed, possibly for weeks and months, must be observed, just as in acute nephritis. During times of improvement and in cases which from the beginning run a slow and mild course, resembling that of the indurative forms, moderate movement and light work may be allowed; but these must never be permitted to fatigue the patient. In favorable weather he may be allowed to go out, take walks, and the like, due precautions being taken against getting wet or becoming chilled. Any change for the worse, any relapse, of course, requires renewed vigilance; and according to circumstances the patient may have to be confined to his room or to bed for a longer or shorter time.

Diet.—The indication to spare and relieve the kidney can be partially satisfied by excluding all highly seasoned and stimulating foods from the diet, and especially whatever is calculated to call upon the epithelial cells of the uriniferous tubules to perform an increased quantity of work. For although in chronic parenchymatous nephritis the glomeruli are also involved, the disease of the epithelium predominates in the morbid process and forms the chief danger to the entire organism. Disease of the glomeruli and disturbance of their function, which is the excretion of water, although not altogether harmless, is much less dangerous and can practically be compensated by other organs—the skin, lungs, and intestine. The function of the epithelium, which is the excretion of nitrogenous excrementitious materials, the end-products of albuminous decomposition, cannot be performed even approximately by any other organ, and the retention of these products is much more dangerous than the retention of water. In order to spare the diseased epithelium, it is necessary, therefore, to cut down the quantity of albumin ingested, and to satisfy the nutritional needs of the organism by increasing the fat and carbohydrates, without, of course, permanently impairing the strength.

Not so very long ago it was reasoned, from the fact that albumin

was lost through the urine, that kidney patients ought to be given a large quantity of albumin. But, in the first place, exaggerated views prevailed at that time in regard to loss of albumin, which, as has been remarked, amounts to only a few grams, rarely more than 10 in chronic nephritis, a loss that could be easily covered with ¼ liter (quart) of milk, or from 40 to 50 gm. (1¼–1½ oz.) of meat; and, in the second place, increasing the ingestion of albumin merely tends to increase the decomposition of albumin, and therefore has no value whatever. On the other hand, it has been urged by many authorities in quite recent times that the particular form of nutriment was of no importance, and that the patients might be allowed to eat whatever they liked.

It is not to be denied that every case does not appear to be affected equally by the diet and that an excess of albumin is not always harmful; on the whole, however, the writer's experience leads him to agree with the majority of practising physicians, and he believes that restriction of albuminous foods, in the form of meat, ham, and sausage, acts favorably rather than otherwise.[1] Other authors have had the same experience (Csatáry,[2] A. Pick[3]). The increased danger of uremia when the patient is kept on nitrogenous food has been pointed out by Strubell, as the writer has mentioned in another place.

But the restriction of albumin has its limits. It is hardly necessary to say that the absolute withdrawal of albuminous food is not to be thought of for a moment in a disease the duration of which in the most favorable cases is computed by months, for that would be equivalent to starvation. The physician must therefore steer a middle course between flooding the organism with albumin and withholding it altogether. It is impossible to give a standard of albuminous diet that shall be applicable to all cases, or even to the same case during its entire course, since, as the writer has said elsewhere, the functional power of the kidneys varies in different phases of the disease, and also because the needs of the organism vary from time to time; the quantity required when the patient remains absolutely quiet in bed will be less than when he is going about and following his usual occupation. An approximate standard of albumin for a middle-aged patient suffering from chronic nephritis may be deduced from the quantity of food, especially albumin, required to maintain the nutritive equilibrium in a man who is not working. According to Voit, such a diet must contain 85 gm. of albumin, 30 gm. of fat, and 300 gm. of carbohydrates, with a total value of about 1860 calories. If, as recent investigations appear to show, healthy men, even when they are at work, can get along with a considerably smaller quantity of albumin—even with half of the quantity mentioned, if the non-nitrogenous food is proportionately increased—how much more a kidney patient, whose nutrition and especially nitrogen metabolism

[1] The writer has in his possession a number of communications from physicians who suffered from chronic nephritis, and determined by observations on themselves that the excretion of albumin is increased by a copious albuminous diet, and decreases whenever the diet consists chiefly of milk and vegetables.

[2] *Deutsch. Arch. f. klin. Med.* xlvii., p. 179.

[3] *Prayer Med. Woch.*, 1899, Nos. 16 and 22.

is at a much lower ebb. In greatly protracted cases it is, of course, possible, as may be inferred from Th. Rosenheim's [1] investigations, that too great a reduction of the albumin in the food might do harm by interfering with the proper utilization of other foodstuffs, especially fat.

Temporarily, when the patient's condition is unsatisfactory, edema is well pronounced, and the urine is scanty and contains an abundance of albumin and morphologic elements, a daily quantity of 30 to 40 gm. of albumin, which is contained in 1 liter (quart) of milk or in 200 gm. (about 6 oz.) of lean meat or 6 eggs, is quite sufficient, and during intervals of improvement, when the patient is on his feet and following his usual occupation, twice the quantity and even more may be given without doing harm. The *average daily quantity* in cases of chronic parenchymatous nephritis with moderately severe course may accordingly be stated as 50 to 70 gm. (1½–2 oz.) of albumin, which corresponds to 1½ to 2¼ liters (quarts) of cows' milk or 250 to 350 gm.(say 8–11 oz.) of lean meat or 8 to 10 eggs. If, in addition, 400 to 500 gm. (12½–14 oz.) of carbohydrates are taken, or the corresponding quantity of fat—100 gm. of which are isodynamic with 240 gm. of carbohydrate —the total daily food will represent on the average 2100 calories, or 300 more than are required, according to Voit, for a healthy resting man. This quantity is therefore certainly enough for a patient not only to maintain his body weight, but to allow him to put on flesh (albumin), even if several grams of albumin are daily lost in the urine.

In giving these figures it is assumed that the assimilation of the food in the intestine is normal. If it is impaired on account of digestive disturbances, the daily quantity of food must be restricted.

As regards the individual articles of food, *milk* should indisputably be placed at the head of the list. Again and again it has been shown to be, when properly used, the most appropriate article of diet, so much so that the physicians of experience (Semmola,[2] Karell,[3] G. Sée,[4] Donkin,[5] and many others) even ascribed to it a specific action on the morbid process in the kidneys, and *milk cures* enjoy a special reputation in the treatment of chronic nephritis. The advantages of milk are: that it is easily digestible, free from any irritating extractives, and in addition possesses certain diuretic properties, as was pointed out in connection with the treatment of acute nephritis (see p. 203). A milk diet thus *flushes out the kidneys* and removes the epithelial débris, casts, etc., which obstruct the lumen of the tubules. Another advantage of milk is that it does not promote intestinal putrefaction; on the contrary, it rather tends to restrict it, and is therefore less likely than other forms of albumin to cause auto-intoxication through the absorption of these products of putrefaction.

An absolute milk cure in which the quantity allowed at first is very slight and is gradually increased from ½ to 1, then to 2, and finally at

[1] *Pflüger's Archiv*, 1889, xlvi., p. 422.
[2] *Loc. cit.*
[3] *Petersburg. med. Zeits.*, 1865, viii., p. 193, and *Arch. gén. de méd.*, Nov.-Dec., 1866.
[4] "Le régime alimentaire," Paris, 1887.
[5] *Lancet*, 1893, p. 1165.

the most to 3 liters (quarts), without any other kind of food, is really a form of denutrition cure, some of the benefit of which is probably due to the restriction of albumin; for the quantity taken at the beginning of the cure and for some time during the course of the treatment contains much less albumin than the above-mentioned average quantity, and it is to be remembered that the assimilation of milk and its albumin in the intestine is not so perfect as that of other kinds of food.[1] Skimmed milk, which is recommended by some authorities, as, for instance, Donkin, is even poorer in albumin and especially in fat.

A strict course of treatment like this is only suitable for short periods at a time, one or at most two weeks, and when the disease is most severe and closely resembles the acute inflammatory forms. At all other times an exclusive milk diet is as unnecessary in chronic diffuse nephritis as in acute nephritis, and may not even be good for the patient. For even if the necessary quantity of albumin, which represents about 2 liters (quarts) of milk, were completely assimilated, there would still be a considerable lack of fat and carbohydrates in any exclusive milk diet. The stomach often rebels against such large quantities of milk, or digestive disturbances, such as meteorism and constipation, or in some cases, on the contrary, diarrhea, may develop. Although distaste for the article and the digestive disturbances may be avoided by administering the milk carefully in small, gradually increasing doses and adding a little lime water, salt, tea or coffee, an absolute milk diet after a time fails to satisfy the patient's needs; nor, as the writer has said, is it altogether necessary. But milk should not be given up altogether, and whenever possible it should form the chief part of the diet.

Buttermilk may be substituted for milk from time to time, at least in part, especially when there is a tendency to constipation; or kumiss and kefir, which are both nutritive and palatable, may be given under certain circumstances instead of milk or to eke out a milk diet if the patient cannot take a sufficient quantity. The alcohol, which is present in such small quantities as not to be in the least objectionable, and the lactic and carbonic acids which they contain, render them more acceptable than milk to many patients, and their greater diuretic action is also desirable for reasons that have already been given.

In order to make up the average quantity of food as indicated above, the patient should receive, in addition to 2 liters (quarts) of milk, which contain the required quantity of albumin, besides 70 to 80 gm. (say 2–2½ oz.) of fat and 80 to 85 gm. of carbohydrates, about 200 gm. (6 oz.) more of carbohydrates. As the latter cannot well be given in the simple form of sugar, a part may be replaced by fat in the form of cream, butter, or lard, of which 40 to 50 gm. are equivalent to 96 to 120 gm. of carbohydrates, and the remainder of about 100 gm.

[1] According to Rubner (*Zeits. f. Biol.*, xv.), an adult assimilates about 93 per cent. of the nitrogen contained in milk. The assimilation is less perfect when more than 2 liters are taken in a day.

may be made up of sugar, either in the form of sweet preserves or fruit jellies, and by farinaceous foods like wheat bread, thick soups, barley or sago broth, and potatoes. The last-mentioned foods contain small quantities of albumin, too insignificant, however, to be taken into consideration.

If milk cannot be taken at all or only in insufficient quantities, one of the many substitutes used for infant-feeding may be recommended, although by themselves they do not afford sufficient nutriment for any length of time unless taken in such large quantities that the intestinal tract, which is sensitive to begin with, rebels. *Milk of almonds* (*emulsio amygdalarum*) proves an acceptable substitute in most cases on account of its high percentage of albumin and fat.

If the patient will not take enough milk he must receive *meat*, the preference, for reasons already stated, being given to the kinds which contain a minimum of extractives and ptomains. Accordingly, *white meats*—veal, lamb, young pig, spring chicken, and mutton—are to be recommended, although other kinds of meat, especially beef (if young animals), need not be prohibited altogether. The writer also recommends *fish*, particularly river fish, and has never known any harm to result from eating them when properly prepared.[1] Dishes containing *calcium*, such as jellies, "jus" and "gluton," are to be recommended, and the loss of albumin may be advantageously equalized by administering *vegetable albumin* in the form of "Aleuronat" and "Roborat," as these preparations are free from the extractives of meat and are equally well utilized by the organism.

On the other hand, pickled and smoked articles of every kind, strong cheese, and the like, are to be eschewed, and in the preparation of the dishes that are allowed, spices and other stimulating condiments should be reduced to a minimum. Stimulating vegetables, as radishes, asparagus, and onions, should also be forbidden.

The question whether *eggs* should be allowed forms the subject of a paper published by the writer[2] some years ago, in which he condemned their use on account of the injurious influence of uncooked egg albumin. The publication of the writer's paper gave rise to a lively discussion and numerous investigations, which show that *cooked eggs* in general do not have the same effect as raw eggs, and even in large quantities have no influence on the albuminuria. There are, however, exceptions to this rule, for the eating of cooked eggs in large quantities has been known in a few instances to cause albuminuria or to increase an already existing albuminuria. It is, of course, a question whether in such cases the eggs are injurious in themselves or whether it is merely the excess of nitrogenous food that is responsible for the mischief, since any

[1] Nollet ("Le régime alimentaire chez les albuminuriques," *Thèse*, Paris, 1885) observed in the case of subacute nephritis in a phthisical patient an increase of the albuminuria after the eating of fish (the variety is not stated), and therefore gives a warning against the use of fish. G. Klemperer was not able to confirm this observation (*Therapie der Gegenwart*, 1901, p. 428).

[2] "Ueber die hygienische Behandlung der Albuminurie," *Berlin. klin. Woch.*, 1882, No. 49.

other diet with too large a percentage of nitrogen, such as a meat diet, occasionally produces albuminuria.[1]

The practical conclusion to be drawn is, that *raw eggs* are not to be recommended in parenchymatous nephritis, while, as a rule, no objection need be raised to the eating of cooked eggs, providing they are given in such quantities as not to cause an excess of the maximum allowance of albumin.

In very emaciated patients, it is advisable to increase the *fats* and *carbohydrates* above the standard given whenever the state of the digestion makes it possible to do so. This also affords a means of securing the variety in the diet which is so desirable, and the patient's wishes may be gratified by allowing fruit, especially grapes, on account of their diuretic properties, and vegetables of which the leaves or tops and the roots are eaten (leguminous and tuberous).

Beverages form an important part of the diet. They are to be taken not only to relieve thirst, but also to help *flush out* the kidneys. A highly concentrated diet containing a high percentage of albumin may in itself cause albuminuria and irritation of the kidneys and aggravate an already existing nephritis, as the investigations of J. Hartmann[2] and Rosenfeld[3] have shown. The disadvantages of withdrawing fluid and the advantages of allowing an abundance of fluid in chronic parenchymatous nephritis have also been demonstrated by the clinical observations of v. Bamberger.[4] Milk, as the writer has already remarked, in part fulfils this indication, which is still more effectively met by the so-called *alkaline* and *alkaline saline* carbonated waters, such as Bilin, Giesshübl, Fachinger, Seltzers, and the like, by *lemonades* made with fruit acids and fruit juices, and lastly by *whey*, either sweet or sour, according to the patient's fancy, particularly when there is constipation.

The daily quantity of fluid may, as a rule, be left to the patient's own taste, merely maintaining the proper relation between the ingestion of fluid and the quantity of urine. More than 1½ or at most 2 liters (quarts) over and above the milk taken is not, as a rule, advisable.

Alcoholic beverages in general must be regarded as injurious to kidney patients, because alcohol undoubtedly acts as an irritant; nevertheless they need not be forbidden under all circumstances. They are to be avoided altogether during acute exacerbations, just as in an attack of recent acute nephritis, except when their use is rendered necessary by extreme weakness and collapse. Under other circumstances, patients who are used to alcoholic beverages and find it a hardship to do without them may be permitted to take their drink in small quantities, diluted as much as possible. The pure fruit wines, such as apple cider and berry

[1] See Senator, *Albuminurie*, pp. 160 and 164; furthermore, Lecorché and Talamon, *loc. cit.*, p. 633 and pp. 703 and 706; D'Arcy-Power, *Barthol. Hosp. Rep.*, xxiii., 1888; R. Saundby, *Vorlesungen über die Bright'sche Krankheit*, translated by W. Lewin, Berlin, 1890, p. 24; Prior, *Zeit. f. klin. Med.*, xviii., 1891, p. 84 and p. 101; Csatáry, *Deutsch. Arch. f. klin. Med.*, 1891, xlvii., p. 179; Ott, *Deutsch. Arch. f. klin. Med.*, 1894, liii., p. 608.

[2] Diss., Zürich, 1885, and *Berlin. klin. Woch.*, 1886, No. 40.

[3] *Verhandl. des VIII. Cong. f. inn. Med.*, 1888, p. 473.

[4] *Wien. klin. Woch.*, 1888, No. 12.

wines, on account of their low percentage of alcohol, and next to these light Moselle, and finally other varieties, may be recommended, providing they are sufficiently diluted with pure or carbonated water. Beer is regarded as peculiarly harmful, and second only in this respect to brandy and the stronger kinds of wine, probably because it contains a high percentage of extractives, since its percentage of alcohol, as a rule, is even lower than that of most wines, even the lighter varieties. But in very chronic cases some concessions may be made to the patient's taste even in the matter of beer, although the urine and the general conditions must, of course, be kept under strict supervision.

Indeed, the physician's chief task in chronic parenchymatous nephritis consists in adapting his dietetic and hygienic prescriptions to the various phases of the disease and the individual conditions of each case, loosening or tightening the reins of authority as circumstances demand.

In addition to these dietetic and hygienic measures, *diuretic remedies* may and even must be employed to *flush out and unload the kidneys* whenever the urine becomes scanty and turbid, the dropsy increases, as it usually does, and the organism begins to show signs that it is being overloaded with excrementitious products (uremic intoxication). Without dwelling on the reasons, which would be superfluous, the writer may say that the preference should be given to those diuretics which act on that portion of the kidney which is especially concerned with the excretion of water—namely, the glomeruli—by stimulating them to increased transudation, and which do not irritate the epithelium of the uriniferous tubules. Measures calculated to increase the arterial tension, the introduction into the body of copious quantities of water or, even better, water containing the salts found in serum, have such an effect. Both indications are satisfied by the *diuretic decoctions* and by *vegetable acid salts* which are converted into carbonates in the blood, and probably act by withdrawing the water from the tissues and incidentally rendering the urine alkaline. They also assist in loosening and dissolving the accumulated tissue débris, casts, and other substances, such as uric acid, which are dissolved with difficulty in acid urine.

Finally the remedies which act chiefly on the blood-pressure are the *digitalis* preparations and certain substitutes that have been proposed. Details on the employment of all these remedies have been given in the section devoted to the treatment of dropsy (see p. 88). As a last recommendation, *inunctions*, for the reasons given under Acute Nephritis (see p. 203), for which they are especially recommended, may be mentioned as a mild and harmless diuretic measure.

In chronic nephritis a number of other precautions must be observed, particularly in the case of patients who are not confined to the bed. Above all they must be guarded against sudden changes of temperature and exposure to cold and wet. They must therefore wear woollen underclothing and avoid cold baths and cold sponging of the entire body. The observance of these precautions is more essential than ever in women at the time of menstruation, because the entire body, and the

kidneys in particular, is more sensitive than usual, and the patients, even if they are not bedfast, will do well to remain in bed or, at least, in their rooms.

Whether *warm baths*, which have often been recommended, are of any special use to combat the renal affection, except in dropsy, by inducing perspiration, is difficult to say. The compensatory action of the skin, which is supposed to be stimulated, may, it is true, make up for the renal disturbance by removing water; but the specific urinary constituents, which are the chief mischief makers, are not removed in any appreciable quantity even by the most profuse sweating (see also p. 114). A disadvantage is that the continued use of warm baths to induce sweating is apt to render the skin delicate and thus increase the danger of catching cold. Such measures as *alcohol rubs* or *dry rubbing of the skin*, or possibly *wet rubs with tepid or cool salt water*, may, on the other hand, be safely recommended for the purpose of stimulating the activity of the skin.

Similarly, the value of *drinking-cures* and *bathing-cures* is difficult to determine. It cannot be denied that patients with chronic nephritis are often benefited by such cures, but the good results are to a large extent due to the combined action of a number of favorable factors—appropriate diet and mode of life in general—and it is doubtful whether much of the benefit should be placed to the credit of the mineral water. However, as the systematic drinking of the water of certain springs, with or without baths, stimulates the secretion of urine and thus flushes out the kidneys or exerts a favorable influence on digestion and assimilation, patients who find it hard to escape from the excitement of ordinary life and from their occupation may be advised to go to a suitable resort at the proper time of the year. The advantage that during such cures, which have a distinct psychic influence, the patient's spirits are improved and he becomes more hopeful is not to be underestimated.

Only patients without dropsy or with only minute traces of edema and with sound heart action should be sent to *bathing-resorts*. The most appropriate cases are therefore those with very chronic course which occupy the boundary between "parenchymatous" and indurative nephritis. The waters to be preferred are *sodium chlorid waters* [this would, perhaps, hardly meet with the approval of those who believe in the dechloridation treatment of nephritis, and who regard the administration of chlorids as tending to increase any tendency to edema—Ed.], *alkaline* and *alkaline saline waters*, and *saline chalybeate springs* (Wiesbaden, Kissengen, Rohinsch, Ems, Gleichenberg, Carlsbad, Elster, Franzenbad, Brückenau). Chalybeate waters should be given the preference for very anemic patients. In the choice of other baths the decision will have to depend on the condition of the digestive apparatus and the presence of complications, and finally on the physician's or patient's personal preference. It is always well to deprecate the extravagant hopes that patients usually entertain in regard to the benefits to be derived from going to a "bath." When the hope of complete

recovery, as usual, fails of realization, the disappointment will not be felt so acutely.

Drinking-cures may also be followed in other appropriate places (summer resorts), and probably with quite as much benefit.

Better results than from bathing- or drinking-cures, by which the patients are placed under favorable conditions for, at most, a few weeks, may be obtained by a *change of climate* during the winter and a prolonged stay in a warm, dry locality protected against abrupt changes of temperature. In company with others the writer has seen considerable improvement and even functional recovery take place after a journey to Egypt (Heluan, Assuan), especially when the patients prolonged their stay beyond the end of the winter; a sojourn to Algiers, at the Cape, and in India may also be recommended. If such long journeys are out of the question, dry localities in southern Italy and southern France (Torre del Greco, Solfatara, Puzzuoli, Hyères, Cannes) or at the Riviera di Ponente (Nizza and surroundings), or possibly in southern Tyrol (Meran, Gries, Arco), may be selected instead.

During the *summer* such patients should be advised to seek a forest climate at not too great an altitude, such as places in Thüringen, in the Black Forest, etc., where they can take walks without doing too much climbing, and seaside resorts on the Baltic and on the North Sea. During the intermediate seasons, fall and spring, the southern coast of England (Bournemouth, Torquay, Ventnor, and the Isle of Wight) or the southwestern coast of France (Arcachon, Biarritz, Henday, St. Jean de Luz) may be recommended. [In America the dry and warm climates are found in southern Texas, New Mexico, Arizona, California, and in Old Mexico. Care should be taken that the invalid goes to some place where he can be comfortably housed and fed—at least nearly as well as at home—and where the surroundings are such as to tempt him to get out of doors daily for a moderate amount of exercise in the open air. And places where his companions would be chiefly tuberculous patients —and these localities just mentioned are favorite haunts of the phthisical —should be avoided, both because of the greater danger of his acquiring a tuberculosis through careless sanitary regulations, and because of the depressing influence upon him of daily and even hourly contact with this class of sufferers.—ED.]

Finally, women the subjects of chronic nephritis should be strictly warned against allowing themselves to become *pregnant*, as that condition has a very unfavorable effect on the course of the disease.

If a case is managed with proper care and with due regard to the above-mentioned therapeutic principles, it is not infrequently possible to keep the most important *symptoms* of the disease—*albuminuria and the attendant urinary changes and the dropsy*—in check for a considerable length of time, and to guard against the occurrence of *uremia* and other sequelæ that would threaten life. Nevertheless the physician often finds himself obliged to resort to *symptomatic treatment* to combat one or the other of these symptoms. Against *albuminuria* as such there is no known remedy; the treatment of *dropsy* and *uremia* has been discussed

(see pp. 88 and 112); other symptoms and complications must be combated by satisfying the respective indications without losing sight of the basal disease and the patient's strength.

[There can be little question that routine treatment of nephritis of every variety is often carried to the extreme. In cases of chronic nephritis particularly, there is often seen a tendency always to prescribe milk as the sole diet and to ignore the particular conditions that may be presented by the case in hand. There should be more of individualization in the treatment. As Senator well says, the physician should adapt his dietetic and hygienic prescriptions to the various phases of the disease and the individual conditions of each case. It is no unusual thing to see patients with chronic nephritis who have been kept upon an exclusive milk diet—often skimmed milk at that—for weeks or months. The degree of emaciation that is present is not realized until, perhaps, the edema disappears and the gaunt relic of previous health, with weak and flabby musculature, is revealed to us. Nor is cognizance taken of the fact that anemia may be in large measure due to insufficient nourishment given or insufficient utilization of what is taken. Disgust for the milk, coated tongue, nausea, meteorism, irregular bowels, may often be traced to the giving of too much milk for too long a time. It is extremely gratifying in many of these cases to see how promptly there is improvement in all these conditions on cutting down the amount of milk, or for a time stopping it entirely and adding to the dietary fruits, such as apples, pears, grapes, and oranges; cereals, bread and butter, simple vegetables, and a moderate amount of meat. Generally, too, no change for the worse can be seen in the edema or albuminuria under this change, although a transitory increase in the amount of albumin seems to result at times. The danger of starving these patients by a too rigid adherence to the milk diet is a real one, and has not been overstated, we think, by Senator.

v. Noorden has also spoken forcibly against the overdoing of the milk diet in acute and chronic parenchymatous nephritis, and believes in allowing much greater liberty in the matter of food than is the common practice. In the acute forms and in those in which the amount of urine is scant and edema marked, he warns against giving too large an amount of fluid of any kind, even water. If the kidneys simply refuse to carry off the extra amount of water, we are certainly not flushing them, no matter how much water may be taken by the stomach. Moreover, v. Noorden contends we are not giving them the physiologic rest that is their due when we ask them to eliminate an unusual amount of water, for water elimination is one of their functions. Hence the amount of fluid administered should not be excessive, say 1½ to 2 liters a day, though when lessening of edema and increased diuresis follow the ingestion of an increased amount of water, larger amounts may be given for the "flushing-out" effect. The thirst of the patient may in a measure be a guide to the amount of water to be allowed. Sweating, v. Noorden believes, is especially helpful in the cases with marked dropsy and is a measure of value for the removal of water, but of

trifling value for the removal of dissolved toxic substances.[1] v. Noorden's views have been collected into a monograph of 112 pages and translated into English. They are well worth careful study.[2]

There is a point that is, we believe, well worth emphasizing. With the exacerbations of the chronic parenchymatous nephritis—and it applies to the chronic interstitial, too—and particularly where the alimentary tract is in great disorder, the best treatment is often absolute rest in bed with an entire cutting off of food for a time, or the substitution of some simple food like rice water or barley water. A brisk purge, rest in bed for a few days, a moderate amount, say one quart, of water or of rice water in the twenty-four hours, will often relieve the nausea, tympany, diarrhea, loathing of food, etc., to a marked degree. The digestive organs and kidneys, too, under this temporary starvation plan, may acquire a certain tolerance, and be able to stand in a few days amounts and kinds of food that would before have produced marked disturbances.—ED.]

CHRONIC INDURATIVE NEPHRITIS OR CONTRACTED KIDNEY.

(Chronic Interstitial Nephritis and Sclerosis of the Kidneys.)

The indurative processes, characterized by destruction of parenchyma and contraction, in the kidneys as in other organs are more or less extensive, depending on the cause and starting-point of the disease to which the induration is due; they may be strictly circumscribed to one kidney or only part of a kidney, or may be diffuse and involve both organs. Circumscribed contraction occurs as the result of embolism (*Embolic Contracted Kidney*, see p. 160) in one or both kidneys; induration of one or both kidneys, after ascending unilateral or bilateral inflammations developing by slow extension from the urinary passages (see *Pyelonephritis*, p. 336); or as the result of obstruction with or without an accompanying hydronephrosis, also after long-continued congestion (*Congestive Contracted Kidney*, see p. 150); and finally diffuse contraction of both kidneys may be caused by an insidious hematogenous inflammation acting through the blood.

Unless the nutrition in general and the blood-supply to the kidneys in particular are very much reduced, the loss of parenchyma is neutralized by a compensatory hypertrophy of the tissue that remains intact and retains its secretory function, the glomeruli and epithelial lining of the uriniferous tubules, and thus the loss of function due to the tissue destruction is to a certain extent restored (see p. 163). In addition, contraction of the kidneys is accompanied by *hypertrophy of the heart*, and in this respect the process in the kidneys differs from similar processes in other organs; the cardiac hypertrophy may be secondary to the kidney affection or it may develop independently from the same

[1] The opposite view is supported by others, and has been advanced in view of his own experimental and clinical observations by H. Strauss (*Deutsch. med. Woch.*, Aug. 18, 1904).

[2] Carl v. Noorden, *Clinical Treatises on the Pathology and Therapy of Disorders of Metabolism and Nutrition*, Part II., Nephritis, New York, 1903.

causes. When added to the compensatory hypertrophy in the kidneys, this cardiac hypertrophy may result in a functional activity of the kidneys *in excess of the usual measure*—so-called "*overcompensation.*" It is in the hematogenous indurations, with which we are here exclusively concerned, that these compensatory processes reach their highest development, ultimately producing a clinical picture which, as Traube taught, is characteristic of fully developed contraction of the kidney. The symptoms vary both as to time of appearance and grouping, as many different causes are capable of bringing about morbid processes that terminate in induration.

Diffuse indurative nephritis may develop either primarily as the product of a protracted or oft-repeated, extremely insidious inflammatory irritation, or it may follow acute, subacute, or subchronic so-called parenchymatous inflammatory states and represent their terminal stage —*i. e.*, as so-called *secondary induration* or *contracted kidney.* The primary form again may be either the result of some irritant acting *directly* on the renal parenchyma on account of some abnormality in the blood, or *indirectly* through the mediation of *arteriosclerosis.* The former is designated "*genuine (primary) renal cirrhosis*" or simply "*chronic interstitial nephritis;* the latter is known as "*arteriosclerotic contracted kidney*" or "*sclerosis of the kidneys.*"

In the historic introduction to this section (p. 167) it has been fully explained how this conception of hematogenous contracted kidney, which is now generally accepted, was slowly evolved, the disease being formerly regarded by some as the "third stage of Bright's disease," by others as a special affection quite independent of other forms of Bright's disease, and designated "granular atrophy," "cirrhosis of the kidneys" or "gouty kidney," and finally by a third group as forming merely part of a general arteriocapillary vascular disease. In the same place it was stated that while these older conceptions all contain a measure of truth, they are not sufficiently comprehensive to be applicable to all cases. The difficulties of the subject are enhanced by the impossibility of strictly separating the individual forms of nephritis clinically, pathologically, or even etiologically on account of the numerous transitional varieties; and this is especially true of indurative nephritis or contracted kidney, which, as the writer has said, represents the final stage of inflammatory processes due to a variety of causes.

ETIOLOGY AND PATHOGENESIS.

When induration of the kidneys develops from acute or chronic "parenchymatous" nephritis—in other words, in cases of so-called "*secondary contracted kidney*"—the disease must, of course, be referred in the last instance to the same known or unknown causes that are at the bottom of the primary disease. Not that these causes always lead to the same evolution of the morbid process in two or three stages culminating in contraction, or necessarily lead to induration by way of an acute and chronic parenchymatous (subchronic) inflammation; on the contrary, the same causes, as has already been pointed out on page 176,

may, depending on the severity and duration of the impression, produce an induration secondary to the acute or subchronic inflammatory stage, or an independent induration. This same community of causes was pointed out in connection with chronic non-indurative nephritis.

There are certain noxious agents which, owing to the length of time during which they act, either continuously or repeatedly, are especially prone to produce a *primary* indurative nephritis directly, and without the prelude of preliminary stages. These agents are the same as those which play an important part in the etiology of *arteriosclerosis*, particularly *gout* and chronic *lead-poisoning*, as well as other forms of chronic metallic poisoning, the *abuse of alcohol*, *chronic syphilis*, and *diabetes mellitus*—another reason why induration due to *arteriosclerosis* cannot be strictly separated from the independent form of induration which is known as *chronic interstitial nephritis*.

The relations existing between induration of the kidneys and *arteriosclerosis* are of a triple character: (1) As a result of the above-mentioned noxious agents or certain others,[1] arteriosclerosis may be the primary affection and bring about induration of the kidney in the manner presently to be described (see Pathologic Anatomy, p. 269), forming the so-called *arteriosclerotic induration of the kidney* or contracted kidney, or, in other words, *sclerosis of the kidneys*. (2) Conversely, induration may result from chronic interstitial nephritis, and later, on account of the cardiac hypertrophy and associated increase in the arterial tension, cause a vascular sclerosis; for it is well known that persistent or repeated increase of blood-pressure greatly favors the development of arteriosclerosis. This form is chronic interstitial nephritis with *secondary arteriosclerosis*. (3) The two conditions may develop independently of one another from the same cause. Indurative nephritis and arteriosclerosis may therefore have a mutual causal relation, or they may represent co-ordinate and more or less simultaneous effects of some other cause.

It is generally acknowledged that among the above-mentioned noxious agents is *gout*, to which fact Todd first called attention. In England particularly, the classic home of gout, the occurrence of contracted kidney is so common in gout, and so greatly surpasses in frequency the cases due to other causes, that the term "gouty kidney," introduced by Todd, is practically synonymous with contracted kidney. But in other countries, particularly here in Germany, where it seems to the writer gout has become more common, one has opportunity enough to study "gouty kidneys." [In America gout is by no means as common as in England, yet it is not so infrequent as many think. Futcher[2] especially has called attention to this fact. It must therefore be reckoned with in this country also as a cause of chronic interstitial nephritis.

[1] Arteriosclerosis may be due to other causes besides those here enumerated; but those causes appear to have a less unfavorable effect on the kidneys than on the vascular system; for example, chronic abuse of tobacco, protracted or repeated attacks of plethora, persistent and profound psychic emotions, and the like. These are followed much later by disease of the kidneys.

[2] *The Practitioner*, July, 1903.

It is to be remembered, too, that it is not by any means limited to the wealthy class of high-livers. In our charity hospitals and among the poor, typical gout can often be seen. The writer has found it among the poor in a few workers in lead—"lead gout"—and the findings indicative of contracted kidney were present. In one old negro gouty tophi gave conclusive evidence as to the cause of the joint, cardiovascular and renal findings.—ED.]

After Tanquerel des Planches [1] and many others had mentioned albuminuria as a symptom of lead-poisoning, and Garrod [2] had pointed the connection existing between gout and *chronic lead intoxication*, that condition was recognized by Lancereaux [3] and Ollivier [4] as a frequent cause of contracted kidney. The connection between gout and chronic lead-poisoning does not concern us here, but the relation existing between lead-poisoning and contracted kidney is demonstrated both by experiments and by clinical experience. Charcot and Gombault,[5] Molenaar,[6] Coën and d'Ajutolo,[7] Prior,[8] Lüthje,[9] have succeeded in producing chronic nephritis experimentally by administering lead for a certain length of time, and the results of their experiments are not invalidated by the fact that others, like Heubel [10] and Rosenstein,[11] failed in a similar attempt; for it is to be remembered that paralysis, the relation of which to lead-poisoning no one doubts, does not develop in every case. Certain special conditions determine in any individual case which organ is to become diseased. From a clinical standpoint the writer may mention—to pass over numerous isolated instances—that Dickinson [12] found contracted kidney in 26 out of 42 leadworkers in St. George's Hospital, and that among 45 cases of contracted kidney, 10 occurred among leadworkers; M. Jacob [13] found that 8 out of 12 cases of contracted kidney were in leadworkers, and E. Wagner,[14] in a series of 150 cases, found chronic lead-poisoning as the cause in 15, and, finally, C. Baumhard,[15] 7 (or 6) cases among 105 from Gerhardt's clinic. The writer's own observations give entirely similar results. Among 250 cases of indurative nephritis of which he has notes, there are 17 in which the cause, after all other possibilities have been positively excluded, is chronic lead-poisoning, and a few in which the cause is somewhat doubtful because other factors (alcohol) are also operative. In 13 of the 17 cases the diagnosis of contracted kidney was confirmed by autopsy; in the remaining 4 the symptoms were so well marked that there could be no doubt of the diagnosis.

In common with most authors the writer believes there is no doubt

[1] *Traité des maladies de plomb.*, ii., 1839, p. 248.
[2] *Med.-Chi. Trans.*, 1854, xxxvi., and *Natur und Behandlung der Gicht*, translated by Eisenmann, Würzburg, 1861, p. 169.
[3] *Union méd.*, 1863, p. 513, and *Dechambre's Dic. encycl. des sci. méd.*, article "Rein."
[4] Thèse, Paris, 1863, and *Arch. gén. de Med.*, 1863, ii., p. 530.
[5] *Arch. des Phys. norm. et path.*, 1881, i., p. 121.
[6] Cited by Rosenstein, *loc. cit.*, p. 336.
[7] *Ziegler's Beiträge zur path. Anat.*, etc., iii., p. 5.
[8] *Zeit. f. klin. Med.*, 1891, xviii., p. 111.
[9] *Ibid.*, xxix., p. 313.
[10] *Pathogenese der Bleivergiftung*, Berlin, 1871.
[11] *Virchow's Archiv*, 1867, xxxix.
[12] *Loc. cit.*, p. 382.
[13] *Deutsch. med. Woch.*, 1886, p. 547.
[14] *Loc. cit.*, p. 293.
[15] Diss. inaug., Berlin, 1898.

that the *chronic abuse of alcohol* is a factor in the production of indurative nephritis, although it must be admitted that its effects are frequently reinforced by other unfavorable conditions, such as exposure to cold and the like, and it is therefore difficult to secure accurate statistical reports. Even Dickinson,[1] who condemns as greatly exaggerated Christison's statements that three-quarters to four-fifths of all the cases of "*granular degeneration*" of the kidneys are due to drunkenness, nevertheless does not deny the influence of alcoholic abuse on the kidney; but from an analysis of the cases that occurred in St. George's Hospital between 1841 and 1871 he finds that cirrhosis of the kidneys is less common than cirrhosis of the liver, which is readily comprehensible. He correctly points out that the liver is more directly and more greatly exposed to the irritation of alcohol introduced into the stomach than are the kidneys; but as the latter are undoubtedly also capable of being irritated by an excess of alcohol, it is not difficult to understand that indurative nephritis should be the result of long-continued alcoholic abuse. Dickinson believes that the excessive drinking of beer is especially harmful to the kidneys. The writer's own observations in regard to the significance of alcohol in contracted kidney also have to do chiefly with beer and wine drinkers, perhaps because in our country the abuse of "schnaps" and the opportunity to observe its consequences have recently become much more rare.

The question of the etiologic significance of *syphilis* in the production of contracted kidney is obscured by the frequent combination of amyloid degeneration with indurative processes. For this reason statistics cannot very well be utilized to decide this question; but the writer has seen several cases of simple indurative nephritis without amyloid disease in which no other cause but syphilis could be demonstrated. He therefore agrees with E. Wagner, who, out of 63 cases of renal disease referable to syphilis, found 7 cases of granular atrophy and, in addition, 6 cases of unilateral atrophy of the kidney, and therefore regarded syphilis as one of the undeniable causes of contracted kidney.[2] It is also to be remembered that syphilis is a fruitful source of arteriosclerosis, that the two processes are frequently associated, and are therefore difficult to distinguish.

Diabetes mellitus until recently was not included among the causes of chronic indurative nephritis, and the writer[3] formerly regarded the condition as rare in the course of diabetes. But a more extended period of observation, during which he devoted special attention to this relation, has taught him not only that albuminuria is quite common in diabetes mellitus, and much more common than was formerly supposed, but also that arteriosclerosis and the corresponding renal changes are not infrequently found in diabetics during the second half of life. *Simple epithelial changes*, consisting in glycogenic degeneration of Henle's loops

[1] *Loc. cit.*, pp. 385 and 600.

[2] Wagner, *loc. cit.*, pp. 253 and 303, and *Deutsch. Arch. f. klin. Med.*, xxviii., 1881, p. 94; Baumhard (*loc. cit.*) found that syphilis was the cause in 10 to 14 cases out of 105.

[3] "Diabetes Mellitus," in *v. Ziemssen's spec. Path.*, xiii., 1, 2d ed., 1879, p. 421.

and fatty degeneration or infiltration of the convoluted tubules, are well-known pathologic changes in diabetic kidneys, but it is not to be assumed that these changes always cause albuminuria. At least, the writer has seen both conditions in the kidneys of diabetic patients who had not had albumin in the urine.

A curious observation and one that it is difficult to explain satisfactorily is the cessation of the excretion of sugar with the appearance of albuminuria or the development of chronic nephritis.

The five causes here enumerated are practically absent in childhood and even later, until the end of the third decennium, in fact; at least their significance is slight as compared with what it is during *middle and advanced age*, the period of life that is most favorable for the development of arteriosclerosis. When it is remembered, besides, that contracted kidney has an exceedingly slow course, often extending over many years, and that for a long time it produces no marked symptoms of any kind, so that the patients frequently do not seek medical treatment until quite late, it is not surprising that most of the cases of fully developed, typical indurative nephritis are observed during the second half of life and become more frequent as age advances. Judging from the hospital reports, which contain chiefly statistics of those who *die* rather than of those who are *ill* of indurative nephritis, because the patients are usually admitted in an even more advanced stage of the disease, the greatest incidence occurs during the fifth and sixth decades,[1] from which it may be deduced that the disease more frequently begins at some time between the third and the fifth decades. Nevertheless, chronic indurative nephritis, although not in the form of a fully developed contracted kidney, is not very rare even in *childhood*. By careful inquiry it is usually ascertained that the condition was preceded for a variable length of time by an acute or subacute nephritis resulting from an infectious disease, which may have been merely an infectious angina—*i. e.*, that the cases do not, strictly speaking, belong to the category of "primary" contracted kidney, which will be presently discussed more in detail.

There is no need to dwell especially on the fact that the *male sex* is much more exposed to the injurious agents mentioned as the causes of indurative nephritis, not even excepting diabetes, and by virtue of this greater susceptibility is attacked oftener than the female sex, in the relation of 2 to $2\frac{1}{2}$: 1. Another factor that contributes to this *preponderance* in the male sex during recent times is that the various *athletic sports* are not only practised but also *carried to an excess* more than they were formerly. It is well known that albuminuria or cylindruria or both (see p. 32) are prone to develop after indulgence in athletic excercise, and although the abnormal conditions subside during rest, they may become more pronounced and later persist as the signs of an insidious chronic nephritis, unless the proper intervals of rest are observed.[2]

[1] L. Dickinson, *loc. cit.*, p. 377; v. Bamberger, *loc. cit.*, p. 1547, and Wagner, *loc. cit.*, p. 252.

[2] Joh. Müller (*Münch. med. Woch.*, 1896, No. 48) found albumin in the urine after a run in 2 out of 4 *untrained bicyclists*. One of the specimens contained casts of

[Albumin and casts are quite regularly found after hard foot-ball games. Blake and Larrabee[1] made some interesting observations on long-distance runners, and in the urine after the race (24 miles) albumin was a constant finding. After the race every sediment contained large numbers of hyaline and finely granular casts, a few coarsely granular and epithelial casts.—Ed.]

But some cases develop independently of the above-mentioned causes, either as the result of repeated exposure to cold and from other unknown causes, or in connection, directly or indirectly, with acute nephritis, in the manner already described in connection with the etiology of the non-indurative form (see p. 224). The mechanism usually is that in the course of an *acute infectious disease* a more or less severe nephritis develops with or without dropsy, runs a favorable course, but leaves behind a slight, or frequently only intermittent, albuminuria which is overlooked or neglected, until after a time unmistakable signs of chronic nephritis make their appearance. These are just the cases referred to here, cases which differ from the ordinary form of indurative nephritis due to other causes, and which occur more during youth or even childhood, and among which the *female sex* is more largely represented than among the forms which develop later in life.

The incidence among women is somewhat increased by the fact that many of these cases have their starting-point in the *nephritis of pregnancy*.

These cases, which, strictly speaking, represent a *secondary* induration or contraction of the kidneys, are usually regarded as *primary* because, owing to the insidious course, the demonstration of a causal connection with an acute nephritis, which may have occurred years before, is difficult if not impossible. They cannot, in fact, be separated from those cases which are not preceded by an acute affection, are insidious from the beginning, and run their course as a true "primary" chronic nephritis —another proof of the gradual merging of one form of kidney disease into another. *Hereditary* or *family predisposition*, while rare, sometimes undoubtedly occurs.

The most interesting observations bearing on this point are the following: Dickinson[2] reports the history of a family in the first generation of which 2 sisters for many years had albuminuria and died at the respective ages of forty-eight and forty-nine. Of the 4 children of their brother, 1 son had albuminuria for fourteen years and died at the age of twenty-six; a daughter died after suffering from the same disease at the age of thirty-four; and 2 other daughters afflicted with the same disease were still alive at the ages of thirty-eight and forty years respectively. In the third generation, which consists of 6 children of these deceased nieces, 5 have albuminuria; 1 daughter, twenty years of age, since the ninth month of life; 1 son, twenty years of age, for an undetermined length of time; 1 son, fourteen years of age, since early childhood; 1 son, fifteen years of age, for two years; and 1 daughter, five years of age, since the sixth month of life. J. Tyson[3] knows a man, thirty years of age, a sufferer

all kinds and renal epithelium, as in acute or parenchymatous nephritis. Of 8 *trained bicyclists*, 7 were found to have albuminuria at the end of the run, and 1 cylindruria. Hyaline, granular, and epithelial casts, as well as leukocytes, were also found in 5 out of the 7.

[1] *Boston Med. and Surg. Jour.*, clxviii., Feb. 19, 1903. [2] *Loc. cit.*, p. 378.

[3] *A Treatise on Bright's Disease and Diabetes*, Philadelphia, 1881, p. 166.

from indurative nephritis, whose father and mother as well as his brother, the latter at the age of thirty-seven, died of Bright's disease. Two of this brother's children had Bright's disease at the ages of four and seven; a second brother died at the age of twenty-nine, of convulsions; 2 other brothers and a sister, at the respective ages of twenty-three, thirty-two, and thirty-six years, were ill for from five to six years; and finally a cousin on the mother's side, and various relatives belonging to earlier generations, had died of Bright's disease. Eichhorst[1] reports the history of a family of artists in which the grandmother died of uremia, although she had never suffered from gout; the mother and twenty-four-year-old daughter, an excellent singer, suffered from indurative nephritis, the former for fifteen years; and 2 sons, excellent pianists, also died of uremia. J. Kidd[2] tells the following story: A woman, sixty years of age, died of Bright's disease after a long illness, and her 2 brothers died likewise; 7 of her 12 children died of the same disease, and 2 others at the time of the report were still affected with it. Pel[3] observed in three generations of one family 18 cases of chronic nephritis, 9 among the male and 9 among the female members of the family; the sons inherited the disease from the father, and the daughters from the mother.

Personally the writer has often seen chronic indurative nephritis in father and son, or mother and daughter or brothers and sisters; and the statement is often encountered that "dropsy" has occurred sometime during the earlier life of a patient suffering from indurative nephritis. There is a remarkable case of 2 brothers who developed subchronic nephritis, 1 at the age of two and 1 at the age of one; each had a *phimosis* which temporarily interfered greatly with the evacuation of urine.

[The editor has at present under his care a woman of forty-nine who has typical chronic interstitial nephritis with cardiac hypertrophy well advanced. Two of her three daughters, aged about twenty-one and twenty-three, have constant albuminuria with occasional casts, and in one the hypertrophy of the heart is becoming manifest. The father of the woman is under observation by another physician, who reports a sclerotic kidney. The editor himself a few years ago examined her uncle, who had traces of albumin with a few casts. Among her grandparents and great-uncles and great-aunts, Bright's disease is referred to as a frequent cause of death.—Ed.]

Finally a *congenital* form of contracted kidney has also been observed, as by C. Weigert[4] and Hellendall[5] in the case of 2 girls whose mother had long been a sufferer from chronic nephritis.

PATHOLOGIC ANATOMY.

As the term "indurative nephritis" implies, the principal change in the kidneys consists in a *hardening process* due to the vigorous development of connective tissue with simultaneous atrophy of the parenchyma. If the destruction of parenchyma is very great the organ becomes contracted and the surface unequal, granular, or bosselated, illustrating genuine "*granular atrophy.*"

The appearance of the kidneys therefore varies with the age of the morbid process. In the less advanced cases the kidneys are normal in size, or the long diameter may slightly exceed the normal; the organs, in fact, resemble the so-called speckled kidney (see p. 233). In more

[1] *Spec. Path. u. Therap.*, 1884, ii., p. 62.
[2] *The Practitioner*, 1882, xxix.
[3] *Zeit. f. klin. Med.*, xxxviii.
[4] *Loc. cit.*, p. 1453.
[5] *Arch. f. Kinderheilk.*, xxii.

advanced cases, on the other hand, the kidneys are greatly diminished in size, sometimes as much as one-half, or even reduced to small remnants weighing not more than 50 gm. or less. When the atrophy is as extreme as this, the two kidneys are not, as a rule, uniformly contracted, one of them exhibiting less contraction than the other. The capsule of fat around the kidney usually increases as the organ diminishes in size.

The true *renal capsule* is thickened, presents in places a tendinous appearance; the surface is pitted here and there with small retracted scars, marking the points where the capsule is firmly adherent to the underlying parenchyma, and where it brings away small shreds of tissue when it is stripped off. It is more vascular than normal and the blood-vessels anastomose with those of the fatty capsule and of the cortex of the kidney.

The *surface* is always irregular from the presence of various-sized wart-like and granular prominences, varying from dark red or dark brown to a paler grayish-red or grayish-yellow color, which is the foundation for the not very important distinction between "red" and "white" contracted kidney. The intervals between the irregular prominences on the surface are frequently occupied by *cysts* which are variable both in number and in size, the latter between that of a pin-head to that of a cherry, and contain a clear, yellowish, rarely purulent fluid. The kidneys are extraordinarily firm and hard, of a *leathery consistence*, and offer considerable resistance to the knife. On the cut surface the cortical substance appears narrowed, particularly over the bases of the pyramids and wherever there is a depressed scar on the surface; in advanced cases the cortical layer may be reduced here and there to a mere line. The strands of connective tissue, which pass in the form of a band or wedge from the depressed scars on the surface toward the pyramids or the interspaces between them, are visible to the naked eye. The pyramids themselves are usually shortened, closer together than in the normal kidney, and contrast by their darker and more uniform color with the striped and speckled cortex.

The *pelvis of the kidney* is sometimes actually dilated, but in most cases the dilatation is only apparent on account of the great diminution of the parenchyma. The *renal arteries* and the larger trunks in the boundary zone between the medullary and cortical layers are frequently rigid and gape widely; the veins are, comparatively speaking, dilated.

In cases following *gout* or *chronic lead-poisoning*, *uric acid* and *calcium infarcts* are not infrequently found; the latter are also found in simple contracted kidney in old subjects.

On *microscopic* examination it appears even more clearly than to the naked eye that the changes, just as in non-indurative nephritis (see p. 230), are most pronounced in the cortical substance and are *not uniformly distributed, but scattered here and there*, the lesions presenting now a *roughly circular* and again a *linear* outline. The nodules and other prominences of the cortex correspond to intact portions of the parenchyma, and the depressed areas between them represent hard

cicatricial connective tissue containing the remains of atrophied parenchyma. Outside and within the more dense connective tissue, which consists of distinct fibers poor in cells and nuclei and which also contains elastic fibers,[1] are found foci of round-cell infiltration, evidently of more recent origin, either surrounding the *Malpighian corpuscles* or in the intervals between the *uriniferous tubules*. Wherever the fibrous connective tissue is abundant and forms broad bands, the tubules have either disappeared or are represented by very much atrophied remains; sometimes they are quite easily recognized, but usually they are greatly contracted; some have lost all their epithelial lining, while in others the epithelium, either as a whole or in patches, has undergone atrophy or fatty degeneration, or the cells may have been cast off and are found free in the lumen. Here and there greatly dilated spaces consisting of one or more dilated uriniferous tubules and containing a pale fluid (urine)—in other words, cysts—are encountered.

The *Malpighian corpuscles* in the most contracted portions are converted into small spheres of dense, fibrous, concentrically arranged connective tissue, sparingly supplied with nuclei and more closely packed on account of the atrophy of the intervening tissue; in others the capsule and the glomerulus are still distinguishable, but the coils of the latter have become homogeneous, contain but few nuclei, and are impermeable, while the capsule may be either normal or thickened and formed of several layers of striped connective tissue containing nuclei. Where the changes are less pronounced the glomeruli contain an abundance of nuclei and, like the capsules, present swelling, proliferation, and desquamation of the epithelium; the capsular space is filled with a more or less cellular exudate, as in chronic parenchymatous nephritis, or the spaces between the coils of the glomeruli are occupied by strands of connective tissue, which grow partly from the point of entrance or exit of the vessels and partly from the capsule and the pericapsular tissue, and press upon the vascular loops as they contract.

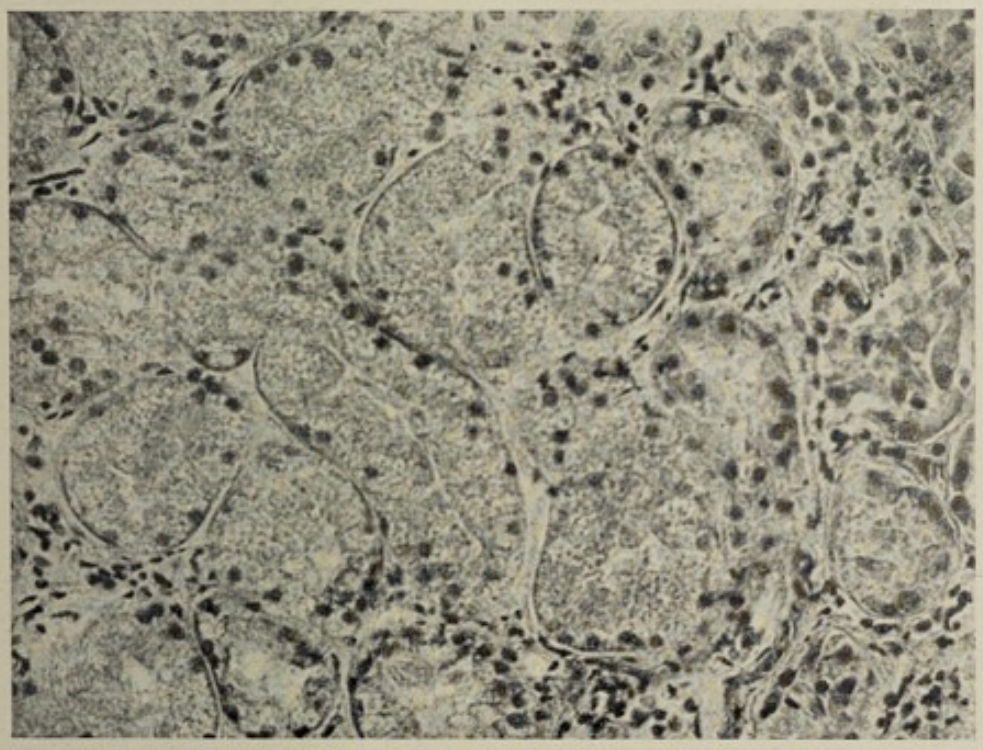
According to H. Engel, the connective tissue between the capsule and the vascular tuft develops from the fibrin contained in the inflammatory exudate (see p. 232).

The *epithelium of the uriniferous tubules* in these recent inflammatory foci also exhibits changes similar to those seen in chronic non-indurative nephritis, but the changes are not so extensive, and especially the fatty degeneration of the cells is much less pronounced. In many of the uriniferous tubules, particularly in the medullary substance, casts may be seen.

As regards the *vascular changes* in the *cicatricial portions*, the intertubular capillaries are mostly obliterated and lost in the connective tissue, here and there a few dilated vessels remain; the small arteries present marked thickening of the adventitia, which becomes fused with the rest of the connective tissue, and the intima and media quite often take part in the thickening also. The veins either show no changes or a thickening of the outer wall.

[1] See Hohenemser, in *Virchow's Archiv*, cxlii.

PLATE V.



CHRONIC DIFFUSE NEPHRITIS.

The illustration shows swelling and necrosis of the working epithelium with moderate increase of the interstitial framework. (Specimen loaned by E. R. Le Count.)

The *uncontracted portions*, which form the irregularities on the surface and are scattered through the connective tissue in the interior in the form of islands, may be entirely normal; or the Malpighian corpuscles may be enlarged and their glomeruli gorged with blood and also enlarged, but in other respects, including their capsules, normal. Some of the uriniferous tubules in these portions of the kidney are normal, others have undergone marked compensatory dilatation, with the epithelial cells lining them either normal or enlarged and in places flattened or the seat of fatty degeneration. The compensatory hypertrophy may go on to the formation of small adenomata, which sometimes appear as small white nodules on the surface of the kidney (Sabourin [1]).

The *renal arteries* and their larger branches often exhibit endarteritic changes, which are most extensive and most pronounced in cases in which *arteriosclerosis* must be regarded as the primary affection—*i. e.*, in so-called sclerosis of the kidneys. In the most typical cases of this kind the larger trunks of the intertubular arteries and some of the afferent vessels are greatly thickened, the corresponding glomeruli, after losing their epithelium and endothelial nuclei, undergo hyaline change and become converted into homogeneous, impermeable balls, while their capsules collapse or undergo hyaline thickening or become infiltrated with calcium salts like the surrounding connective tissue. The uriniferous tubules belonging to the obliterated glomeruli also collapse, the epithelium degenerates, and ultimately the tubules are represented merely by narrow cords containing numerous densely packed nuclei. This contracting process, due to the destruction of parenchyma, is followed usually by the appearance of secondary foci or small-cell, circumcapsular and intertubular infiltration in the neighborhood of the obliterated glomeruli or uriniferous tubules, which later give rise to a proliferation of connective tissue, so that ultimately the picture resembles the one described above, except that the interstitial connective-tissue formation is not so abundant as in the cases which do not depend on arteriosclerosis, the so-called genuine chronic interstitial nephritis, in which severe inflammatory irritation of the stroma is present from the beginning.

Whatever may be the mechanism, whether inflammation is primary and followed by atrophy, or degenerative atrophy is followed by reactive or compensatory connective-tissue proliferation, the termination in both cases is practically the same—induration with atrophy. Thus the two processes are obviously closely connected, and in those cases in which the exciting cause (gout, lead, and the like) is capable of producing simple inflammatory as well as arteriosclerotic processes, a distinction between the various renal inflammations characterized by induration and atrophy becomes absolutely impossible.

Under certain circumstances sclerosis is not followed by cell proliferation and hyperplasia of the connective tissue, and the process does not go farther than simple degenerative atrophy. (See Appendix to this Section.)

[1] *Revue de Méd.*, 1884, iv.

The contraction and obliteration of large portions of the cortical parenchyma is accompanied by the destruction of extensive vascular areas, which is the occasion for the formation of new channels for the venous blood and anastomoses, to which Thoma [1] and v. Buhl [2] have particularly called attention. Part of the blood is carried off through greatly dilated vessels into the renal capsule and the surrounding bed of fat (see p. 267); another part, after flowing around the obliterated glomeruli, makes its way through the dilated and tortuous vasa recta in the boundary zone between the medulla and cortex, chiefly enters the medulla, and thus reaches the veins more directly. In addition Thoma found that after obliteration of the glomeruli direct communication is established between the corresponding afferent vessels and the efferent vessels or the interstitial capillary plexus. These changes in the vascular conditions, in part at least, explain the behavior of the urinary secretion in indurative nephritis, which will be discussed later.

In advanced cases of renal contraction the *medullary substance* of the kidneys appears broad in comparison with the narrowed cortex, although its width is not actually increased. Not infrequently it contains narrow granular markings formed by strands of connective tissue and atrophied sections of loops which have made their way in from the cortex. The collecting tubules are usually greatly dilated and may also be tortuous, others are sacculated and dilated into cysts filled with a colloid material, while others again contain hyaline casts which are often excessively broad.

In the cadavers of persons who have died of indurative nephritis or its sequelæ, *hypertrophy of the heart* is a quite common finding. This subject, and especially the distribution of the hypertrophy in the various cavities of the heart, the presence or absence of dilatation with the hypertrophy—*i. e.*, so-called simple (and concentric) and eccentric hypertrophy—have already been discussed at length (see p. 115). The writer would like, however, to emphasize once more in this connection that in the form of induration originally due to arteriosclerosis—in a word, *arteriosclerotic* induration—the hypertrophy is usually eccentric, while in genuine interstitial nephritis (genuine contracted kidney) simple hypertrophy is more frequent. It is true that a distinction between the two forms at the autopsy table is difficult, because the great majority of the cases that come to autopsy are old and very far advanced; for, as the writer has said, arteriosclerosis usually develops during the later stages, even in the forms originally due to other causes, and, as a result, especially of disease of the coronary arteries, a secondary dilatation may complicate the originally simple cardiac hypertrophy.

In fact, more or less generalized *atheroma and endarteritis* of all the arteries in the body, going on to complete sclerosis involving the media and adventitia, is a very common condition, possibly quite as common as cardiac hypertrophy, being absent only in youthful individuals or those who from some cause have died in an early stage of the chronic

[1] *Virchow's Archiv*, lxxi., 1877, p. 42.
[2] *Mittheilungen aus dem pathologischen Institute in München*, 1878, p. 38.

nephritis. *Insufficiency of the aortic valves* is also a not infrequent result of the arteriosclerosis.

In connection with 4 of his own observations, Lancereaux [1] pointed out that *congenital narrowing of the aorta and of the arterial system* may be the cause of chlorotic symptoms and later give rise to primary atrophy of the kidneys (*néphrite diffuse scléreuse*). Besancon [2] and Poillon [3] have also reported cases in *young* individuals in whom chronic intertubular nephritis was found associated with congenital narrowing of the aortic system. Moutard Martin [4] reports the case of a girl, twenty-two years of age, very small but otherwise well formed, who died of uremia and granular atrophy of the kidneys, and in whom the arteries were found to be very narrow. The aorta measured 10 cm., and above the renal arteries barely 1 cm. The writer has for a long time kept the question of the width of the aorta in the various forms of chronic nephritis in view,[5] and at first found no perceptible differences; more recently, however, he has encountered several cases which corroborate the statements and views of Lancereaux.

According to Bizot, the circumference of the aorta at its origin in normal individuals measures on the average 7 cm. in men and 6.4 cm. in women, and according to Beneke at least 6 cm. in youth. In the cases of renal atrophy referred to, on the other hand, the measurement was only 4.2 to 5.2 cm. In the writer's own cases of granular atrophy the circumference of the aorta in a man, twenty-eight years of age, was 5.1, in a man thirty-three years of age 5.3, in 2 women, aged twenty-four and thirty years, 5.3 and 5.4 respectively, and in a woman, eighteen years of age, 4.5 cm. The measurements in other portions of the aorta were correspondingly diminished; in the case of the last-mentioned girl, for example, the circumference immediately above the celiac axis (tripus Halleri) was only 2.3 cm.

In chronic *uremia* marked inflammatory swelling of the gastric, and particularly of the intestinal, mucous membrane is usually found and may go on to ulceration. (See Uremia, p. 99.) Other postmortem findings are referable either to the disease that has caused the induration (gout, lead-poisoning, lues, alcoholism, diabetes) or represent the immediate cause of death, such as cerebral hemorrhage, pulmonary edema, and the like, or they are merely accidental complications.

It is important to remember that contraction of the kidneys is not infrequently encountered in the cadavers of persons who have died of other diseases, and for a variable length of time before death had presented no signs of the renal disease, especially albuminuria, cardiac hypertrophy, or increased arterial tension. Such cases demonstrate that a nephritis that has not progressed too far and that is confined to isolated foci may be arrested and recovery brought about.

SYMPTOMATOLOGY.

With the exception of the small minority of cases that follow more or less immediately after an acute nephritis, and are therefore

[1] *Loc. cit.*, p. 216, and *Gaz. méd.*, 1891, No. 15.
[2] *D'une Néphrite liée à l'aphasie arterielle*, Paris, 1889.
[3] *Contribution à l'étude de la Néphrite arterielle*, Paris, 1891.
[4] *Revue méd.*, Feb. 9, 1898, Soc. des Hôpitaux.
[5] *Virchow's Archiv*, 1878, lxxiii., p. 20.

"secondary," indurative nephritis begins as insidiously as non-indurative parenchymatous nephritis and escapes detection even longer than the latter, because it does not give rise to any subjective symptom for a considerable period, and because the only objective sign that can be demonstrated in the beginning and for many months or even years is albuminuria, and even this is very frequently intermittent, especially during the early stages. (See Cyclic Albuminuria, p. 33.) Such cases are therefore readily overlooked in the beginning, because the urine either is not examined at all or only at a time when it is free from albumin; for instance, during the morning hours. Quite frequently the physician contents himself with the diagnosis "cyclic" or "functional" albuminuria and leaves the disease to itself. In a few of these patients, if they are not too imprudent in their mode of life, the albuminuria may disappear permanently, and the isolated inflammatory foci in the kidneys, which at first are quite small, may heal completely. But in most of the cases the disease develops further.

So-called *primary interstitial nephritis*, which is not dependent on a sclerosis, is particulary apt to run a slow and tedious course, especially in those cases which, as has been remarked (p. 265), occur without any palpable etiologic factor in youthful individuals, cases which the physician rarely has an opportunity of observing continuously, and even less in hospital than in private practice. If the patients lead the wrong kind of life, these cases progress gradually in the course of years; the *albuminuria*, which at first was slight and only periodic, becomes more marked and persistent; hyaline casts appear in the urine, which may also contain leukocytes and red blood-cells; there is at first an imperceptible increase in the quantity of urine, which gradually becomes more marked, and frequent micturition, especially during the night, is complained of (*polyuria* and *pollakiuria*). Later the signs of *cardiac hypertrophy* and *increased arterial tension* gradually develop and become steadily more marked, until at last, usually at the end of many years, there is produced the typical picture of contracted kidney, the subsequent course of which is entirely dominated by the functional power of the heart and the condition of the vascular system.

It is possible, therefore, in these cases to distinguish *two stages:* the *first*, aside from certain variable and inconstant symptoms, is characterized solely by abnormalities in the urine, while the *second* presents the typical vascular symptoms of contracted kidney. It is needless to say that one stage merges into the next by imperceptible gradations.

So long as the heart is not overstrained and the vessels are sound, the only danger to life lies in the development of *uremia*, which may occur unexpectedly at any time in any patient who presents the typical picture of contracted kidney. If the vessels are likewise diseased, life is endangered from other quarters, particularly by *cerebral hemorrhage*, *thrombosis*, and *embolism;* and when the heart fails to respond to the increased demands made upon it, *disturbances of compensation* develop, as in valvular disease of the heart, with the phenomena of passive congestion in the greater and lesser circulation, and asthmatic symptoms.

True "*renal dropsy*," which occurs so early in chronic parenchymatous nephritis as at once to arouse the attention, may be altogether absent in indurative nephritis, at least during the greater portion of its course, or it may reveal itself in slight temporary swelling over the tibia and ankles or as puffiness of the eyelids, the latter especially during the morning hours. When compensatory disturbances occur later, *congestive edema* also develops and this signifies the beginning of the end.

Arteriosclerotic induration of the kidneys or *sclerosis of the kidneys* presents certain variations in its course. The vascular symptoms, the hypertrophy of the heart, the thickening and tortuosity of the arteries, and the concomitant symptoms, especially *cardiac asthma*, and not infrequently signs of aortic insufficiency, develop early, often a long time before the urine shows any distinct or, at least, any characteristic changes. Thus *polyuria* with the secretion of a pale urine of somewhat low specific gravity usually occurs some time before the *albuminuria*. In this form the signs of failing cardiac power, described as "fatty heart" or "weak heart," as well as passive congestion in the greater or lesser circulation, also occur earlier, and accordingly the fatal termination takes place sooner than in the form first described—chronic interstitial nephritis in the narrower sense of the term.[1]

It appears, then, that *two stages* may be distinguished in this form also; but the cardiac and vascular symptoms appear first, and are later followed by the urinary symptoms, which is the opposite of what takes place in primary interstitial nephritis.

There are, of course, many transitional forms between these two main types of renal induration, and the above-mentioned five noxious agencies, which are regarded as the chief causes of contracted kidney (gout, chronic lead-poisoning, etc.), are the most fruitful cases of these transitional forms, as has been mentioned, because they act on the kidneys as well as on the vascular system, although at first either the renal affection or the vascular changes may be more prominent.

As for the individual symptoms, the quantity of *urine* at the very beginning of the disease is normal or but little above the normal, but quite gradually, and especially in the slowly progressing cases in youthful subjects, a frequent desire to urinate develops, first during the night and later also during the day (*pollakiuria*), and the urinary excretion becomes very abundant (*polyuria*). These symptoms and the increased sense of thirst to which they give rise frequently induce the patient to seek medical aid. When the disease is fully developed, the daily quantity of urine fluctuates between 2000 and 3000 c.cm. (4–6 pints), occasionally going down to normal or below normal, and in exceptional cases amounting to 4000 to 5000 c.cm. (8–10 pints).

Quantities in excess of the latter figure are exceedingly rare and are observed only temporarily, when the individual has taken an extraordinary quantity of fluid. Bartels reports the case of a gentleman, forty years of age, who voided

[1] See E. Leyden in *Zeits. f. klin. Med.*, ii., 1881, p. 148, and H. Senator, *Albuminuria*, 2d ed., 1890, p. 147.

6000 c.cm. (12 pints) in one night between eight o'clock in the evening and eight o'clock in the morning. Lecorché and Talamon had under their observation a young man, twenty-four years of age, who voided between 8 and 10 liters (quarts) in twenty-four hours.

In accordance with this increase in the quantity, the urine is *paler than normal, clear or only slightly turbid*, of *faintly acid reaction* and *low specific gravity*, usually about 1010, or very rarely going below 1005. The molecular concentration of the urine is in general somewhat reduced—*i. e.*, the freezing-point is not much below —1°.

When passive congestion and fever are present the urine becomes scantier and darker in color, but not in the same degree as other urine under the same circumstances. Traube's[1] assertion that the urine of indurative nephritis does not become red and of a darker color and higher specific gravity in the presence of fever and congestion, as other urine does under similar circumstances, is confirmed by a number of cases that have come under the writer's observation.

As a rule, the urine contains only small quantities of *albumin;* even at the height of the disease it rarely exceeds 0.5 in 1000, and quite frequently consists of a mere trace. The daily variations to which every albuminuria is subject are especially well marked in indurative nephritis, both at the beginning and for some time afterward. It is not uncommon to find the nocturnal or morning urine and that obtained during the day after a long rest nearly or quite free from albumin, while after exercise, a hearty meal, excitement, particularly sexual excitement, and shortly before, during, and after menstruation, it again becomes albuminous. *Sclerosis of the kidney* (*arteriosclerotic induration*), as has been mentioned, is distinguished by the fact that the albuminuria develops late, is slight, and frequently disappears for considerable periods at a time. The reports of "contracted kidney with total absence of albuminuria" almost always refer to cases of this kind. (See also Appendix to this Section.)

Owing to the moderate degree of albuminuria, the daily loss of albumin, notwithstanding the increase in the quantity of the urine, rarely exceeds a few grams, and practically never amounts to as much as 10 gm. Lancereaux,[2] however, reports that in advanced stages of the disease he has observed a daily excretion of albumin amounting to 10 to 15 gm.

As usual the urinary albumin consists of serum-albumin (serin) and globulin. The percentage of the latter, as appears from the numerous very careful investigations of Csatáry,[3] is in the main quite small, so that the "albumin quotient" is large. In 4 separate examinations Csatáry obtained an averge of 6.7 per cent., and in 5 more extensive series of investigations his average maximum was 12.6 and his average minimum 2.9 per cent. F. D. Boyd[4] found that the quotient varied from 1.3 to 30 per cent.

The quantity of urea is lower than normal in proportion to the dilution of the urine, although not absolutely diminished unless grave disturbances have made their appearance; when the nutrition is good,

[1] *Deutsch. Klin.*, January 7, 1860, and *Berlin. klin. Woch.*, 1864, No. 4.
[2] *Loc. cit.*, p. 204. [3] *Loc. cit.* [4] *Rep. Royal Col. Phys.*, v. 1894,

it may attain a considerable figure. The *proportions of the individual nitrogenous substances in the urine* frequently present no noteworthy deviation from the normal; in other cases the percentage of urea is diminished and may fall to 70 (instead of about 85). A similar change occurs in the excretion of *ammonium* and *uric acid*, while the remaining extractives are more likely to be increased. With the appearance of *uremic phenomena* the urea becomes greatly diminished, down to 58 per cent., while the ammonium values increase, although not without some exceptions. The excretion of uric acid in such cases is slight, while that of the remaining xanthin bases is increased. During the intervals of freedom from the attacks, the nitrogen of the remaining xanthin bases also exceeds that of the uric acid.[1] (See Uremia and Non-indurative [Parenchymatous] Nephritis.)

As regards the urinary ash, the *chlorids* and the *sulphates* in the main behave like the urea, except that the sulphates are apt to show a diminution; the *phosphates* were found by Fleischer[2] and P. Laidlaw[3] to be both absolutely and relatively diminished. When a certain quantity of phosphoric acid (combined with sodium as a salt) was given to healthy individuals and to kidney patients, the same quantity was excreted by the former in twenty-four to thirty-eight hours, while the latter showed little or no increase in the excretion of phosphoric acid in the urine (Fleischer).

Fleischer observed a certain parallelism between the excretion of *nitrogen* and that of *phosphoric acid*, and observed that during *menstruation* both are somewhat increased.

As regards the *excretion of other substances* (methylene-blue, iodin, salicylic acid, and potassium iodid), it is often impossible to detect any notable difference between healthy individuals and kidney patients; in more advanced cases the excretion is delayed and diminished. After the inhalation of turpentine, the characteristic odor of violets develops in such kidney patients after a variable length of time; at times more rapidly, at times more slowly, than is normal.

The urine usually contains no *sediment* at all, or such a small amount that it is impossible without centrifugation to obtain enough for a microscopic examination. Besides amorphous detritus, hyaline or slightly fatty and finely granular casts and sometimes broad casts, probably derived from the dilated tubules of the medullary substance (see p. 270), and in addition occasional renal epithelial cells, leukocytes, urates, and oxalate crystals, and very rarely red blood-cells, are found. On the other hand, *considerable quantities of blood* in the urine (hematuria) occasionally occur, especially after overexertion.

Deviations from the typical behavior of the urine in contracted kidney as here described occur in acute exacerbations, in uremia, and especially when the heart, either temporarily or permanently—and then

[1] After investigations by P. Fr. Richter in the writer's clinic; see also Kolisch, *loc. cit.*

[2] *Deutsch. Arch. f. klin. Med.*, 1881, xxix., p. 129.

[3] *N. Y. Med. Rec.*, Sept. 3, 1898.

usually toward the end of life—fails and passive congestion develops. The writer has already called attention to these deviations.

[It is important to remember these deviations from the typical urinary findings of the contracted kidney, for it often happens—one might say it is the rule—that the patient with this form of kidney disease presents himself to us with atypical urine. For it is when there is an acute exacerbation of his trouble and edema of the face alarms him, or when he notices the darker color of the urine, or when failing heart and dyspnea have occurred, that he consults the physician, and the urine of the acute exacerbation or of congestion might be misleading from its scantiness, relatively high specific gravity, and richness in albumin and formed elements. Rest in bed under these circumstances is indicated, not alone as a therapeutic measure, but as well for purposes of diagnosis. Closer and continued observation of the urine, especially after rest and appropriate treatment, will usually show that the transitory conditions due to acute exacerbation or to congestion disappear and leave revealed the typical urine of the chronic interstitial nephritis.—Ed.]

Next to the behavior of the urine, the most characteristic changes in *typical contracted kidney* are observed in the vascular apparatus, the *heart and the arteries.* It has long been known that hypertrophy is more frequent in this than in any other form of renal disease. Traube especially brought this out very clearly and pointed out its significance. The frequency of the association of cardiac hypertrophy with contracted kidney as compared with the other forms of nephritis, and other aspects of the subject of cardiac hypertrophy, have been fully treated in a previous section (see p. 116).

The writer must repeat, however, what he has already said in that place, that the true condition of things is better appreciated by *clinical* investigation than by postmortem studies; for the former enables one to watch the origin and development of cardiac hypertrophy, and he believes that he is justified in stating definitely, on the basis of numerous observations extending over a long time, that in the cases of renal induration in which sclerosis unquestionably forms no part of the clinical picture, especially in young individuals—*i. e.*, cases of genuine so-called chronic interstitial nephritis—(1) the *urinary changes*, especially albuminuria and a certain degree of polyuria, exist for some time before the slightest sign of cardiac hypertrophy becomes perceptible, and that (2) the hypertrophy, as a rule, exists for some time without dilatation and affects the left ventricle, either exclusively or, at least, more than any other chamber. Dilatation in these cases develops late—after the nutrition of the heart begins to suffer or the intracardiac pressure exceeds a certain limit (see p. 120).

The condition of the *arteries* and the *pulse* is quite similar. At a stage of the disease when the urinary findings leave no doubt of the diagnosis of beginning chronic indurative nephritis, there is still not the slightest sign of increased pressure in the aorta, the arteries are soft, as under normal conditions, nor does the pulse curve or sphygmomanometric examination reveal any abnormality unless arteriosclerosis is present.

Not until later do distinct signs of *hypertrophy* and *increased aortic pressure* make their appearance, signs which, since Traube's classic description, are regarded as characteristic of "contracted kidney"—forcible, heaving apex beat with or without downward or outward displacement, accentuation of the second aortic sound, increase in the cardiac dulness, hard, tense pipe-stem arteries (like wire), and changes in the *pulse curve*, such as especially an oblique or even anacrotic ascending limb, flattened or broadened apex and a smaller and higher secondary curve. At this time *gallop rhythm* is often observed in the heart, either in the form of an anapest (⏑ ⏑ ⊥), according to Potain, or more rarely in the form of an amphibrach (⏑ ⊥ ⏑)—unquestionably a sign of cardiac fatigue—and as it develops fairly early, is quite valuable for the diagnosis, although it occasionally occurs in other conditions.

The writer will now give abstracts of a few cases which illustrate the above-described earliest development of the non-arteriosclerotic, genuine interstitial nephritis.

T., apothecary's son, developed pleurisy in the winter of 1880. At that time albuminuria was discovered, which had probably been present before, as his parents had noticed a change in him for some time, the boy having suddenly become abnormally lazy, especially in school. I first saw the boy on the 18th of March, 1882. He was then ten years old, well developed but pale. Neither the heart nor the arteries showed the least abnormality; the eye-grounds were normal. The parents stated that the quantity of urine had been increased for some time and that the boy voided frequently at night. The specimen which the boy brought with him was pale, clear, of a specific gravity of 1010, and contained a considerable quantity of albumin. The urine had been examined by the boy's father, who stated that it had never been free from albumin for some time. Edema was never present. The advice to take the child out of school and guard him as much as possible against exertion was neglected or disobeyed. The patient came to see me from time to time at intervals of many months. In June, 1884, I found the patient exceedingly pale, without edema, with heaving apex beat in the fifth interspace, barely extending beyond the mammillary line to the left, intense cardiac dulness, marked accentuation of the second aortic sound, and moderately tense but soft arteries.

B., Russian, schoolboy, consulted me in 1890 on account of renal trouble. He said he had had scarlet fever six months before, and that the urine had contained albumin ever since. He was strongly built and well nourished; on examination all the organs were found to be sound, especially the heart and the arteries. The urine which he voided at the time was pale, clear, of a specific gravity of 1010, and contained a moderate amount of albumin. During the succeeding days the daily quantity varied between 1½ and 2 liters (quarts). He did not often have to void urine at night. After he had been treated several weeks the albumin disappeared, except for a trace during the day. Since then I have seen the patient once or twice a year, and found him in the main in splendid condition; edema never developed. In 1893, feeling perfectly well, he took up his studies again and engaged a room on the fourth floor, so that he was obliged to exert himself physically, climb stairs and the like. In the following summer I found that the apex beat was distinctly displaced to the left, the heart dulness had increased, the second aortic sound was markedly accentuated, and a systolic murmur was heard at the apex. The arterial tension was not excessive. The quantity of urine was about the same as before; the specimen obtained was pale, of a specific gravity of 1012, contained a moderate quantity of albumin, and the very scanty sediment showed nothing characteristic. By rest and proper diet I succeeded in reducing the albumin to a mere trace in the day urine and dispelling it altogether from the night urine. Since then signs of slight cardiac hypertrophy have persisted. The murmur has disappeared. The quantity of urine still varies between 1½ and 2 liters (quarts); there is a trace of albumin, varying from 0.5 to 1 in 1000. Edema has never been present. During the succeeding years the cardiac hypertrophy

has become more and more distinct, and from time to time a systolic murmur has been heard at the apex.

Mrs. Valerie H., fifty-two years of age, was admitted to the Augusta Hospital on the 1st of November, 1876, complaining of pain in the knees and in the left shoulder, of occasional deafness, and of formication in the left arm. The history contained nothing of interest. Menopause five years ago. The patient was exceedingly pale, but no abnormalities were discoverable in the thoracic or abdominal organs or in the nervous system, although she complained that her sight was failing. She said that she had frequent micturition and voided urine also during the night. A painful edematous swelling had been occasionally present in a circumscribed area on the inner aspect of the left leg ever since in her youth she had erysipelas at that point. During the four weeks that she stayed at the hospital, the daily quantity of urine varied between 1750 to 2200 c.c. It was always pale, the specific gravity ranged from 1009 to 1014; the percentage of albumin was variable but never exceeded a moderate amount; the sediment was very scanty, appearing only after the urine had stood for some time, and contained nothing but a few pus cells and squamous epithelium, which were due to a slight leukorrhea. She was discharged improved on the 3d of December, but was readmitted on the 30th of December with severe tracheobronchitis and very slight fever, the highest temperature being 38.4° C. (101° F.). The fever occurred occasionally in the evening hours during the following weeks and finally subsided altogether, reappearing with every returning exacerbation of the catarrh. During this time of periodic fever the quantity of urine fluctuated between 1600 and 1900 c.c. (say 3–4 pints), the specific gravity ranged from 1013 to 1015, the color was always pale, there was practically no sediment, and the albumin percentage was fairly high. When the catarrh and the mild febrile symptoms subsided toward the middle of January, 1877, the quantity of urine increased, ranging between 2500 to 2900 c.c. (5–6 pints), with a specific gravity of 1010 to 1015, a moderate percentage of albumin, pale color, and occasionally long, narnow, pale tube casts, a few fine fatty granules, and some isolated leukocytes in the scanty sediment. The patient complained a good deal of headache and a reddish glow before the eyes, but the ophthalmoscopic examination revealed nothing abnormal. The heart and arteries were entirely normal, and the sphygmographic curve, which was repeatedly taken, was also perfectly normal. During the night of the 8th of February the patient had a chill, followed by severe attack of dyspnea, clonic and tonic convulsions in the extremities, some mental hebetude, and very violent headache. The quantity of urine, which on the day before had been 2500 c.c. (5 pints), dropped to 2000 c.c. (4 pints). During the attack the pulse was much slower than its customary rate and the arterial tension was high. On the 9th of February and the days following the patient improved. The quantity of urine again became more abundant.

In the beginning of March there were *repeated attacks of epistaxis.* As the patient's condition was otherwise fairly good, she left the hospital and presented herself from time to time at the clinic. Her condition was variable; she suffered a good deal from headache, a feeling of oppression and occasional nausea, and voided urine frequently through the night, but never had edema.

On the 26th of June, 1879, she presented herself again on account of headache and an intense feeling of oppression. She looked very pale, but was fairly well nourished. There was no edema; the lungs were normal. The radial arteries were as hard as wire and thickened; the pulse quite frequent and of high tension. The apex beat was found in the normal situation, forcible and heaving; the second aortic sound was distinctly accentuated, especially in comparison with the pulmonary sound. The dulness, although not greater in extent than normal, was very intense. Ophthalmoscopic examination revealed in both eyes a few whitish-yellow patches near the papilla, and in the left eye a recent hemorrhage at the nasal border of the papilla. Shortly after, in July, she died suddenly, it was said, of a stroke.

Karl G., shoemaker, forty-four years of age, was admitted to my clinic on the 10th of December, 1894, because he suffered from swelling of the legs whenever he walked any distance. He stated that he had "nerve fever" thirty years, "typhus" twenty-one years, and facial erysipelas sixteen years previously. Since the attack of erysipelas he had been well until the spring of the present

year, when his feet began to swell. He admits some abuse of alcohol, but denise syphilitic infection.

When he was examined on the day of his admission, slight edema was found over the ankles and in both eyelids; this disappeared on the second day and did not return during the three and a half months that he spent in the hospital. Although the patient was rather emaciated, the apex beat could not be distinctly seen or felt in any position, whether lying down, sitting, or standing; the heart dulness was normal in extent and not very intense; the heart sounds were muffled and there was no sign of accentuation. The remaining organs exhibited no abnormalities. The pulse was slightly accelerated, and during the entire period ranged from 76 to 90; the pulse wave was low, the tension somewhat diminished, and the arteries soft. Sphygmographic tracings were taken repeatedly, and the pulse waves were sometimes so low that the tracings showed nothing, nor did they ever indicate any heightened tension. Even with v. Basch's sphygmomanometer great difficulty was experienced in getting a reading, which varied from 89 to 95 mm. of mercury, while in other patients, chronic nerve cases and convalescents, the reading varied from 90 to 110.

During the entire time the patient was under observation, which was three and a half months, the quantity of urine, with the exception of four days during which there was diarrhea, for which opium was given, averaged 3 liters, the minimum being 2000 c.c. (4 pints); the specific gravity averaged from 1005 to 1024; usually it was 1010 or 1011. The urine was pale yellow in color, perfectly clear, and contained from 0.1 to 0.35 per cent. of albumin, as determined with Esbach's instrument. It was difficult, even by centrifugation, to obtain any sediment. This contained only a few uric acid crystals and an occasional hyaline cast. While the patient had diarrhea the quantity of urine went down to 1200 to 1800 c.c. (say 2½–3½ pints), the specific gravity rose to 1014 to 1021, and the albumin from 1.5 to 4 per mille.

Aufrecht[1] has also reported a very instructive case of postscarlatinal chronic interstitial nephritis lasting twenty years, and Dixon Mann[2] has reported a case that lasted twenty-eight years.

When distinct changes in the vascular apparatus are present, the *subjective* symptoms, which before had been absent or insignificant, become more frequent. They almost all depend on the vascular changes; they consist of palpitation, vertigo, ringing in the ears, and attacks of oppression going on to marked cardiac asthma.

The changes in the vascular apparatus also cause the appearance of *objective symptoms*, which are in addition favored by the hypertrophy of the heart. The objective symptoms consist principally of *hemorrhage*, which becomes most grave when it takes place into the brain. Since Senhouse Kirkes[3] called attention to the frequency of cerebral hemorrhage and the possibility of confounding *apoplexia sanguinea* with uremia, its occurrence has been universally acknowledged, although authorities differ in regard to the frequency. According to Dickinson, it occurs in 4.3 per cent. of the cases, a figure that is too low; Grainger Stewart observed cerebral hemorrhage with apoplexy in 15.3 per cent. of his cases; Barclay,[4] 17 times in 250 cases, or 6.8 per cent.; Wagner, 25 times in 180 cases, or 17 per cent.; v. Bamberger, 52 times in 583 cases, or 14 per cent. The seat of the hemorrhage in the great majority of the cases is the internal capsule and its neighborhood, rarely any other part of the brain. Diffuse punctiform hemorrhages scattered throughout the entire brain are also found in some cases. A more common form is *epistaxis*, which is sometimes so severe and proves so

[1] *Deutsch. Arch. f. klin. Med.*, xiii., p. 515.
[2] *Lancet*, Sept. 14, 1895.
[3] *Med. Times and Gaz.*, 1855.
[4] *Med.-Chi. Trans.*, xxxi.

refractory to treatment that death results from loss of blood, as the writer has himself observed in 2 cases. *Hematuria* not rarely occurs to interrupt the usual course of the urinary secretion, and the hemorrhage may at times attain an alarming degree. Among the rarer forms of hemorrhage may be mentioned that from the intestine, especially the rectum; metrorrhagia, hematemesis, hemoptysis, hemorrhage from the tympanum, the pharyngeal and laryngeal mucous membranes (Schwartze,[1] Haug[2]), and finally hemorrhages into the skin in the form of petechiæ.

Except in uremic conditions, the function of the *digestive organs* is almost always normal. The disturbances that occur occasionally are in no sense characteristic of contracted kidney, except possibly a great feeling of *thirst* caused by increased diuresis.

The *respiratory apparatus* shows a certain tendency to catarrh of the larynx and of the bronchial mucous membrane, but in a much less marked degree than in chronic parenchymatous nephritis. The same is true of inflammation of the lungs and of the pleura.

Apart from the conditions of uremia and disturbances of compensation, the *nervous system* rarely presents any structural changes except the above-mentioned hemorrhages into the brain; subjective disturbances, on the other hand, are somewhat more frequent. *Headache*, especially in the form of hemicrania or migraine; *insomnia*, *neuralgias* in various nerve regions, *rheumatoid pains*, a *feeling of deafness*, and other like symptoms, are not uncommon, but cannot always be attributed to the renal disease itself. They may in part be due to the causal disease, as, for example, gout and lead, or alcoholic intoxication, or may be uremic in nature and precede an attack of acute uremia. As regards the *organs of special sense*, the most important change is *albuminuric retinitis*, which is much more frequent in indurative nephritis than in any other form of kidney disease. Its frequency is variously stated because the observer's attention is not called to it in every case, and examination of the eye is sometimes neglected; for the visual disturbances caused by the retinitis may occur so early and be so severe as to form the first noticeable symptom which leads the patient to seek medical aid; or the eye changes are not discovered until later, when the existence of renal disease has already been determined. Eates[3] found retinitis present in 28 out of 100 cases of granular atrophy. In most cases there is cardiac hypertrophy, which was regarded by Traube as the cause of the retinal affection, though he was in error in this, for there is no doubt that it occurs without it. The inability to recognize blue (*blue blindness*) was observed by A. König and Simon, and by C. Gerhardt.[4]

The remaining organs—the *organs of locomotion*, the *skin*, and the *genital organs*—do not present any notable changes, with the exception of the above-mentioned hemorrhages, unless compensation is disturbed or uremic intoxication takes place.

The composition of the *blood* and *metabolism* do not appear to suffer

[1] *Arch. f. Ohrenheilk.*, 1868, iv.
[2] *Deutsch. med. Woch.*, 1896, No. 45.
[3] *Birmingham Med. Review*, January, 1880.
[4] *Münch. med. Woch.*, 1900, No. 1.

any marked changes during the *initial period* unless one of these two conditions—disturbed compensation or uremia—is present, as may be inferred by the fact that the nutrition is good and the excretions normal. Very little is known about the composition of the blood during the period when the general condition is fairly good, except that, as Hammerschlag[1] has shown, there is no hydremia as in other forms of Bright's disease, and the specific gravity of the blood is accordingly almost always normal. The *excretion of nitrogen* and *mineral constituents* has already been discussed in connection with the urine (p. 275); it may be added, however, that according to Fleischer's investigation[2] *phosphoric acid*, although diminished in the urine, does not appear to be increased in the feces, and it may therefore be inferred that the acid is at least temporarily retained within the body. Fleischer also repeatedly found urea in the *saliva* and in the *sputum* in cases of contracted kidney.[3]

In cases of *well-developed contracted kidney* with cardiac hypertrophy and heightened arterial tension the character of the blood changes; the molecular concentration is apt to become higher than normal, the quantity of nitrogen retained (residual nitrogen) increases, and with it the toxicity of the blood (see p. 127).

The general condition which, as the writer has said, is fair on the whole, is at once affected by the occurrence of one of the two accidents which have been repeatedly referred to—*failing heart action* and *uremia*. Whenever characteristic symptoms of one or the other of these two conditions are well marked, the resisting power of the entire body is impaired. Even if the patient is not destroyed on one or the other of these reefs at the first onset, he nevertheless resembles a wreck and is continually exposed to a variety of other dangers, such as inflammation of various organs, particularly pneumonia, pleurisy, and pericarditis, which bring on or, at least, hasten the fatal termination.

There remains to explain the two most important symptom groups that occur in indurated and contracted kidney—the *changes* in the *urine* and in the *vascular apparatus*, including the *heart*, and their relation to one another. To consider first *interstitial nephritis without arteriosclerosis*, the above description of the course of the disease, from the imperceptible beginnings to the fully developed clinical picture, when compared with the pathologic findings, cannot fail to show that the inflammatory process, which is exceedingly slow and at first invades small scattered regions in the kidneys in succession one after the other, produces no disturbances other than albuminuria, which, in accordance with the limited distribution of the inflammatory process, its moderate severity, and its intermittent mode of spreading, is likewise slight and variable, and may at times disappear altogether whenever the conditions are favorable for a temporary cessation of the inflammatory process. In every other respect the urine remains normal because enough functionating parenchyma and to spare remains to compensate for what has

[1] *Zeits. f. klin. Med.*, 1892, xxi., p. 491. [2] *Loc. cit.*
[3] *Verhandl. des II. Cong. f. inn. Med.*, 1883, p. 119.

been destroyed; for it is well known that even the loss of an entire kidney may under favorable circumstances be made good if the other kidney is healthy[1] (see p. 163). When the process of contraction continues to spread in the cortex the effect is twofold; other healthy portions hypertrophy as a result of the continued increase in function, and the blood-stream is diverted toward the medullary substance, but under increased pressure and velocity. (See Pathologic Anatomy, p. 270.)

The effect of these pathologic changes is that the specific urinary constituents continue for a long time to be excreted in normal or approximately normal quantities, and the urine as a whole passes through the medullary substance with a greater velocity, so that less time is allowed than under normal conditions for the absorption and concentration. This explains why watery urine in quantities exceeding the normal is excreted. The kidneys possess the faculty of completely equalizing the functional loss for a long time, so that urinary constituents do not accumulate in the body.

At the same time, as has already been explained (p. 127), the heart is gradually stimulated to increased activity by the same slowly acting irritant by which the kidneys are damaged; only the heart reacts later than the kidneys. It is a well-known fact, and the writer has repeatedly insisted upon it, that the kidneys are, generally speaking, the first to suffer from any injurious substances circulating in the blood, unless the substance has a specific action on some one apparatus in the body. This protracted increase in the cardiac activity in this case also results in hypertrophy. The latter still further increases the pressure and velocity of the blood in the kidneys and stimulates the organs to secrete a quantity of urine that far exceeds the normal—overcompensation results, although the excess of excretion is confined to water. For the excretion of water, it is to be remembered, is specifically a function of the arterial blood-pressure and increases in direct proportion with it, while the excretion of the *specific urinary constituents* depends on the number and efficiency of the glandular elements. In cases of contracted kidney the number of these elements, even if numeric increase (hyperplasia) takes place, which is not certain (see p. 163), is smaller than the normal, and the efficiency of the glandular elements, even when they are hypertrophic, has definite limits and does not continue to grow in proportion to the quantity of the nutritious materials received. The overcompensation, which depends on cardiac hypertrophy and the increased velocity of the blood in its passage through the medullary substance, while it may and does cause a marked increase in excess of the usual quantity in the secretion of water, even in advanced cases of contracted kidney, cannot affect the excretion of specific urinary constituents, for the latter is limited by the destruction of the true secreting parenchyma. This explains why it is that dropsy may be entirely absent until the end or very nearly the end, while the blood gradually becomes overloaded with (nitrogenous) metabolic products, and finally that uremic intoxi-

[1] See H. Senator, "Ueber renale Hämophilie," *Berlin. klin. Woch.*, 1891, No. 1.

cation may take place even when the quantity of the watery urine is normal or exceeds the normal.

The remaining disturbances, that occur later as a result of heart tire and diminished cardiac activity, and may be transient or permanent, require no special explanation.

In *arteriosclerotic induration of the kidneys* the heart, as a result of the arterial disease, early becomes hypertrophic, often long before any signs of kidney disease can be discovered (see p. 129). As the true inflammatory phenomena occur only later as a result of the destruction of the parenchymatous tissue, and are never very extensive, albuminuria is less pronounced than in true interstitial nephritis, is more transitory and yields more readily to treatment, and the albumin does not, as a rule, appear until the quantity of urine has been increased for a variable length of time and the specific gravity has somewhat diminished. It is needless to say that the heart in these cases begins to fail much sooner, especially when the coronary arteries themselves are involved, and loss of compensation therefore takes place earlier.

Secondary contracted kidney presents certain differences. This condition is undoubtedly preceded by an impairment of the function of the kidneys, which must have been either permanent or have recurred repeatedly at short intervals and caused the retention of excrementitious substances which, being irritants to the vessels and to the heart, may be regarded as the cause of the cardiac hypertrophy (see p. 127). It is possible that the original cause of the kidney disease, which resides in the blood and which in time loses its virulence and thus permits the transition into the chronic form of induration and contraction, also acts as an irritant to the heart. The structural changes in the kidneys, which develop gradually, and the cardiac hypertrophy ultimately have the same effect on the excretion of urine—dropsy and uremia—as in the case of primary contracted kidney or so-called chronic interstitial nephritis.

It is hardly necessary to say that when the cause primarily acts injuriously upon the kidneys as well as upon the vascular system, and the two become diseased practically at the same time, the morbid process is not so characteristic nor so distinctly recognizable as in the typical forms, and the phenomena of the two conditions are more or less intermingled.

COURSE, DURATION, AND TERMINATION.

The duration of indurative inflammation of the kidneys is always counted by years, although the exact time of the beginning of the disease is seldom known because of the insidious nature of the onset.

In *chronic interstitial nephritis in the narrower sense of the term*—primary or genuine contracted kidney—the course is slowest of all, and an entire year or even a number of years may elapse without any appreciable change. For although the inflammatory process in the kidneys themselves, especially during the initial period, is not quite uniform in its progress, but shows a tendency to spread irregularly and with periods

of exacerbation, as may be inferred from the variations in the percentage of albumin, the symptoms nevertheless, as has been described, may be quite inconsiderable for a long time, and the disease may affect the patient subjectively but little, or interfere but slightly or not at all with his ability to work, so that he often considers himself well, and fails to take advantage of the favorable moment for the treatment of the renal disease. In rare cases he may be roused to a sense of his danger, after overexertion or excess of any kind or after some unexpected accident, by the appearance of edema, or blood in the urine, or obstinate hemicrania.

In such cases, if the appropriate treatment is instituted early enough —*i. e.*, when the albuminuria is still quite insignificant or even only intermittent—the disease may be brought to a standstill by arresting the inflammatory process in the kidneys, and the patient may recover completely, as the writer has repeatedly pointed out and as is proved by the occasional finding of small cicatricial depressions in the kidneys of persons who had not shown the slightest sign of kidney disease during the last days of life (see p. 271).

When the cardiac hypertrophy or the arterial disease has attained a certain degree of severity, more marked symptoms usually make their appearance and the clinical picture becomes more changeable ; but this is not always the case. It is not at all uncommon for an apparently healthy man to suffer an attack of apoplexy as the result of violent mental excitement or bodily exertion, such as mountain-climbing, and the explanation of the accident is perhaps found in a contracted kidney which had not been suspected. In other cases uremia or the signs of cardiac incompetency may occur unexpectedly. Even if these first grave accidents are survived, as not infrequently happens, and the patient recovers more or less completely, they nevertheless mark the beginning of the last stage of the disease, which rarely lasts more than one to two, or at the most three, years.

The entire duration of the disease cannot, as a rule, be positively determined on account of the exceedingly insidious onset. Cases lasting from five to ten years, counting from the first *demonstration* of albumin in the urine until death, are quite common ; but even a duration of more than ten years, counting from the discovery of albumin, is not at all rare. The writer has seen a typical case of granular atrophy of the kidneys, confirmed by autopsy, in which the physician had demonstrated the existence of nephritis seventeen to eighteen years before death, and the literature contains a number of cases with a duration of fifteen to twenty years and even more (Oppolzer, Rosenstein, Dickinson, E. Fränkel [1]). G. Johnson [2] relates the case of a very busy physician who for sixteen years suffered from albuminuria following scarlet fever, and retained his healthy appearance and good nutrition. The writer knows a physician who discovered albumin in his urine almost twenty years ago, and although he now presents distinct signs of cardiac hypertrophy, asthmatic symptoms, and the like, he still attends to his practice, which, it is true, is not quite so large as it used to be.

[1] *Deutsch. med. Woch.*, 1896, No. 6; *Vereinsbeilage*, p. 43. [2] *Loc. cit.*

[Not long ago the writer was consulted by a middle-aged woman, who had apparently reached nearly the terminal stage of contracted kidney. She had been under the care of physicians for fourteen years for this trouble. From her history one might surmise that the kidney disease had had an insidious beginning some time before this. But to her certain knowledge albumin and casts had been present at every one of the frequent urinalyses made in the fourteen years.—ED.]

If physicians will develop the habit of examining the urine for albumin even in apparently healthy individuals, cases of chronic nephritis lasting a number of years will probably be more and more frequently seen.

In *arteriosclerotic induration* the course is not quite so slow, and the duration also is shorter because the vessels and the heart, on which so much depends, have been diseased before the beginning of the renal affection. For similar reasons *secondary contracted kidney* is characterized by a more rapid course, counting from the time when the signs of induration become clearly marked.

The *termination of indurative nephritis*, when it has reached the stage of fully developed contracted kidney, and especially when cardiac hypertrophy is pronounced, is always *fatal*. Death, however, does not always occur as the immediate consequence of the renal or vascular disease, being not infrequently brought about indirectly by more or less incidental complications, such as inflammation of the lungs or of the intestines, erysipelas, or the like, to which the organism, whose powers of resistance have been impaired, more readily falls a prey than under normal conditions. In other cases death is caused by uremia, hemorrhage into the brain or some other form of hemorrhage, or by passive congestion of internal organs. In the arteriosclerotic form death may be due to softening of the brain from thrombosis, or to gangrene of the toes, or to other results of the general sclerotic change in the arteries.

During the first stage of the disease, before any signs of cardiac or arterial disease are present, partial recovery is possible and is not even rare if appropriate treatment is instituted in time. This is indisputably shown by clinical observation as well as by the postmortem finding of old indurative nephritis with contraction in persons who, as has been said, had not shown any sign of kidney disease for a variable time preceding death, and this fact should be emphasized again and again in connection with the diagnosis of "functional or cyclic albuminuria."

DIAGNOSIS.

Fully developed contracted kidney is so well characterized by the clinical picture as described by Traube—copious watery urine containing a small amount of albumin, the signs of cardiac hypertrophy and increased aortic pressure—that it cannot well be mistaken for any other condition except by a physician who is so unprogressive as not to make an examination of the urine, especially for albumin, unless dropsy is present, or to examine the heart unless the patient complains of palpitation and asthmatic symptoms. If the heart and kidneys are systematically examined in every case, contracted kidney will not be overlooked,

and will often be found when the symptoms are quite insignificant. The only feature that may be occasionally absent from the complete picture is albuminuria. Now, when all the other symptoms are present, the diagnosis of contracted kidney may be made with a high degree of probability even in the absence of albuminuria, especially when there is albuminuric retinitis or gallop rhythm without cardiac lesion, or when after repeated examination it can be positively demonstrated that certain substances, such as methylene-blue, iodin, and sugar after the administration of phloridzin, are eliminated too slowly in the urine; but to remove every possible doubt, it is always desirable to demonstrate the presence of albumin, and the attempt will rarely prove unsuccessful if the urine is examined repeatedly, especially if the precaution is observed —which unfortunately is often neglected—of examining the urine obtained at various times during the day and not alone the night urine, and in doubtful cases the urine passed after active exercise and a copious meal (see p. 33).

The differential diagnosis from other conditions associated with polyuria is usually quite easy when contracted kidney is fully developed. From *diabetes mellitus* and *diabetes insipidus* it is distinguished by the absence of cardiac hypertrophy, which does not occur in these two conditions [or rarely—Ed.]; from the former also by the lower specific gravity and absence of sugar from the urine, and the latter by the presence of albumin. The specific gravity of the urine does not often fall so low in contracted kidney as in diabetes insipidus.

A *combination of diabetes mellitus with contracted kidney* (see p. 263) may be suspected when albumin is found in addition to sugar for a protracted period without any, or with only very few, morphologic constituents, and the diagnosis becomes assured if there is hypertrophy of the left side or of both sides of the heart, not due to a valvular lesion. It should be mentioned again, however, that the excretion of sugar in the urine often ceases when nephritis develops.

The *combination of diabetes insipidus and contracted kidney* cannot be recognized with certainty unless the presence of diabetes alone had already been demonstrated; but such a combination may be suspected in cases in which there is cardiac hypertrophy and the patient complains of severe thirst and voids excessive quantities of very watery albuminous urine of a specific gravity of less than 1005.

Pyelitis might, on account of the polyuria which is frequently present, and the albumin in the urine, arouse the suspicion of indurative nephritis, but an examination of the urinary sediment and due consideration of the conditions of the circulatory apparatus, etc., will suffice to guard against error.

The assumption of renal sclerosis on an arteriosclerotic base—*i. e.*, *primary sclerosis of the kidneys*—is justifiable when the signs of arteriosclerosis have been present before the symptoms pointing to disease of the kidneys, such as polyuria and albuminuria, are observed, when marked hypertrophy with dilatation of the heart, and cardiac asthma set in early, and when there exist causes which are especially favorable

for the production of a primary arteriosclerosis, such as old age or the abuse of tobacco. But without these factors, especially without a knowledge of the history and the development of the disease, it is difficult if not impossible, when signs of contracted kidney and arteriosclerosis coexist, to determine which is the primary condition.

In the case of so-called *secondary contracted kidney* a knowledge of the history of the course of the disease, particularly of the former existence of a chronic parenchymatous nephritis, is essential for the diagnosis. But in many cases, as has been said in connection with the diagnosis of chronic parenchymatous nephritis (see p. 245), it is impossible to differentiate positively between the various forms of chronic nephritis, to say whether they are "parenchymatous" or "indurate," and in a case of fully developed contracted kidney, therefore, it is not always possible to determine whether it has resulted from a parenchymatous nephritis—in other words, whether it is secondary or not.

When disturbed compensation with marked passive congestion in the kidneys and in the peripheral venous system, dropsy, etc., are superadded to one of these forms, the diagnosis of contracted kidney cannot be made positively without a knowledge of the patient's former condition; for the clinical picture in such a case, even when cardiac hypertrophy is present, may also be produced by disease of the myocardium or a valvular lesion, and the systolic heart murmur cannot be utilized with absolute certainty in the diagnosis. When, however, in spite of the congestion the urine is comparatively pale and of a low specific gravity, contracted kidney may be suspected (see p. 274).

For therapeutic purposes it is of the greatest practical importance to recognize indurative nephritis before the condition has reached the fully developed stage of true contracted kidney—*i. e.*, before cardiac hypertrophy and the increase in the arterial tension are marked and while polyuria is still moderate. Such a diagnosis can be made only after a prolonged observation, and must be based on repeated examinations of the urine made at different times and on the ability of the kidneys to excrete certain substances (see p. 275); by these means a positive diagnosis can usually be arrived at.

The conditions which might be confounded with the *beginning* of indurative nephritis, and which must therefore be taken into consideration in the diagnosis, are: (1) An acute or subacute nephritis at its terminal stage—*i. e.*, just as resolution is occurring—in which the characteristics of the urine may be the same as are found in the initial stage of indurative nephritis. The history of a preceding acute nephritis with the characteristic scanty and more or less bloody urine containing typical morphologic constituents, the occurrence of dropsy, the existence of certain etiologic factors, such as inflammations and intoxications, and finally the complete disappearance of albuminuria and polyuria in a short time under appropriate treatment will put the physician on the right track. (2) *Amyloid kidney.* The insidious onset, the absence of cardiac hypertrophy, and the composition of the urine, which in many cases is increased in quantity and of a low specific gravity, con-

taining a very small percentage of albumin and very few morphologic constituents, lend to amyloid disease a certain resemblance to the initial stage of indurative nephritis; but the etiology, which is usually quite definite, and the presence of enlargement of the spleen and liver, the digestive disturbances, the great pallor and much greater general debility of the patients, and the early appearance of dropsy are so characteristic of amyloid kidney that it is almost always possible to avoid mistaking the one condition for the other. (3) Finally, *beginning* indurative nephritis, owing to the fact that for a long time the general health remains practically unimpaired, and the albuminuria is very slight and even disappears, is not infrequently overlooked or mistaken for a *simple or transitory*, also called "*cyclic*," albuminuria, or even for "*physiologic*" albuminuria, and treatment is accordingly neglected. The writer has already pointed out (see p. 33) that it is a mistake to regard the temporary appearance of albuminuria in apparently healthy individuals as physiologic in every case; on the contrary, the individual must not be of an advanced age, the demonstration of a *definite*, even though unusual, *physiologic* cause, such as muscular exertion and the like, and the immediate disappearance of albumin from the urine on removal of the cause, are imperative conditions; besides, the urine must not be abnormal in any other respect, must not contain casts, or at most only hyaline casts, and in any event the quantity of albumin must be exceedingly small. Even when all these conditions are fulfilled, the decision may be difficult and may require *protracted observation;* indeed, in many cases it may be altogether impossible to come to a definite decision, because there is no sharp dividing line between physiologic and pathologic albuminuria any more than between physiologic and pathologic glycosuria, or between health and disease in general. Sometimes, it is true, changes are found even in these comparatively early stages which leave no doubt of the diagnosis, as, for example, retinitis (Ostwald[1]).

Whenever granular casts, leukocytes, or renal epithelium are found in the urine, physiologic albuminuria is out of the question, even when the excretion of albumin is quite insignificant and transitory, and irrespective of whether a distinct cycle can or cannot be demonstrated; the condition in such a case is either a mild acute nephritis, or a chronic interstitial nephritis either in the stage of inception or already somewhat advanced. The fact that such a transitory cyclic albuminuria disappears completely with or without medical interference does not affect the diagnosis of a nephritis of this sort, a peculiarity of which is that it sometimes comes to a standstill of its own accord.

As has been observed in connection with the diagnosis of non-indurative ("parenchymatous") nephritis, there will be found many cases that cannot be classified among any of the typical forms, and in which, therefore, the physician will have to content himself with the diagnosis of "chronic nephritis."

[The sure way, of course, of recognizing nephritis is, as said, to make it a routine practice to examine the urine and cardiovas-

[1] *Wien. klin. Rundschau*, 1897, No. 41.

cular system in all patients. He is a careless physician who neglects to do this when seeing a patient for the first time. It is the family doctor who, having examined his patient on other occasions and having found him sound, is most liable to neglect urinalysis or careful physical examination when, later, this patient comes to him with what seems to be a slight ailment. It is well to keep in mind the various manifestations of chronic uremia discussed under that heading; the trifling complaint may be one of the stigmata of chronic uremic intoxication. Often these complaints are of such a nature as to lead the patient to consult the specialist or to be sent to him by the family doctor. We need not mention them all here, as it would be merely a repetition of what has been said elsewhere, but one should not forget that anorexia, nausea, vomiting, and diarrhea may mean uremia, and so may pruritus, cramps in the muscles, as in the calves of the legs; dizziness, tinnitus, blurring of vision and other ocular disturbances be uremic, as may headache. We should always think of the kidney as the possible cause of an obstinate headache in one in middle life who has heretofore been free from it. Careful attention to the subjective history will often arouse our suspicions as to the renal origin of symptoms, and lead us to examine more critically the heart, vessels, retina, urine, and save us from an exasperating, if not serious, error in diagnosis.—ED.]

PROGNOSIS.

The prognosis of fully developed contracted kidney, so far as recovery is concerned, is altogether unfavorable; as regards life, on the other hand, it is not quite so hopeless, although far from favorable. It depends, in the first place, on the condition of the vascular system and the power of the heart; for so long as there are no disturbances in these organs, the patient's condition may remain comparatively good for a number of years, and he may even enjoy a certain measure of comfort and be able to follow some light occupation. The case is quite different, however, so soon as compensation is disturbed or hemorrhages, particularly cerebral hemorrhages, make their appearance. Even if the patient recovers from one or more of such accidents, his days are nevertheless numbered. [This statement is in general true, yet occasionally, even after cerebral or other hemorrhage in nephritis, the patient will, with care, manage to live with a fair degree of comfort for some months or even years.—ED.] There is one danger to which an individual with pronounced contracted kidney is always exposed—namely, uremia—and it is impossible to predict with certainty whether it will or will not occur. All that can be said is that it is more likely to occur after excesses of any kind, whether bodily or mental, than in the absence of such excesses.

But so long as the condition of contracted kidney is not fully developed, and the heart and blood-vessels particularly are not involved, or at least show no signs of being diseased by the presence of increased arterial tension, there is always hope that the morbid process may become arrested or, that functional recovery, at least, may take place. The outlook is, of course, better if the disease is recognized early, and

if the changes in the urine, especially albuminuria, are slight and respond readily to treatment.

TREATMENT.

As in the case of chronic parenchymatous nephritis, there is no doubt that indurative nephritis can in many cases be *prevented* by careful management and suitable after-treatment of every attack of *acute* nephritis (see p. 202). To prevent the transition of chronic *parenchymatous* to indurative nephritis (secondary contracted kidney) is not in the physician's power; nor is he often called upon to do so, as the former affection rarely ends in complete recovery, and its conversion into the latter (indurative nephritis) must be regarded as the most favorable event under the circumstances.

The *prophylactic* treatment may be regarded as including the appropriate treatment of the various well-known causes—*gout* and *chronic lead-poisoning*, chronic *alcoholism*, *syphilis*, and *diabetes*—although such treatment, as has already been remarked (p. 247), must be instituted even if nephritis is not to be feared.

It is needless to say that in the treatment of the disease itself the *cause* must receive due consideration, and that therefore, as in all diseases of the kidney, irritants must be avoided as much as possible. As regards *syphilis*, the writer must repeat what he has already said in connection with parenchymatous nephritis, that mercurial treatment has either no effect at all or an unfavorable effect on chronic nephritis. On the other hand, the writer is quite prepared to recommend the use of *iodin*, be it in the form of *potassium iodid* (or *sodium iodid*), tincture of iodin, iodinvasogen, iodalbacid, or iodipin, not only when syphilis is the cause of the nephritis, and not only, as Grainger Stewart recommends in chronic lead-poisoning for the purpose of forming iodid of lead, but in all other cases, especially when there is either primary or secondary arteriosclerosis. Whether iodin has a favorable effect on the chronic inflammation or produces a specific action on the vessel walls or, as G. Sée believes, lowers the blood-pressure, the writer will not pretend to say. He cannot offer any convincing proof of its utility, because in prescribing it he has never neglected the hygienic and dietetic measures that are indicated. But he has seen its use followed by improvement such as cannot always be achieved by means of the hygienic and dietetic treatment alone. He therefore regards it as a useful adjuvant, and endorses its recommendation by Bartels, Crocq, Lecorché and Talamon, Semmola, and others. Potassium iodid or sodium iodid is most effective in adult males in the dose of 0.2 to 0.5 gm. (about 3–8 gr.), and in women and children in correspondingly smaller doses, given three times a day in a little milk and continued for several weeks, withdrawing it from time to time if coryza develops. When the stomach is sensitive an enema of potassium iodid (10 to 15 c.c.—2½ to 4 dr. —of a 5 per cent. solution) administered three times a day is to be heartily recommended. Tincture of iodin in 5-drop doses given internally in Seltzer water, or iodinvasogen (6 per cent.) internally in doses of

5 to 10 drops in water several times a day, and externally by inunction, are also to be recommended. Iodipin is useful when the stomach and intestines are very sensitive, and is given by hypodermic injection in doses of 5 to 10 c.c. (1–2½ dr.). All other remedies that have so far been recommended are distinctly less useful or of no value whatever. [Iodin as an alterative is regarded by some as of considerable value also in cases that are not syphilitic. It may be given in small doses, 3 to 5 gr. of potassium iodid, or even in the form of the syrup of hydriodic acid, the latter being especially suited to children. It has seemed to the writer, at times, that he has seen good follow the use of Donovan's solution of arsenic (liq. arseni et hydrargyri iodidi) in doses of 1 or 2 drops. And where anemia is pronounced the syrup of the iodid of iron or the pill of the iodid of iron may be of benefit.—Ed.]

On the other hand, the *hygienic* and *dietetic* treatment is of the greatest importance and must be adapted to the various stages of the disease and to individual conditions. During the initial stage, before the development of marked polyuria and of cardiac and vascular complications, when albuminuria is slight or is only moderate or perhaps even intermittent, the same treatment may be employed as during recovery from acute nephritis (see p. 205), to which the condition is in many respects similar. It is always advisable at the beginning to insist on *absolute rest in bed as an experimental measure*, in order to determine whether the morbid process in the kidneys can be influenced, and if so, to what extent. If the albumin is made to disappear from the urine by that measure, as it sometimes does after several days or after one or two weeks, the patient should be kept in bed continuously for a longer period, say four or five weeks or even longer, after which he should gradually accustom himself to getting up and staying out of bed in the manner that has already been explained. At the same time, particularly in cases of intermittent albuminuria, a careful search should be made for any possible cause. In addition to the usual causes, such as fatigue, mental excitement and exposure to cold, the writer must call attention to *masturbation*, after the correction of which he has repeatedly seen an otherwise refractory intermittent albuminuria disappear.

If rest in bed during the first one or two weeks proves ineffective or appears to have little influence on the condition itself, its further continuance usually proves futile. Under such circumstances patients should on the whole receive the same treatment as in the advanced cases. [Many patients with incipient chronic interstitial nephritis, in whom the condition has been detected perhaps accidentally, as in examination for life insurance, can hardly be viewed in the light of invalids; and even though after the experimental rest albumin persists, they do not always need the treatment of an advanced case. They will, of course, exercise caution as regards excesses in diet, physical exercise, exposure to cold, etc., but by modifying their modes of living a little, by creating for themselves a slightly different environment, they may have months or years of comfort and usefulness ahead of them. But it is unwise and often impossible to treat these patients as though they were seriously

ill with some disease of an immediately threatening character, and to keep them by much drugging and frequent visits to the office, constantly reminded of their illness. The mental effect is bad, and there is no necessity for excessive treatment in this early stage. A life of temperance and moderation in all respects—eating, drinking, physical and mental work, freedom from anxiety—is often the only rational prescription.—Ed.]

After the disease is well developed the most important symptoms are cardiac hypertrophy and increased pressure in the aortic system, hence the therapeutic indications are to sustain the power of the heart, so as to prevent any disturbance of compensation as long as possible, and at the same time to combat so far as one can the unfavorable effects of increased tension which have been repeatedly discussed. We must steer a middle course so long as it is feasible, aiming to avoid weak and inefficient heart action on the one hand, and overaction and cardiac excitement on the other. The food must therefore be ample, nutritious, and yet not overstimulating, and above all not excessive in quantity, since too rich a diet would favor the development of plethoric conditions which are a distinct menace to the vascular system. The patient must also avoid the excessive ingestion of fluid, which might prove disastrous to the heart. Thirst may be relieved by sucking small pieces of ice or peppermint lozenges, or by rinsing the mouth with menthol solution, or by eating fruit.

As for the *character of the food*, the ingestion of albumin need not be restricted to the same degree in indurative as in parenchymatous nephritis, because the danger of injuring the organ by nitrogenous excrementitious products is not so great. Nevertheless an excess of albuminous food may do harm in very advanced cases of contracted kidney, because the small remainder of functionating parenchyma in the kidneys in the end becomes inadequate in spite of their power of compensation. (See Uremia.) In general it may be said that a *mixed diet* with the avoidance of specially irritating articles of food is most suitable during the greater part of the course of indurative nephritis, although certain deviations and concessions in one direction or the other may be made in accordance with individual conditions, such as marked anemia and cardiac debility, or, on the other hand, a vigorous constitution and good nutrition. Strong alcoholic beverages, tea and coffee, and tobacco are to be forbidden or, at least, restricted to a minimum; exercise in the open air may be taken to a greater or less degree, depending on individual conditions, overexercise and exposure to cold being always avoided. [What was said under the head of Chronic Parenchymatous Nephritis about the dangers of a too rigid adherence to a milk diet applies here as well.—Ed.]

Every change for the worse, every acute exacerbation calls for the institution of more stringent measures, as has been explained in connection with acute nephritis and chronic parenchymatous nephritis.

Drinking- and *bathing-cures* are usually not indicated in indurative nephritis because there is no indication to increase the diuresis and flush

out the kidneys. The drinking of hot and of strongly carbonated waters, and the indulgence in hot or even very warm baths are to be forbidden on account of their exhausting effect on the heart. For anemic persons the easily tolerated *saline chalybeate waters*, such as Franzenbad, Elster, and Wernarzer Brunnen in Brückenau, are useful. The best thing to do with such patients, however, is to send them to an *ordinary summer resort* where they can be properly fed and have exercise in the open air without any exertion on their part. *Climatic health resorts* are of advantage only if they permit the patients to spend more time in the open air during the unfavorable season than would be possible at home. In making a selection the physician should see that the place offers plenty of opportunities for walking without any laborious mountain climbing. Thus, the same places that have been recommended for the parenchymatous form are suitable for indurative nephritis also. When the damaged heart is the most prominent feature and there is no widespread disease of the vessels, *hot-water cures*, such as are used for heart patients in Nauheim, Rehme, Kissingen, and other places, and suitable *gymnastic exercises*, may be employed with caution.

As regards the influence of *pregnancy*, what has been said in connection with parenchymatous nephritis (see p. 258) applies in the case of indurative nephritis.

Among the *symptoms* that require treatment in cases of contracted kidney with compensation may be mentioned *palpitation of the heart*, which is to be combated by means of cold compresses, ice-bags, or the wearing of heart bags filled with cold water and pieces of ice, and, if necessary, by the administration of potassium bromid, bitter-almond water, and digitalis; *cardiac asthma*, which may be relieved with the ethereal tincture of valerian or with digitalis and nitroglycerin or by nitrites, such as sodium nitrite, amyl nitrite and sweet spirits of niter, as, for example, in the following prescription:

℞ Nitroglycerin, 0.05 (1 gr.);
Sweet spirits of niter, 25.00 (6 oz.).—M.
Sig. 12 to 15 drops, repeated if necessary.

[There can be no question of the great value of nitroglycerin in some of these cases where arterial tension is unusually high. Tolerance for the drug seems often to be established, so that the initial dose of $\frac{1}{100}$ gr. may have to be increased to $\frac{1}{75}$, $\frac{1}{50}$, or even $\frac{1}{30}$ gr. Combined with digitalis, it at times seems to act well. Perhaps by dilating peripheral vessels while the digitalis increases the action of the heart, it acts as a diuretic.—Ed.]

In very bad cases an injection of morphin may be required. When there are signs of *determination of blood to the head*, ringing in the ears, headache, and redness of the face, cold compresses or an ice-bag to the head may be tried, or in full-blooded persons wet cups to the back of the neck, or the administration of saline laxatives and bitter waters. In vigorous persons with strong heart action and full, high-tension pulse, blood-letting, as recommended by Bartels, may prove useful under such circumstances.

In regard to the treatment of *uremia, disturbances of compensation,* and other accidents, the reader is referred to what has been said in the preceding paragraphs.

[THE SURGICAL TREATMENT OF NEPHRITIS.

So much has been said lately regarding the treatment of acute and chronic nephritis by surgical procedures that mention must be made of it, though the editor would say at the start that he is far from favorably inclined toward this as a routine procedure in any form of nephritis, believing, as he does, that it is not founded on scientific principles and that the results thus far do not warrant the drawing of any general conclusions. Those who are interested in seeing the subject presented by the advocates of that line of treatment can find the same in Edebohls' *Surgical Treatment of Bright's Disease,* New York, 1904. Edebohls, as the result of his own extensive experience and from a study of cases reported by others, believes that he is warranted in advocating the decapsulation of the kidney in every case of chronic nephritis as soon as a diagnosis is made, provided the case is not practically *in extremis,* and provided further, the proper surgeon is at hand—that is, one who is skilled and experienced. He believes his own results and those of others warrant him in giving this radical advice. Without going into details one may say that the reports of many of the cases are far from complete, some of them leaving grave doubt as to the correctness of the diagnosis of nephritis; the results in some instances are too uncertain and have not lasted long enough to warrant one in saying there has been a cure, nor is it sufficiently emphasized that in the natural course of chronic nephritis marked variations in the symptoms and urinary findings are frequently seen, so that the changes met with after operation are not necessarily the result of the surgical procedure.

The theory upon which Edebohls and others operate is that in the chronic cases the decapsulation induces an "arterial hyperemization of the kidney. The result of this improved circulation in and between the tubules and glomeruli is the regenerative production of new epithelium capable of carrying on the secretory function." When we think of the nature of a chronic nephritis, of a chronic interstitial nephritis, for instance, and consider the widespread cardiovascular changes, the toxemic origin of the condition, the influence of heredity, etc., it is difficult to understand how the improvement of the mechanical conditions in the kidney, or even its nutritional activity, can work a cure. Temporary improvement would be all one would expect. The citation by Edebohls of the success of the Talma operation for cirrhosis of the liver as giving warrant for what he considers a somewhat similar operation on the kidney is not a happy one, for the results in cirrhosis have been far from satisfactory; many surgeons have discarded the Talma operation.

In cases of acute nephritis and congestion, where the condition of the kidney is one of swelling and the capsule is tense, Harrison and others have advocated a splitting of the capsule or a puncture of the same for the relief of this tension. Even this treatment is decidedly uncertain

in its results, for the majority of cases of acute nephritis recover, anyway. In general it may be said that the profession looks askance—and rightly—at the indiscriminate operation upon every patient who has albumin and casts in the urine; and while in individual cases the operation may perhaps be justified, an operation upon every case of nephritis is certainly to be condemned. More logical reasoning will have to be employed and more reliable statistics brought forth before it can be granted that a cure has been wrought of a disease of the character of a chronic interstitial nephritis.—ED.]

[THE VALUE OF THE METHODS OF DETERMINING THE FUNCTION OF THE KIDNEY.

Several times in the course of the discussion on nephritis mention has been made of the methods by which the function of the kidney is examined—cryoscopy, methylene-blue, etc. This will be as fitting a place as any to say a brief word concerning the value of these methods. Details as to technic, etc., can be sought in the original articles and monographs upon these topics.

Cryoscopy.—By this is meant the determination of the freezing-point. The principle upon which it is based is that the greater the molecular concentration of a solution, the lower is its freezing-point—in other words, the freezing-point depends upon the *number* of molecules in solution. The degree to which the freezing-point is lowered varies with the dissolving substance; thus, a substance dissolved in water would lower the freezing-point to a different degree from what it would if dissolved in alcohol. If a molecular weight in grams of a substance could be dissolved in 1 gm. of solvent, the depression of the freezing-point is a constant (K), varying with the solvent. This value is fictitious, as it is practically impossible to dissolve in 1 gm. of solvent this weight of most substances. But by using larger amounts of solvent—*e. g.*, 1000 gm., or smaller amounts of solute, the value is determined. For water, $K = 1870$. The depression of the freezing-point below that of the solvent—for water 0°C.—is represented by Δ. The greater the amount of substance in solution, the greater the depression; the greater the amount of solvent, the less the depression; the greater the molecular weight of the dissolved substance, the less the depression. So if S represent the weight of the dissolved substance (the solute), K the constant, L the weight of the solvent, and M the molecular weight of the dissolved substance, the formula for Δ should show a variation directly as the constant and the weight of dissolved substance, and inversely as the molecular weight and the weight of solvent,

or
$$\Delta = \frac{S \times K}{L \times M},$$

or for water,
$$\Delta = \frac{S \times 1870}{L \times M}.$$

Now, a moment's study of this equation will show how easily Δ can be modified, and how, if we use this formula in the case of the urine, it will explain the difficulties encountered in interpreting the results of cryoscopy as there applied. It will be seen that increase in the amount of solvent will lessen the value of Δ; hence the amount of water in the urine must be considered, and all the influences that may modify this have to be noted, especially the amount of water ingested. Such diurnal variations in the amount of urine are seen, that single specimens are valueless, and only a twenty-four-hour specimen can be presumed to have any value whatever. Again, there is a marked variation in Δ according to the molecular weight of the substance in solution. A substance with a small molecular weight, say 50, would give a much greater value for Δ than a substance with a greater molecular weight, say 1000. We thus see why many of the inorganic salts, and especially such as ionize—*i. e.*, electrolytes—produce more marked depression than most of the organic molecules, such as sugar or albumin. But we can also plainly see how complicated must be the influences that change the value of Δ, when we consider how many different substances of different molecular weights are in the urine. Interpretation of these changes in Δ is therefore not simple. Still, with marked bilateral renal inadequacy and retention of solids the value of S is small, and Δ is therefore small. By many observations the average of Δ has been found to be between —0.9° C. and —2.6° C. In health there are these wide limits. In disease of the kidney certain variations are fairly constant. In congestion of the kidney, largely owing to the concentration of the urine, Δ is low—*i. e.*, approaches —2.6° C. or even goes below it. In acute nephritis, for the same cause, small amount of water—*i. e.*, small value for L—Δ will be low. This is less true of the chronic parenchymatous form, where values nearer —1° C. are met with. In the chronic interstitial nephritis the freezing-point is rather uniformly higher—*i. e.*, near —1° or even less than —0.9° C. It has been found that edema and anemia influence the freezing-point of the urine, and should be taken into consideration when attempting to draw conclusions.

From these considerations it will be seen that the interpretation of the changes in the freezing-point demands careful consideration of many things—the amount of fluid ingested, the amount lost in sweat and stool, the total urine for at least twenty-four hours, the kind and quantity of food, the presence or absence of dropsy or anemia. Of special value in determining the functional capacity of one kidney is the study of urine obtained from each kidney separately by ureteral catheterization, though the reflex nervous influence of such a procedure—including as it sometimes does an anesthesia—in producing relative anuria is not to be entirely slighted. But this study of the secretion from the one kidney is of especial value in cases of suspected abscess, tumor, or tuberculosis of one kidney, where the question of surgical removal of the diseased kidney comes up.

Cryoscopy of the urine alone is therefore of very limited practical

value. In fact, one could learn nearly or quite as much by a study of specific gravity and estimation of the total solids. Its value, however, is enhanced if at the same time the freezing-point of the blood is determined. This in health is nearly constant, —0.56° C. to —0.57° C. If the kidneys are markedly inadequate and there is retention in the blood of substances that should be eliminated, the molecular concentration of the blood increases and its freezing-point (∂) is lowered—*e. g.*, to —0.65° C. Such readings are met with in uremia. A study, therefore, of the freezing-point of the urine and of the blood is of some value in prognosis in threatened uremia, and of especial value in unilateral lesions, where surgical removal of one kidney would scarcely be attempted if the blood showed a low freezing-point—*e. g.*, below —0.60° C.[1] In general, one may say the closer the freezing-point of the blood and the urine approach each other, the graver the prognosis. Yet anemia and edema tend to elevate the freezing-point of the blood (hydremia?), while cyanosis, jaundice, diabetes, abdominal tumors, tend to lower it. Hence, caution in interpretation is essential.

The technic of carrying out cryoscopy, and the apparatus, will not be described here. For obtaining results that are reliable, practice with the freezing of water, salt solutions, normal urines, and blood is necessary. Details as to theory and technic may be found in English in books on physics and physical chemistry. (See Walker, *Introduction to Physical Chemistry*, 3d ed., p. 194, 1903; Jones, *Elements of Physical Chemistry*, p. 203, 1902; Cohen, *Physical Chemistry for Physicians and Biologists*, translated by Martin H. Fisher, p. 168, 1903. Tieken has an excellent brief résumé of the subject (*Chicago Medical Recorder*, April 15, 1904), especially from the clinical point of view, with bibliography. Cryoscopy as well as the tests by methylene-blue and phloridzin are considered in *Casper and Richter's Functional Diagnosis of Kidney Disease*, translated by Bryan and Sanford, 1903, and in *Croftan's Clinical Urinology*, 1904.)

Methylene-blue Test.—If 0.05 gm. of methylene-blue in watery solution (1 : 20) be injected subcutaneously, it will be found, if the kidneys are healthy, that: (1) the blue will appear in the urine within thirty minutes; (2) it will continue to be present for about forty to sixty hours; (3) about one-half the quantity injected (0.025 gm.) will appear in the urine within twenty-four hours. Some of the methylene-blue may be present in the urine as a colorless chromogen. If the urine be acidified with acetic acid and then boiled, the chromogen becomes converted into pigment. By adding chloroform to the urine and shaking, minute traces of methylene-blue can be detected, as they will be absorbed by the chloroform and color it. The quantitative estimate of the methylene-blue in the urine is a tedious and rather unsatisfactory test made by comparing the color of the urine to be tested—with the chromogen converted into pigment by acidifying and boiling—with the same amount of urine (from the same patient), to which an amount of methylene-blue solution of known strength is

[1] See Kümmel, *Arch. f. klin. Chi.*, 1903.

added until the color of the two solutions corresponds, and then estimating the amount of methylene-blue from the data thus obtained. This quantitative test is seldom necessary, however, for whatever benefit comes from the test is really derived from noting the time of appearance of the color and the duration of the elimination. In contracted kidney there is generally a delay in each respect, and in unilateral disease a retarded function of the one kidney may be found. But results to be accurate necessitate the use of the ureteral catheter, and require also that it be left in place at least twenty-four to forty-eight hours, making the test rather impracticable. In the parenchymatous forms of nephritis, in amyloid and congested kidney, results are too uncertain to be of much value.

The test with iodid of potassium is also not to be relied upon to any greater extent.

In either one of these tests, too, one is confronted by the fact, and it is a valid objection to the method, that because a kidney will not eliminate methylene-blue or iodid of potassium as promptly as in health, we cannot conclude that it may not eliminate normal or abnormal products of body metabolism. Again, we do not know what influence other body- and blood-conditions—*e. g.*, edema or anemia—may have in altering the metabolism of these test substances, and thus cause uncontrollable variations in the test.

Phloridzin Test.—The glucoside phloridzin is capable of producing glycosuria without hyperglycemia, the glucose formation being dependent on the action of the kidney. This fact of the part played by the kidney in producing this glycosuria seems proved, no matter what view is taken of the mechanism or the chemistry of the process. It has been employed, therefore, as a test of the health of the kidney cells, of their secretory power. By many it is regarded as superior to the methylene-blue or iodid test, and it certainly has the advantage of being less time-consuming. If 0.005 gm. of phloridzin be injected subcutaneously, sugar should appear in the urine within twenty to thirty minutes, and continue to be eliminated for about three to four hours. The ureteral catheter, if unilateral examination is attempted, need not be kept in, therefore, longer than four to six hours. It is best gently to warm the phloridzin solution, or to add a minimal amount of potassic hydrate solution, in order to insure free solution of the phloridzin. The results are practically the same as with the methylene-blue injections—a delay in the time appearance and disappearance in chronic interstitial nephritis, varying results in the parenchymatous forms, and delay—with ureteral catheterization—in many cases of unilateral disease where the bulk of the kidney is destroyed.

These varied tests for the renal function are not to be relied upon implicitly, and should be viewed merely as confirmatory of the ordinary and longer known methods—testing for albumin, casts, urea, nitrogen, total solids, etc. When there is an agreement of all these methods of examination, the old and the new, especial value attaches to the results. Of these newer methods, cryoscopy of the urine and blood, together

with the phloridzin test, are the most reliable; and especially when applied to the urine collected by ureteral catheterization they become of great importance in surgery in furnishing an indication as to the safety of operations on the kidney.—Ed.]

APPENDIX.

Simple Non-inflammatory Atrophy of the Kidneys.—In a variety of conditions which have in common a diminished blood-supply to the kidneys and consequent impaired nutrition of the organs, there develops a simple atrophy of the kidneys due to diminution and disappearance of the secreting elements. The reduction in the blood-supply may be due to the congenital hypoplasia of the arterial system, or in very rare cases of the renal arteries alone (see pp. 166 and 270), or to acquired stenosis of the arteries; but it may also be dependent upon a general anemia and impaired nutrition, and occurs therefore in severe anemic and cachectic conditions of various kinds, if they are sufficiently protracted.

The most frequent and most familiar form is the senile granular atrophy of the kidneys, in which the changes are usually more pronounced than in any other, because two factors co-operate in this condition—the general diminution of vital energy incident to old age and the sclerosis of the arteries, especially of the renal arteries. The kidneys are red or grayish red in color, moderately diminished in size, although never in cases of simple atrophy to the same degree as in inflammatory indurative atrophy. The surface is smooth or slightly irregular from the presence of cicatricial depressions, and may present a few isolated cysts. The capsule is not thickened and, as a rule, strips readily. The parenchyma feels hard, and on the cut surface the cortical substance appears diminished in width.

Microscopically it is found that some of the glomeruli have been destroyed, and in places are closer together than normal. The vascular coils appear to have lost some of their nuclei, and are at first hyaline, but later merge into a uniform, impermeable mass, in which here and there a nucleus may be seen. The capsular epithelium also disappears, and the capsule itself contracts or may be hyaline, thickened on its inner side, and eventually becomes adherent to the glomerulus, and forms with it a uniform spheric mass much smaller than the normal structure. Striated connective-tissue thickening of the capsule, as in inflammatory induration of the kidneys, is uniformly absent in simple atrophy.

The uriniferous tubules belonging to the glomeruli that have been destroyed also present a variable degree of atrophy. They become narrowed, the epithelial lining becomes flattened, and the nuclei are more closely massed. Ultimately the epithelial cells are destroyed, the tubules collapse in places and form solid cords, while others present local dilatations which form cysts filled with a colloid material. The smaller vascular trunks present thickening of the intima which may go on to a complete obliteration of the lumen (endarteritis obliterans). The connective-tissue stroma presents no changes whatever; but in the areas

in which the destruction of uriniferous tubules has been extensive, it appears on that account to occupy a larger space than under normal conditions. Small-cell infiltration is either absent altogether or quite insignificant. If it is well marked during the later stages, usually around the afferent vessel and around Bowman's capsule, it is a sign that simple atrophy has gone on to inflammatory induration with arteriosclerosis (see p. 269). Indeed, there is no sharp line of distinction between the two conditions.

The minute tissue changes are somewhat different when the atrophy develops solely as the result of impaired nutrition, especially in cases with severe anemia and cachexia, without any atheroma or sclerotic narrowing of the blood-vessels. In old age, which is always attended by changes in the blood-vessels, this form, although rare, has been observed occasionally; as, for example, by Rosenstein.[1] It is, however, more frequent, although still rare, in severe anemic conditions occurring in younger individuals, as pulmonary tuberculosis, cancer of the stomach and liver, severe anemia from ulcer of the stomach with repeated hemorrhages, and leukemia.

In this form the principal change outside of the shrinking of the glomeruli, which have lost some of their nuclei and whose capsules have become wrinkled, is *fatty degeneration* of the epithelial lining of the uriniferous tubules, which terminates in destruction of the cells and narrowing of the tubules. Small-cell infiltration of the connective tissue appears to be more common and more extensive in this form than in senile arteriosclerotic atrophy.

Non-inflammatory contraction of the kidney is practically devoid of characteristic *symptoms*. The quantity of urine is not markedly, and certainly not permanently, diminished, as might be supposed on account of the destruction of parenchymatous tissue. The urine is usually pale, which is probably attributable to the general impairment of the nutrition, clear, without any sediment worth mentioning, and free from albumin. When albumin is found temporarily, usually in very small quantities, it is not due to the atrophy, but represents the expression of the mild inflammatory conditions, the foci of small-cell infiltration which, as has just been remarked, are sometimes found in these kidneys.

It follows that a positive *diagnosis* of the affection is not possible; at most a tentative diagnosis may be hazarded in aged patients, or in cases of severe anemia and cachexia if the urine is found to contain albumin from time to time and no characteristic morphologic elements.

This form of atrophy does not require any special *treatment*. Whether it is capable of improvement, if the cause—*i. e.*, the lowered state of of nutrition—is removed, the writer is not able to say.

[1] *Loc. cit.*, p. 463.

SUPPURATIVE INFLAMMATION OF THE KIDNEYS AND ABSCESS.

LITERATURE.—G. König, *Prakt. Abhandl. über die Krankh. der Niere*, Leipzig, 1826, p. 104. Rayer, *loc. cit.*, i., p. 295. Johnson, *Krankh. der Niere*, translated by Schütze, Quedlinburg, 1856, p. 332. Virchow, *Gesammelte Abhandl.*, 1856, pp. 636 and 711, and *Virchow's Archiv*, x., p. 179. Beckmann, *ibid.*, xii., p. 59. Cohn, *Klin. der embolischen Gefässkrankh.*, Berlin, 1860, p. 569. H. Fischer, *Die septische Nephritis*, Breslau, 1868. Waldeyer, *Virchow's Archiv*, lii., 4, 1871. Lecorché, *Traité des mal. des reins*, 1875, p. 426. v. Wunschmann, *Zeits. f. Heilk.*, 1895, xv., p. 287. Lancereaux, *loc. cit.*, p. 195. Klebs, *Lehrb. der path. Anat.*, 1876, i., p. 653. Fürbringer, *Die Krankh. der Harn- u. Geschlechtsorgane*, p. 152. M. Litten, *Zeits. f. klin. Med.*, iv., p. 191. Ebstein in *v. Ziemssen's Handb. der speciellen Path.*, ix., 2, p. 3. Rosenstein, *loc. cit.*, p. 407. E. Sehrwald in *Zülzer-Oberländer's Klin. Handb. der Harn- u. Sexualorgane*, ii., 1894, p. 82. See also literature accompanying Pyelitis and Pyelonephritis.

Suppuration in the urinary organs, especially in the kidneys, is mentioned by the most ancient writers—Hippocrates, Rufus, Galen, Aëtius, and others. Aretäus was the first to distinguish between acute and chronic suppuration of the kidneys and to describe the cerebral symptoms which develop as the result of suppression of urine and often prove fatal, recommending among other things the application of wet cups to the region of the kidneys. The first attempt to classify the suppurations according to their source was made in 1761, by Friedrich Hoffmann, who divided them into superficial, benign, and deep suppurations involving the entire kidney substance. Sauvages[1] distinguished a *nephritis vera*, a *nephritis calculosa*, and a *nephritis arthritica*. This classification, especially the division *nephritis calculosa*, remained in force until it was demonstrated by Rayer that many affections regarded as suppuration of the kidneys in reality consist of suppuration of the pelvis of the kidney—pyelitis—or at least have their starting-point in the pelvis of the kidney (pyelonephritis purulenta). Rayer mentions several causes of true renal suppuration, such as traumatism, the irritation of stimulating diuretics, exposure to cold, and suppurations in neighboring structures (perinephritis) or in distant organs; but he had no clear notion of the mechanism of inflammatory processes not due to purely local causes. The earliest light on this subject was obtained through the epoch-making investigations of Virchow on embolism and metastasis, and our knowledge of it was enlarged by the subsequent discovery of the parasitic nature of suppuration. The first intimation in regard to the invasion of the urinary passages by microparasites and the suppuration thus produced was given by Traube,[2] while the first observations of microparasites in the kidneys were contributed by Waldeyer and Klebs. Koch's investigations and the technic he developed, together with Lister's studies on the course and repair of wounds, which he pursued almost at the same time, finally left no doubt of the importance of the microparasitic element in all forms of suppuration, including that of the kidneys.

[1] *Nosologia Method Amstelod*, 1768, i., p. 503.
[2] *Berlin. klin. Woch.*, 1864, No. 2.

ETIOLOGY AND PATHOGENESIS.

In the present state of our knowledge, it must be assumed that the cause of any inflammatory process that leads to suppuration, except when experimentally induced—*i. e.*, in all *clinical cases*—is always of a *parasitic* nature. It is true that there are some germ-free chemical substances that are capable of producing suppuration, among them a few that are marked irritants to the kidneys, such as turpentine and petroleum; but these substances, in order to produce suppuration, must be highly concentrated, and it is impossible that they should reach the kidneys in such a state of concentration, no matter what the manner of their administration, unless they were directly injected into the organs.

The microparasites that have been found as causes of suppuration are in most cases *Staphylococcus pyogenes* (aureus) and *Streptococcus pyogenes*, more rarely *Bacterium coli commune*, and *proteus* (Hauser), besides many *specific microbes*, as *gonococcus*, *Bacillus tuberculosis*, *Diplococcus pneumoniæ*, the *Bacillus typhosus*, *actinomyces*, etc. The growth as well as the virulence of these pus producers is favored by invasion of the organs in large numbers, by diminished blood-supply, and by a lowered state of nutrition and consequent impairment of the powers of resistance.

The pyogenic micro-organisms may enter the kidneys in one of four ways:

1. Directly from the outside through a perforating wound—that is, one which extends to the kidneys, or through a fistula. On account of the position of the organs, deep within the tissues and well protected, suppuration produced in this way—in other words, traumatic suppuration of the kidneys—is extremely rare, and, for reasons that will readily be understood, is almost always confined to one kidney. Without exception, the surrounding tissue, which is invaded at the same time as the kidney, becomes implicated in the suppurative process—*i. e.*, traumatic suppurative nephritis is practically always attended by purulent paranephritis.

In rare cases, such as those that have been reported by the older writers, as Rayer and Johnson, and in more recent times by Rahn,[1] Duffin,[2] J. Singer,[3] and others, suppuration of the kidney and paranephritic abscess have been observed after *injuries* affecting the region of the kidneys and unattended by any external wounds. Unless some other source for the pus was overlooked, these cases are to be explained on the assumption that the injury had caused hemorrhage and contusion of the tissues in the kidney or its immediate neighborhood, and had thus prepared a most favorable soil for the invasion and development of *microbes* present in the blood. These cases ought therefore, strictly speaking, to be included under the group Hematogenous Suppurations (see No. 4).

2. From the connective tissue surrounding the kidneys a suppurative process readily spreads *by contiguity* to one or both kidneys, attack-

[1] "Ueber Paranephritis protopathica," Diss., Berlin, 1873.
[2] *Trans. Path. Soc.*, 1873, xxiv.
[3] *Prager med. Woch.*, 1883, No. 47.

ing first the fatty capsule (paranephritis) and then passing to the kidney itself. Infection, as a rule, is derived from *pelvic suppuration*, which may be due to a variety of causes (paratyphlitis, parametritis, psoitis, and peripsoitis), more rarely from infiltrations of the tissues with urine, and still more rarely from suppurations in the bony portions of the pelvis, which, on account of the long-continued dorsal position of the patients, are very apt to spread to the kidneys. But pus from a burrowing abscess in some part situated higher up may also find its way to the kidneys. In the case of the right kidney, pus may have its origin in abscess of the liver; in the case of the left kidney, in subphrenic abscess secondary to gastric ulcer and in suppurations in the spleen.

3. A suppurative process in the *urinary passages* may *ascend in the mucous membrane* and thus extend to the kidney; hence, anything that may cause a purulent inflammation of the urinary passages, from the meatus through the urethra, bladder, and ureters as far as the pelvis of the kidney, may be followed by a purulent nephritis, and the etiology of the inflammation of these parts therefore comes into consideration. Suppuration most frequently and most easily results from a purulent *pyelonephritis*. As will be more fully explained (see p. 339), pyelitis, especially when it is primary and not derived from the bladder, is more commonly unilateral than bilateral, and accordingly pyelonephritis more rarely affects both kidneys than one. But when the purulent inflammation starts in the bladder both kidneys become involved, either at the same time or one soon after the other, because the vesical inflammation is transmitted by both ureters, although the condition is not equally severe in both kidneys.

The passage of pyogenic micro-organisms from the bladder into the ureter is greatly facilitated by the fact that, owing to the protracted stagnation of the urine, the orifice of the ureter into the bladder fails to close as under normal conditions and does not offer the customary resistance to the backward flow of the urine. Pyelitis and pyelonephritis are therefore observed chiefly after inflammatory conditions of the bladder attended by continued ischuria—*i. e.*, in cases of cystitis with stricture of the urethra and in cases of compression of the urethra by a prostatic tumor. Another favoring factor is that under these conditions the walls of the bladder and of the ureter suffer in their nutrition and in their structure, and therefore more readily permit the intestinal bacteria to pass through them even in the absence of gross solutions of continuity (Posner[1]). But even in the absence of stagnation the contents of the bladder may pass into the ureters, and the passage of pyogenic micro-organisms into these tubes is possible, as may be inferred from the experiments performed on animals by L. Lewin and H. Goldschmidt,[2] who found that the mere retention of urine without stagnation, and injections into the bladder were capable of producing a backward flow of fluid into the ureters and, by virtue of the antiperistaltic movements in those structures, as far as the kidneys.

[1] *Verhandlungen der Naturforscher-Versammlung in Lübeck*, 1895.
[2] *Virchow's Archiv*, cxxxiv., 1894, p. 33.

Inflammations of the kidneys that originate in this way are frequently called *urogenetic* or urinogenetic, to distinguish them from inflammations originating in some other way.

There are, however, other channels through which the causal micro-organisms of infections and inflammations may reach the kidneys from the urinary passages—the ureters, bladder, and urethra; they may enter the blood through the lymph vessels and the perirenal tissue, reach the kidney through the blood, and thus set up inflammation and suppuration in the kidneys by *metastasis*.

[The question of the origin of suppurative nephritis is fully discussed by Sampson,[1] who emphasizes the fact that there are various vascular and lymphatic channels by which a primary suppuration in the bladder may extend to the kidney, and also the fact that lowered local and general resistance favors localization of pus germs in the kidney. The mechanism of contamination of the pelvis of the kidney by way of the lumen of the ureter is also gone into in detail. The paper is an exhaustive one and well worth consulting by one desiring a clear knowledge of "ascending renal infection."—ED.]

4. When the pyogenic micro-organisms invade the kidneys *by way of the blood*, both organs are affected almost without exception. In point of frequency this form of suppuration occupies a third place among metastatic suppurations in organs, the commonest being those in the lungs, and those next in order the liver abscesses. The mechanism of this *hematogenous* suppurative inflammation of the kidneys is the same as that of embolism of the kidneys (see p. 158), except that, owing to the minute size of the pus producers or the infected emboli, the capillaries, especially those of the glomeruli, are occluded and become the lodging-place of the embolus more frequently than do the larger vascular trunks. According to v. Recklinghausen,[2] a *retrograde transport* from the inferior vena cava to the kidneys may also take place.

In this condition the deposition and subsequent development of the pyogenic organisms is favored by retardation of the blood-stream, both because, owing to the diminished velocity, the tissue is less perfectly supplied with arterial blood, and therefore loses some of its vitality, and also because the excretion of urine is diminished, thus retarding the removal of any microparasites that may have passed through the glomeruli with the urine.

The commonest cause of metastatic suppuration is found in all those processes which, in the widest sense of the term, are designated *pyemia* or *septicopyemia*, among which ulcerative endocarditis occupies the first place. For in these conditions the infectious germs not only enter the arterial circulation directly from the left ventricle, but, as the result of the direct injury sustained by the heart muscle, the two factors which have just been mentioned as favoring the deposition of germs become particularly prominent. In the great majority of cases the micro-organism which causes the inflammation is the *streptococcus*. Other

[1] *Bull. Johns Hopkins Hosp.*, vol. xiv., No. 153, pp. 334–352.
[2] *Virchow's Archiv*, 1885, c.

parasites are those that have already been mentioned; these have sometimes been demonstrated as the cause of suppuration in the kidney. In a few cases, chiefly from the older literature, it was impossible to find the source of the suppurative process in the form of a primary infectious focus, and the renal suppuration was therefore regarded as a primary, idiopathic or spontaneous condition, or was attributed to exposure to cold. But it is more in accord with our present views to assume in such cases a hidden source that is not susceptible of demonstration—in other words, a "cryptogenetic" pyemia.

Age and *sex*, *occupation* and *mode of life* have a certain influence in the case of some of the above-mentioned causes; thus, for example, among those mentioned under 1, as the danger of injury and concussion of the region of the kidneys is greater in the earlier half of life and among the working portion of the population. Of the suppuration in the neighborhood of the kidneys, mentioned in 2, especially pelvic suppurations, the greater contingent is furnished by women during their sexual period, on account of their liability to parametritis; while, conversely, suppuration caused by stagnation of the urine from stricture, compression of the urethra, etc. (see 3), is far more frequently found in men in the middle or the advanced period of life. Metastatic suppuration (4) may occur in such a great variety of conditions that there can be no question of any special predisposition. It is worth noting, however, that even in the *newborn*, be it as a result of puerperal infection or of pyemia beginning in the umbilical wound or infection through some other portal, suppuration of the kidney may take place, and that in women *puerperal fever* may sometimes operate as an exciting cause.

PATHOLOGIC ANATOMY.

Suppurations due to traumatic causes or originating by contiguity from neighboring structures are usually confined to one kidney. Almost always, even when the suppurative process originates in some other way, the diseased viscus is surrounded by tissue infiltrated with pus and, in the case of traumatic inflammations, with blood, or it is embedded in a true pus cavity and more or less adherent to the surrounding parts.

In *traumatic* inflammation the kidney in recent cases exhibits traces of external violence in the form of lacerations which usually run transversely through the entire organ, or in the form of stab wounds and bullet wounds passing through various portions of the viscus, or the tissue may be totally demolished. When the greater part of the organ is preserved, it is at first enlarged and brittle, and presents both on its surface and in the interior larger and smaller hemorrhages and purulent foci, which are scattered through the parenchyma, but chiefly in the cortex, or unite to form large abscesses. During the subsequent course of the disease the necrotic remains of parenchyma—discolored offensive shreds of tissue—are found free in the pus cavity, or still retain some connection with the remainder of the organ, although surrounded by a purulent zone; and finally, in the severest grades, the entire kidney is converted into a pultaceous sac filled with a semi-fluid, purulent and

sanguineous material, and shreds of tissue. The purulent or fetid contents may make their way to the surface in various directions—in the case of penetrating wounds through the original wound channel, in other cases through fistulæ that form secondarily; or the material may be discharged into the pelvis of the kidney and thence into the bladder; or finally rupture may take place into other organs to which the kidney has previously become adherent, especially into the intestine or into the peritoneal cavity or even through the diaphragm into the pleura and even, after rupture into the pulmonary tissue, into the bronchi. Finally the condition may result in a general *pyemic* or *septicopyemic infection* with *metastatic abscesses* in other organs.

Suppuration of the kidneys by extension from neighboring structures by contiguity differs from the traumatic variety only by the absence of lacerations of the tissue from external violence and the associated hemorrhages.

Suppuration of the kidneys derived from the *urinary passages* will be more fully described in the section on Pyelonephritis.

Finally, *metastatic* suppuration, as has been stated, almost without exception affects both kidneys. The organs appear swollen and flaccid, and through the thin capsule a number of yellowish or grayish-yellow punctate or spheric foci surrounded by a hemorrhagic areola may be seen. In these situations the capsule is adherent to the parenchyma. On the cut surface the tissue appears to be swollen, turbid, and flabby, and also presents numerous foci in the form either of barely visible yellowish points or patches as large as a pea, those in the cortex spheric or wedge-shaped, with the base directed toward the surface, and arranged in groups, those in the medullary substance having a linear shape, running parallel to the uriniferous tubules, and extending as far as the center of the pyramid, while the papillæ usually escape.

On microscopic examination the foci are seen to consist of accumulations of microparasites, in the immediate neighborhood of which the tissues show a reactive inflammation with pus formation. Usually the coils of some of the glomeruli are filled with the parasites, the lumen occluded, so that the epithelium and even the vessel wall may become necrotic. Later, a circumcapsular infiltration of the connective tissue with pus cells takes place. At the same time, if the parasites have also entered the larger vascular trunks, or later, if they pass from the glomeruli into the uriniferous tubules, foci of cellular infiltration make their appearance in the interstitial tissue also, and by their coalescence form miliary, and gradually larger, abscesses. The epithelial cells in the areas invaded by the bacteria and infiltrated with pus are soon destroyed and their débris mingles with the purulent contents of the foci, which may also contain blood and hemoglobin. These purulent foci may rupture into uriniferous tubules and discharge their contents into them or entirely occlude them.

Any form of suppuration, whatever may be its cause, may, after the causative agent has ceased to act, be terminated by cicatrization, and *local* healing may take place, particularly if the pus cavity is small.

The contents either undergo fatty degeneration and become absorbed or inspissated, the cavity collapses, becomes filled with granulation tissue, and ultimately converted into a brawny and sometimes calcareous cicatricial mass. From the nature of things the most favorable conditions for such a result are found in traumatic suppuration of the kidney of moderate extent, and the most unfavorable in pyemic and septic suppuration, in which death occurs so rapidly that no time is afforded for the reparative process to take place. When death is delayed for some time in extensive suppuration, some areas are found in various stages of healing side by side with active abscesses.

If the suppurative process is very much protracted, there develops as a sequel *amyloid degeneration* of the same, and in cases of unilateral suppuration often of the other kidney as well. In cases of unilateral partial suppuration of the kidney, *hypertrophy* of the intact tissue or of the other organ may take place; and finally the second kidney, which was originally healthy, may fall a prey to *inflammation* from absorption of irritating substances from the pus cavities contained in the other kidney.

As these inflammations of the kidney, with the exception of the traumatic forms, are always secondary, other changes, which form the *starting-point* of the renal affection, such as suppurative or infectious processes, are almost always found in the cadaver; and in addition others which like the renal degeneration represent *sequelæ*, such as abscesses in the lungs, in the liver, and in other situations. But, as the writer has already mentioned, it is sometimes impossible to find the source of the suppurative process. Traumatic suppuration may be complicated by diseases elsewhere in the body caused by the same injury.

SYMPTOMS, COURSE, AND TERMINATION.

Many cases of suppuration of the kidney run their course without producing any symptoms, or the symptoms cannot be distinguished from those of the *causal* disease and are lost in the general symptom-complex of the primary trouble.

Accordingly the clinical phenomena are most characteristic in the primary traumatic forms. Aside from the traces of external violence and the effects of shock, which are not necessarily always present, *pain in the region of the kidneys*, either spontaneous or elicited by pressure and radiating downward or more rarely upward, is usually the first symptom, and to this *hematuria* or complete *suppression* is frequently superadded. *A chill* or *repeated chills* followed by fever may occur at the very outset or not until several days after the reception of the injury, when suppuration has taken place.

The subsequent course in cases in which the injury is not extensive enough to bring on speedy death is quite variable. It is most favorable when the *pus* can discharge itself into the pelvis of the kidney and *pass off with the urine*. In such a case the fever subsides and recovery may follow after a variable period of illness, its occurrence being favored by rapid and complete evacuation of the pus, as retention of

the pus at once causes a return of the fever and other symptoms. The case may run a mild course when the pus either spontaneously or through an artificial opening finds an outlet on the surface of the body, but the fistula which is very likely to form is always liable to become occluded or to afford an opportunity for purulent infiltration and burrowing abscesses elsewhere. The result of such an event is a long-continued fever of a more or less pronounced pyemic character which gradually destroys the patient's life, unless the pus ruptures into a dangerous locality, such as the peritoneum, or the erosion of a large blood-vessel takes place, when sudden death ensues.

In suppurations caused by *extension from neighboring parts* the onset of the disease is usually less distinct because fever, pain in the abdomen and in the back, retention of urine and other urinary symptoms are usually present before the kidney itself is involved. In some cases distinct localization of the pain in the region of the kidneys, swelling in that locality, and perhaps the presence of a tumor corresponding to the organ, that can be distinctly felt, may indicate that the morbid process has invaded the kidney. The appearance of pus in the urine in these cases is not a positive proof that the kidney has become involved, because the pus may have entered the urinary passages directly from the already affected neighboring parts. It is only when the sudden collapse or, at least, marked diminution in the size of a tumor corresponding to the kidney coincides with the appearance of pus in the urine that the existence of renal suppuration may be assumed with a certain degree of confidence. In other respects this variety may run about the same course as the traumatic, except that a favorable termination is much rarer, because the suppuration is usually much more extensive and the patient's strength becomes greatly undermined even before the kidney is involved.

In both forms the *urine* may be in every respect normal as regards its appearance and composition, or, at least, it may show no sign whatever of the existence of a suppurative nephritis. This is the case when, as is the rule in these forms of the disease, the process is confined to one kidney, the pus is walled off, and there is no communication with the uriniferous tubules. The healthy kidney by itself or assisted by that portion of the diseased organ which has remained intact is quite equal to the task of performing the normal function.

In some cases, however, the urine may be greatly changed, be it because the case is exceptional in so far as both kidneys are from the first involved in the purulent inflammation, or because the other kidney has become diseased secondarily, although the suppuration was originally unilateral (see above), or, in cases of functional impairment of the second kidney, from some other cause. The urinary changes as regards both kind and degree depend on the proportion of renal tissue that is still capable of functionating, on the extent of the suppurative process, and especially on the completeness with which the pus can be evacuated into the urinary passages.

Accordingly the *quantity* of urine may be normal or more or less

diminished; the *reaction* may be acid, or from the admixture of a large quantity of pus neutral or even alkaline; the *appearance* may be turbid, and the *odor* ammoniacal on account of the decomposition which is apt to begin in purulent urine before it leaves the body. The sediment of such a urine always contains triple phosphates in addition to pus corpuscles in a more or less advanced stage of decomposition. The filtered urine, freed from pus, may contain little or no *albumin*, or it may contain large quantities if the suppurative process is complicated by a non-suppurative (parenchymatous or diffuse) nephritis. In such a case the urine may also contain various *morphologic constituents*, especially casts and renal epithelium, which are characteristic of these non-purulent affections of the kidney. In very rare cases *particles of renal tissue* which could not be mistaken for anything else under the microscope have been cast off—an accident of the greatest importance to the diagnosis, but having no special influence on the ultimate outcome. Such cases have been reported by H. Taylor,[1] Wiederhold,[2] Rackgreyn and Greig Smith.[3]

For the sake of completeness it should be mentioned that when the quantity of urine is greatly diminished, and in cases of complete anuria, there is a possibility of *uremic intoxication*, and that stagnation of a very much decomposed urine may cause the absorption of toxic substances contained in the urine, and thus lead to so-called *ammoniemia*. In reality uremia very rarely occurs in the two above-mentioned varieties of purulent renal inflammation, because, as has been repeatedly remarked, the disease is, as a rule, confined to one kidney; ammoniemia also is a rare complication in renal suppuration.

The symptoms of renal suppuration originating by contiguity from the urinary passages, or pyelonephritis, will be discussed in the section devoted to that subject.

Metastatic suppuration of the kidney cannot, as a rule, be recognized, because the other symptoms of pyemic or septicopyemic infection dominate the clinical picture, and the purulent foci in the kidney are, as a rule, too small to produce any local and recognizable disturbance—changes in the urine, and the like. But when the glomeruli and uriniferous tubules become packed with microparasites, the early diminution in the quantity of the urine, which may go on to anuria, is sometimes a conspicuous symptom. (Compare Litten and Letzerich, p. 183.)

DIAGNOSIS.

A positive diagnosis of metastatic suppuration of the kidneys is practically impossible; the condition may be suspected when in the course of pyemic or septic infection albumin and pus suddenly appear in the urine in the total absence of any signs of catarrh of the urinary passages.

Some of the diagnostic difficulties experienced in other forms of

[1] *Arch. of Med.*, ii., 1861. [2] *Virchow's Archiv*, xxxiii.
[3] *Brit. Med. Jour.*, January, 1894.

renal suppuration have already been referred to in the description of the symptoms, and the writer will now proceed to sum up everything that bears on the diagnosis.

It is important above all to find a *cause*—*i. e.*, a trauma or a possible source of infection or suppuration—and among the *symptoms* the seat of the pain, the presence of fever of a pyemic character, a swelling belonging to one kidney, and possibly the appearance of pus in the urine are significant.

Among all these symptoms the demonstration of *enlargement of the kidney* is the most important, but it is unfortunately difficult to demonstrate, both because the kidney is not necessarily very much enlarged even though it is the seat of suppuration, and because it is not always possible to guard absolutely against confusion with other tumors, particularly as the examination is painful and therefore difficult to carry out. The conditions that are most likely to cause error are neoplasms of the kidney, enlargements or tumors of the liver, of the spleen, of the colon, especially its flexures, and ovarian tumors, not to mention certain rarer conditions.

The writer will not enter upon the differential diagnosis of all these affections in detail at this place, but he may point out certain aids in the diagnosis that should never be neglected, especially when, as is usually the case, the question of operative interference for therapeutic purposes is to be decided.

1. *Examination under anesthesia*, repeated if necessary, which should include in addition to the external bimanual examination of the abdomen, and especially of the region of the kidneys, an examination through the rectum and vagina and, if necessary, inflation of the stomach and intestine.

2. *Exploratory puncture* and *exploratory injection*. By means of the former it can be demonstrated whether pus is present or not and, in rare cases, it is true, whether the kidney itself is the seat of the suppurative process, for in the latter case the pus obtained is mingled with urine or, at least, with a fluid of distinctly urinous odor. If a *fistula* is present and urine in addition to pus is evacuated at intervals (see above), exploratory puncture is, of course, unnecessary. In these cases *exploratory injection* may be the means of deciding whether the tumor belongs to the kidney, as in that case the injection fluid, which must, of course, be harmless, will at once enter the urinary passages and may be demonstrated in the urine. The substance usually selected is a 1 per cent. solution of methylene-blue, a Pravaz syringeful, or half that quantity, being sufficient. In order to determine whether the substance at once enters the urine, a catheter or the cystoscope may be introduced immediately before the injection is made. If the test results negatively —*i. e.*, if the urine is not colored green within a few minutes or, at most, within a quarter of an hour after the injection—the tumor does not belong to the kidney or has no communication with the ureter, or else the ureter itself is impermeable.

3. *The effect on the tumor of the appearance of pus in the urine.* The

diminution in the size of the tumor occurring coincidently with the evacuation of pus in the urine is in favor of suppuration, especially if the rupture of an abscess in some other part of the body (from paratyphlitis, parametritis, and the like) can be excluded.

4. A high percentage of albumin, and the presence of *morphologic constituents*, such as bloody casts, hyaline and granular casts, and renal epithelium in the urine, while they point to renal disease, are not characteristic of purulent inflammation and cannot be utilized in the diagnosis, especially as in cases of unilateral suppuration they may be derived from the other kidney.

5. On the other hand, the finding of *shreds of renal tissue* in the urine is an absolutely positive sign; unfortunately, however, it is extremely rare.

From the standpoint of treatment, the diagnostician's duty is not always fulfilled when he has determined the existence of renal suppuration and its cause; for if the question of operative removal of the diseased kidney is to be decided, it is necessary to determine whether the other kidney is present and capable of functionating. For this purpose a *cystoscopic examination* is of the greatest value, as it enables us to determine (1) that both ureters are present and that urine flows from the ureter belonging to the healthy kidney—for the mere presence of two ureteral orifices in the bladder is not proof in itself that two kidneys are present (see p. 130); and (2) by collecting the urine from each kidney it affords an opportunity of investigating the condition and functionating power both of the affected and of the other kidney. The methods of cystoscopic examination are discussed in the section on pyelitis (see p. 347). [The importance in these cases of determining the freezing-point of the urine from each kidney, and of the blood has already been referred to. Before surgical removal of one kidney this should always be done. Kümmel as well as others regard it as extremely hazardous to remove a kidney when the blood freezes below —0.6° C. If the retention of the diseased kidney is, of necessity, attended by death, the operation could, of course, be attempted, even though serious risk be run of death from an imperfectly functionating other kidney—*i. e.*, death from urinary retention or uremia.—Ed.]

PROGNOSIS.

In *secondary* renal suppuration the prognosis is in general unfavorable because the causal disease is usually incurable or practically so. The prognosis is accordingly most unfavorable in metastatic renal suppuration; in the other forms it is not absolutely bad, both because they are not an immediate menace to life and because, although a favorable termination is not the rule, yet it is not beyond the realms of possibility. As, however, it is impossible to foresee when and in what way recovery will take place, great caution should always be exercised in giving the prognosis, and even in the most favorable cases the prospect of recovery or improvement should be held out only as a possibility. It is needless

to say that the general rules governing prognosis in regard to such factors as the degree and obstinacy of the fever, the strength of the patient, and the condition of the digestive organs must be observed in determining the extent of the danger.

While the prognosis in *primary* traumatic renal suppuration is in general *relatively* better, the individual cases vary greatly in this respect, and the outlook depends on the general factors, chiefly on the degree of destruction, which cannot, especially at the beginning, always be determined, on the extent of the suppurative process, and particularly on the opportunity for thorough evacuation of the pus.

TREATMENT.

There is no doubt that the occurrence of renal suppuration by contiguity from neighboring parts may in many cases be *prevented* by timely treatment of the causal condition. Even in the *traumatic* forms an attempt should, at least, be made to prevent the occurrence of suppuration in the kidneys, either by strict antiseptic precautions in the case of perforating wounds, or by the early institution of antiphlogistic measures in the form of rest, the local application of cold (ice-bag) and, under certain circumstances, by withdrawing blood from the affected region.

When suppuration of the kidney has developed and its presence has been recognized, the indications are evacuation of the pus or total removal of the kidney. The choice between the two procedures, as well as the methods to be employed, belongs to the domain of surgery. The caution may, however, be once more repeated, that in deciding whether to perform extirpation, the presence and the condition of the remaining kidney must first be determined, although unfortunately the most painstaking examination does not absolutely preclude the possibility of error.

If operative removal of the pus must be deferred, or if for any reason such a course is altogether impossible, there are certain symptomatic indications to be fulfilled, such as to relieve the pain, control the fever, correct the digestion and build up the patient's strength, and these indications must be satisfied in accordance with general rules of practice.

AMYLOID DEGENERATION OF THE KIDNEYS.

LITERATURE.—Rokitansky, *Handb. der path. Anat.*, 1842, iii., p. 421. H. Meckel, *Ann. des Charité-Krankhenh.*, Berlin, iv., 1853, 2. R. Virchow, *Arch. f. path. Anat.*, etc., vi., viii., xi. Luxemburg, "De morbo Brightii ex suppurationibus chron. exorto," Diss., Greifswald, 1855. Friedreich and Kekulé, *Verhandl. des naturhist. Vereines zu Heidelberg*, v., 1858. C. Schmidt, *Ann. der Chem. u. Phar.*, lx., 1859. Kühne and Rudneff, *Virchow's Archiv*, xxiii., p. 66. S. Wilks, *Guy's Hosp. Rep.*, ii., 1856. Todd, "Clinical Lectures on Certain Diseases of Urinary Organs," 1857. Traube, *Med. Centralzeit.*, 1858, Aug. 14, and *Deutsch. Klin.*, 1859, Nos. 1, 7 and 8. Hayem, *Compt. rend. de la soc. de Biol.*, Paris, 1864. H. Fischer, *Berlin. klin. Woch.*, 1866, No. 27. Ed. Münzel, "Ueber amyloide Degeneration der Nieren," Diss., Jena, 1866. A. Fehr, "Ueber amyloide Degeneration," etc., Diss., Bern, 1867. Hennings, "Zur Statistik und Aetiologie der amyloiden Entartung," Kiel, 1880. M. Litten, *Berlin. klin. Woch.*, 1878, No. 22, and *Charité-Ann.*, 1879, iv., p. 170, and in *Zülzer-Oberländer's, Klin. Handb. der Harn- u. Sexualorgane*, 1894, ii., p. 109. Bull, *Nordisk med. Ark.*, 1878, x., No. 23. Kyber, *Vir-*

chow's Archiv, 1881, lxxxi., pp. 278 and 420. Strauss, *Union méd.*, 1881, No. 146. Modrzejewski, *Arch. f. exp. Path.*, etc., i., p. 426. Kostjurin, *Med. Jahrb. der k. k. Gesellschaft der Aerzte Wiens*, 1886, p. 181. A. Czerny, *Arch. f. exp. Path.*, etc., xxxi., p. 190. A. Tschermak, *Zeits. f. physiol. Chem.*, xx., p. 343. Krawkow, *Arch. f. exp. Path.*, etc., xl., 1897. Lubarsch, *Virchow's Archiv*, cl., 1897. Petroner, *Arch. de méd. expér.*, x., 1898. C. Davidsohn, *Virchow's Archiv*, cl. J. Nowak, *ibid.*, clii. Maximow, *ibid.*, cliii. Zenoni, *Riforma med.*, 1901, after *Deutsch. med. Woch.*, 1901, No. 27. Lit. supplement. See also the text-books on Diseases of the Kidneys.

Of the various forms of disease included under the term Bright's disease of the kidneys, Rokitansky, in the year 1842, described one of an especially characteristic appearance which he called "*Speckniere*" ("bacon kidney"). He pointed out the accompanying changes in the liver and spleen and showed their relation to certain cachectic conditions. His assumption that the condition was one of lardaceous or fatty infiltration was refuted by Meckel, who demonstrated the characteristic color reaction of the substance under consideration with iodin and sulphuric acid, and accordingly regarded it as cholesterin. Meckel's theory was again declared erroneous by Virchow, who on account of this color reaction considered the substance as related to amyloid and cellulose and gave it the name of "amyloid," which is still in use at the present day. But this theory was again upset by the demonstration of Kekulé and C. Schmidt that the substance cannot be converted into sugar and contains nitrogen, as well as by the investigations of Kühne and Rudneff with artificially prepared amyloid substance as pure as could be obtained, in which they found in addition sulphur and a composition almost identical with albuminous bodies, and in contradistinction to these substances a marked resistance to solvents, especially to a mixture of pepsin and hydrochloric acid, and also to putrefaction. Later, however, Kostjurin (and E. Ludwig) succeeded in bringing about almost perfect solution of the amyloid substance by means of a mixture of hydrochloric acid and pepsin, leaving only a few solid particles consisting of nuclein; and Modrzejewski, by boiling amyloid with dilute sulphuric acid, obtained leucin and tyrosin in quantities identical with those obtained when substances that are unquestionably albuminous are subjected to the same treatment. Tschermak also succeeded in obtaining albumoses and peptone by digesting with pepsin and trypsin, and thus finally demonstrated beyond doubt that amyloid belongs to the group of albuminous bodies. Krawkow believes that it consists of a combination of albuminous bodies with chondroitin-sulphuric acid, to which he ascribes the characteristic amyloid reactions.

The mechanism by which the peculiar conversion of bodies originally albuminous into amyloid substances is effected is not definitely known. *Hyaline* (v. Recklinghausen's[1]) appears to be closely related to amyloid, as the former possesses many morphologic properties in common with amyloid, although it does not give the same color reactions. In addition, it is found in association with amyloid in the tissues and, judging from Lubarsch's experiments, probably represents

[1] *Handb. der allg. Path.*, 1883, p. 404.

a preliminary stage of that substance. This view is supported by the discovery of Litten,[1] that tissues the seat of amyloid degeneration, after they have been in the abdominal cavities of animals for some time, become similar to hyalin. Th. Leber's[2] investigations on the animal conjunctiva appear to show that in certain cases amyloid degeneration is produced by the infiltration with albuminous bodies of connective tissue that has undergone fatty change. Finally Petrone believes that amyloid disease produced artificially in animals (see p. 315) is caused by the disintegration of red blood-cells and infiltration of the tissues, especially of the arteries, with hemoglobin; but he regards the amyloid degeneration observed in man as different from the change which is produced artificially.

The clinical manifestations of amyloid disease of the kidney were first described by Wilks and Todd in England, and by Traube in Germany.

ETIOLOGY.

It was known to Rokitansky, and the observation has been confirmed by later investigations, that amyloid degeneration of the kidneys almost always follows in the wake of *certain cachectic conditions;* that it is therefore a secondary affection, which in all probability depends on some morbid condition of the blood—a *dyscrasia*. One argument in favor of this view is that amyloid degeneration is not confined to one organ, but affects several viscera, especially the liver, spleen, intestinal mucous membrane, and suprarenal bodies in addition to the kidneys, and that both kidneys are regularly attacked by the degenerative process. The fact that the arterial vessels and capillaries are preferably and first affected also argues in favor of this view. The nature of the morbid blood-change is, however, quite unknown. Amyloid substance does not occur as such in the blood itself; it cannot therefore be imported into the organs and deposited there. It is quite possible, however, that the albumin which circulates in the blood is first deposited in the organs and there coagulates in a special form, or that the already coagulated substance is brought into the organs by the leukocytes as a fully formed amyloid body or as a preliminary stage of the same, and there deposited (Czerny, Tschermak). But the opposite view, according to which the conversion of the albuminous bodies of the tissues themselves takes place under the influence of an abnormal condition of the blood or of juices of which nothing is known, cannot be summarily discarded.

That albumin may under certain conditions be converted into amyloid may be inferred from the fact that tube casts sometimes present the characteristics and give the color reactions of amyloid quite independently of the presence of amyloid disease in the kidneys; sometimes, in fact, as a result of a mere change in the physical conditions

Dickinson surmised that there was an impoverishment of the blood in potassium salts, the result of severe suppuration; but, as Grainger

[1] *Deutsch. med. Woch.*, 1887, Nos. 24–26. [2] *Arch. f. Ophthal.*, li., 1900.

Stewart rightly objects, the disease also unquestionably occurs when there neither is nor has been suppuration.

Not every form of cachexia, however, is equally prone to produce amyloid disease. Judging from experience, there are only certain ones that should be particularly mentioned in this connection, and of these especially *chronic pulmonary phthisis*, particularly when it is associated with the presence of tuberculous ulcers in the intestine. In 265 cases of amyloid disease of the kidney, E. Wagner found pulmonary tuberculosis 133 times, and 96 of the cases were associated with tuberculous ulcers in the intestine; 2 cases presented nothing but tuberculous ulcers in the intestine, and in 1 the lesion was merely a caseous change in the mesenteric glands, without intestinal tuberculosis. The most productive cases are those that are characterized by cavity formation and the presence of an abundant purulent expectoration. But fibroid changes in the lungs with bronchiectasis also, although more rarely, lead to amyloid disease.

The next most frequent cause is found in *protracted suppurative processes*, particularly suppuration of the bones or joints, or chronic suppurative or ulcerative processes in other parts of the body, old ulcers of the foot, pemphigus, profuse suppurations in mucous membranes, cystitis, pyelitis, or empyema.

Third in importance among the causes of amyloid disease is *constitutional syphilis*, the acquired as well as the hereditary form, and it is rather noteworthy that the nutrition is not necessarily depraved and cachectic—in fact, many of these patients show a tendency to obesity. To the same etiologic group, as stated by Rokitansky, belong severe cases of *rachitis*, in which the writer has occasionally observed amyloid degeneration of the spleen and of the kidneys; but in these cases it is possible that a hereditary syphilitic predisposition was also partly responsible.

After severe *malarial cachexia* amyloid degeneration of the kidney has sometimes been observed, and finally in isolated cases of *carcinoma* and *gout* (Litten,[1] Ebstein,[2] Stumme,[3] and others). In some instances the cause is quite unknown.

Amyloid disease, as Birch-Hirschfeld[4] (long ago) and Ch. Bouchard and Charrin[5] have shown, can be produced in the rabbit and also in the dog. Krawkow, Czerny, Davidsohn, Lubarsch, Maximow, and Nowak succeeded, by injecting Staphylococcus pyogenes aureus or turpentine under the skin, in producing amyloid disease with and without suppuration. But the experiment is not successful in every instance, and some animals are more refractory than others.

As regards the length of time required for the development of amyloid disease in man, J. Cohnheim[6] found that in the case of 3 wounded soldiers it developed once in the spleen and twice in the kidney within

[1] *Virchow's Archiv*, lxvi.
[2] *Deutsch. Arch. f. klin. Med.*, xxvii.
[3] *Ibid.*, lxiv.
[4] *Lehrb. der path. Anat.*, 2d ed., 1882.
[5] *Compt. rend. de la soc. de biol.*, 1888, Ser. viii., vol. v.
[6] *Virchow's Archiv*, liv., p. 271.

from four to six months. In a case of empyema and in another of spondylitis observed by Litten, an interval of two and a half and three and a half months respectively elapsed from the beginning of the disease till the appearance of the characteristic changes in the urine. But as amyloid disease may exist before the urinary changes make their appearance, the time necessary for its development may possibly be shorter. Krawkow,[1] by inducing suppuration artificially with Staphylococcus aureus, was able to demonstrate the existence of amyloid degeneration in the spleen in rabbits after eleven days, and in chickens after from one and a half to eleven weeks; Lubarsch, in rabbits in less than three weeks and in dogs in four weeks; and Maximow, in twenty-one days at the earliest. The writer does not mean to deny, however, that a much longer interval may elapse in man before amyloid disease begins to develop.

Along with the amyloid degeneration, the kidneys often present changes referable to *chronic inflammatory* and especially *fatty* and *indurative conditions*, and Johnson regarded these morbid changes, especially the albuminuria to which they give rise, as the cause of a consecutive cachexia and amyloid degeneration. The loss of albumin alone, however, cannot be held responsible for the production of cachexia, because on the whole it is not considerable in chronic nephritis, and because the body can afford to lose large quantities of albumin.

This occurrence of amyloid degeneration in association with other, especially inflammatory, disease of the renal parenchyma is susceptible of various interpretations. In the first place, both conditions may be the independent effects of a common cause, since the commonest causes of amyloid degeneration—phthisis, syphilis, and protracted suppuration—also figure in the etiology of chronic nephritis. On the other hand, the amyloid degeneration may be the primary condition and may lead to nutritive disturbances in the parenchyma, and, according to Weigert (see p. 178), to reactive inflammatory processes in the interstitial tissue; and finally the chronic inflammatory changes in the kidney may take place first and lead to amyloid degeneration secondarily, either on account of the nutritive disturbances and cachexia which develop or by virtue of local causes situated in the kidneys.

The want of uniformity in the distribution of amyloid disease, on the one hand, and of inflammatory and fatty conditions on the other hand argues in favor of the view that the conditions for the occurrence of the two processes are not always the same. It is obviously impossible to decide in every instance what has been the mode of development of the different morbid processes and what is their temporal and causal relationship. There appears to be no doubt, however, that when amyloid disease is only moderate in the kidneys and is associated with extensive contraction, as in the so-called *amyloid contracted kidney*, the interstitial process is primary; and for his part the writer thinks it is absolutely certain that such is the case when amyloid contracted kidney is complicated by *cardiac hypertrophy*, for our knowledge of the nutri-

[1] *Centralbl. f. allg. Path.*, etc., vi., May 20, 1895.

tive conditions in amyloid degeneration makes it impossible to assume that cardiac hypertrophy develops only as a sequel.

Amyloid degeneration of the kidneys may occur *at any age* except perhaps in the newborn, but it is most common in early life, during which the basal diseases are most frequent. According to the extensive statistics collected by Fehr, out of 146 cases, 2 occurred between the ages of one and five, and 4 between the ages of six and ten, or a total of 6 during the first decade; the second decade furnished 24; the third, 43; the fourth, 36; the fifth, 23; the sixth, 7; the seventh, 7. The male *sex* furnishes a somewhat larger contingent than the female. Among 152 cases collected by Fehr, 89 were men and 63 women.

PATHOLOGIC ANATOMY.

Although amyloid degeneration is recognized at once by the practised eye, not only macroscopically but even more readily under the microscope, by the peculiarly stiff, homogeneous, glassy, and colorless appearance of the affected tissue, the diagnosis cannot be positively established without resort to a test with the specific color reactions. Of these the test with *Lugol's iodin solution* occupies the first place, as it is the most trustworthy. This solution, as is well known, stains amyloid tissue a brownish-red or a dark-mahogany or nut-brown color, while the rest of the tissue turns yellow, and on the addition of dilute sulphuric acid or a solution of zinc chlorid the red coloration often, but not by any means always, changes to violet or blue. Another reaction is obtained with the various *anilin stains*, especially methyl-violet, gentian-violet, and methyl-green, which stain amyloid tissue red, and with thionin, which stains it blue. In rare cases the iodin and sulphuric acid reaction has been found to be absent in tissue which presented every other characteristic of amyloid disease, while the reaction with anilin colors was present, although it presented certain deviations from the usual behavior (Hansemann,[1] Schuster,[2] Davidsohn[3]); and, conversely, the reaction to anilin stains is sometimes negative when the iodin reaction is positive. All of which goes to show that the substance termed amyloid is not a uniform, homogeneous body, but probably represents albumin coagulation at various stages of the metamorphic scale. Davidsohn believes that those portions which give the positive iodin-sulphuric acid reaction have been longest affected by the process.

The *macroscopic* appearance of amyloid kidneys is not always the same, as it depends partly on the intensity and distribution of the amyloid process and partly on whether amyloid disease is the only condition present, or whether there are in association with it other tissue changes, especially indurative inflammation and contraction.

When the distribution is limited and only the glomeruli and a few interstitial vascular segments in variable numbers are attacked, the appearance and general characteristics of the kidneys, so far as naked-eye

[1] *Berlin. klin. Woch.*, 1893, p. 684. [2] *Virchow's Archiv*, cxxxiv., p. 653.
[3] *Ibid.*, clv., p. 382.

inspection goes, may be entirely normal, and the disease is only recognized by testing the cut surface, after it has been thoroughly washed and freed from blood, for the characteristic amyloid reactions.

When the disease is well developed and the kidneys can be recognized as being diseased by the naked eye, two main types are observed:

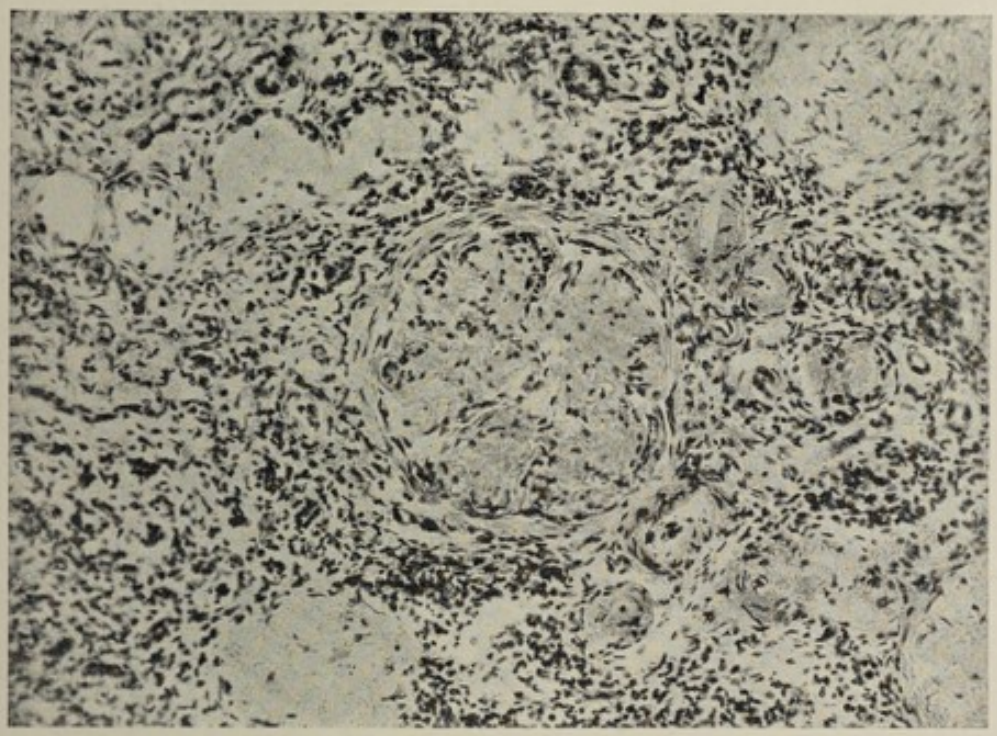
In one form which closely resembles the *large white kidney* (see p. 232) or may even be quite indistinguishable from that condition externally, the kidneys are greatly enlarged—often to twice their normal size—the edges are swollen and round, and the organs are remarkably pale and abnormally heavy. The capsule is attenuated and strips readily, and the stellate veins are distinctly seen through it on the pale background of the kidneys. The surface is smooth, reflects the light, and presents the appearance of wax or butter. On the cut surface the cortical portion, which is greatly widened, presents the same shiny, yellowish-white appearance; on close inspection the Malpighian bodies are seen to project like glistening dewdrops, and after the specimen has been treated with the iodin solution are rendered even more distinct by the red colorization. The medullary substance is also more or less enlarged and, in contrast to the pallor of the cortex, usually appears dark bluish-red.

The second so-called *amyloid contracted kidney* presents the picture of *indurative or contracted kidney*, except that the diminution in size is not so marked as in the ordinary non-amyloid contracted kidney; the surface of the organ and the cut surface appear paler, and on the latter the Malpighian bodies are more prominent on account of their size and glistening appearance, while the characteristic color reaction demonstrates their amyloid nature.

There are numerous transitional forms from the apparently normal kidney to the greatly enlarged lardaceous or waxy kidney and the contracted kidney, and these intermediate forms are recognized by the more minute tissue changes revealed by microscopic examination. The latter, assisted by the above-mentioned color reactions, enables one to determine the degree and distribution of the amyloid degeneration as well as the presence of other morbid processes in the tissues.

Amyloid disease attacks chiefly the *vessels*, and with very rare exceptions always the glomeruli; frequently those structures are the only ones affected. The walls become glassy and thickened, the nuclei more and more indistinct, and the lumen gradually becomes narrowed until the vessel is impermeable. In less advanced cases, in which the kidneys appear scarcely changed at all to the naked eye, only a few isolated glomeruli are affected, and these contain only a few diseased vascular coils; in advanced cases, on the other hand, hardly a single glomerulus is found to have escaped. Their coils are completely converted into homogeneous glassy lumps. Next to the glomeruli the afferent vessels are most severely affected by the disease, and later still the intertubular arteries and capillaries and the vasa recta of the medullary substance, while the capillaries of the cortex and the efferent vessels of the Mal-

PLATE VI.



AMYLOID DEGENERATION.

From a case of chronic nephritis. The illustration shows a large amyloid glomerulus with thickened capsule, a tubule containing an amyloid (?) cast, and high grade chronic inflammatory changes. (Specimen loaned by E. R. Le Count.)

pighian bodies, as well as Bowman's capsules, are very rarely attacked and apparently last of all.

In the majority of cases amyloid disease is confined to the vascular apparatus; but in a few the *uriniferous tubules*, and among them those in the medullary substance more frequently than the cortical, are attacked. The membrana propria presents the peculiar thickening and changed appearance with the characteristic color reactions. The epithelium fuses with the membrane, or desquamates and forms in the interior of the tubules cylindric homogeneous masses which sometimes also give the color reactions of amyloid.

Finally, in very advanced cases, the interstitial tissue and the capsule of the kidney have been found to present signs of amyloid degeneration in places.

There is no regularity in the appearance of the amyloid substance, even in the less advanced cases, except, of course, that the vascular apparatus and especially the glomeruli are attacked first. Within this region, however, the distribution appears to be quite arbitrary. Isolated glomeruli or groups of glomeruli are attacked here and there, and in the glomeruli themselves sometimes only individual coils, sometimes all the coils, present the characteristic change. In places the efferent vessels are diseased, in others they appear to be normal; finally it may happen that the vessels of the medullary substance are preferably or even exclusively affected, while the glomeruli nearly or altogether escape.

The epithelium of the uriniferous tubules, especially of the convoluted tubes, is usually in a state of *fatty degeneration*, and frequently represents the only other disease in the rest of the renal tissue besides the amyloid degeneration of the glomeruli. The fatty change may also affect the *epithelium of the glomeruli* and of Bowman's capsules, and ultimately the *intertubular tissue* may also present fatty changes in the form of finely granular, irregularly disseminated foci. In addition the stroma in some, probably in the majority of the cases, presents *small-cell infiltration*, both between the lobules and around the capsules; there are occasional hemorrhages; the uriniferous tubules contain casts, and in fact all those changes which occur in chronic parenchymatous nephritis are found, and in every stage, from the recent inflammatory to the indurative, the latter forming the transition to the fully developed contracted kidney.

The varying degree with which that part of the parenchyma which is not the seat of amyloid degeneration takes part in the fatty degeneration or in the true inflammatory processes accounts for the difference, as the writer has already remarked, in the microscopic appearance of the kidneys. Thus, when amyloid is the only condition or when it is associated with fatty change in the epithelium, the picture of the *large white kidney* is presented; when amyloid disease is combined with a recent inflammatory process in the stroma we have the picture of the *many-colored kidney;* and finally there is a great variety of transitional forms from the latter to *granular atrophy*. When the peculiar character and the color reactions of amyloid disease were still unknown, the condition

was included under the same head with the simple inflammatory processes of the kidney and was described with one of those forms.

In almost every case other organs besides the kidneys are implicated in the amyloid degeneration, as the writer has already remarked. In these cases the body and all the organs present a remarkable *pallor* and *anemia;* a variabe degree of *edema* is another common finding; and finally the subjects present the morbid conditions or pathologic changes in the organs which represent the cause of the amyloid disease. In contrast to the diffuse simple *inflammatory* processes of the kidneys, *cardiac hypertrophy* does not occur in extensive and *uncomplicated* amyloid disease except in a very small fraction of the cases; it is somewhat more frequent with indurative (inflammatory and arteriosclerotic) processes in which amyloid degeneration has developed secondarily. (See Etiology and Symptoms.)

SYMPTOMATOLOGY.

There are many cases in which amyloid disease of the kidneys does not reveal itself during life and is only discovered at the autopsy. Not that there is a complete absence of morbid symptoms and that the condition of the urine is normal—not at all; but the clinical phenomena observed belong to the primary disease, and the changes in the urine are in no sense characteristic and do not even always point to the existence of a renal affection of any kind; for even albuminuria may be absent, as was first stated by Fleischl and Klob[1] and confirmed by others.

In other cases, especially in those which are associated with inflammatory processes in the kidneys, the urine presents in a variable degree the characteristic changes of those processes, be it a chronic parenchymatous or an indurative form; but the clinical picture as a whole frequently, although not always, presents some differences from that which is observed in renal disease that is not complicated by amyloid degeneration, owing to the implication of other organs—liver, spleen, intestine—and the presence of dropsy, anemia, and cachexia, which are usually well marked in amyloid degeneration.

In a third class of cases, finally, in which the kidneys are extensively affected by amyloid degeneration and possibly the epithelium is the only tissue attacked by fatty change, while no acute inflammatory process is present, the urine presents certain peculiarities by which it is distinguished from the urine of other renal diseases, and which, since they were described by Traube, have been regarded as more or less characteristic of amyloid kidney. But these changes are not found constantly and in every case, and are often not well marked or pronounced. The description of a typical amyloid urine is as follows:

The urine is abundant in quantity, either equal to the normal maximum or far in excess of it, the *color* is usually a pale yellow, the *appearance* is clear, the *reaction* faintly acid, the *specific gravity* low (1012

[1] *Wien. med. Woch.*, 1860.

to 1005), the *albumin percentage* high, and a *sediment* is either absent or very slight. When present it usually contains only a few hyaline or fatty casts and occasionally a few isolated leukocytes, rarely renal epithelium recognizable as such, or masses of fatty granules, and still more rarely red blood-corpuscles, and then only in very small numbers. There may be some deviation from this description in certain particulars, but without altering the general characteristics of the urine as a whole, which may be either pale or dark, but is always clear or very slightly turbid, contains much albumin, and few, if any, morphologic constituents, consisting chiefly of hyaline or finely granular casts.

The quantity need not necessarily exceed the normal and may, even for a variable interval, either permanently or temporarily fall below the normal; the *color* at such times is correspondingly less pale and may be darker than normal or even brownish red. The *specific gravity* is also somewhat higher and the reaction is more distinctly acid. This change in the urine is usually observed toward the end of life, or is the result of profuse sweats, diarrhea, or marked fever. Such a concentrated urine precipitates a heavier sediment which consists of *urates*, but in other respects contains no constituents other than those found in the typical pale-yellow urine.

The *percentage of albumin* is also variable, but on the whole is usually high in proportion to the quantity of urine, sometimes remarkably high, the proportion being much greater than is usually observed in other renal affections—although, of course, there are exceptions—characterized by a similar quantity of urine with an equally scanty sediment consisting of morphologic elements. The albumin, as in most other cases, consists of serum-albumin and globulin; but the latter, as the writer said years ago,[1] and as has been confirmed by numerous later investigators, is present in greater proportion than is observed in other chronic renal diseases, so that the "albumin quotient" (p. 20) becomes smaller.

The albumin which is described as globulin probably also contains *nucleo-albumin*. The proportion of globulin to the serin—*i. e.*, the "albumin quotient," according to Lecorché and Talamon[2]—is smallest in the large white kidney which is so frequently complicated with amyloid disease, while in amyloid kidney the globulin may even exceed the serin in quantity. In his numerous and painstaking investigations which have been repeatedly referred to (see pp. 235 and 274) Csatáry found as an average in five series of examinations that the maximum "albumin quotient" is 2.4 and the minimum 1.1; and he gives it as the result of all his investigations that the smallest albumin quotient is found in nephritis complicated with amyloid. Rosenstein reports three investigations in which the average figure for the albumin quotient was only 1.6. Grainger Stewart[3] communicates a single observation of Roberts' which yielded an albumin quotient of 2.5—*i. e.*, a comparatively high percentage of globulin, almost the same as in blood-serum! Finally Fr. D. Boyd[4] obtained from 4 cases of amyloid disease an average albumin quotient of 1.5 (maximum 2.3, minimum 0.39). If these results are compared with the figures obtained in chronic parenchymatous and interstitial nephritis, the statement made by the writer years ago and quoted above cannot well be refuted. Nevertheless it has found opponents, who base their objection on the statements of Petri.[5] It is enough, in answer, to point out that the

[1] *Virchow's Archiv*, lx., p. 476. [2] *Loc. cit.*
[3] *Clinical Lectures on Important Symptoms, Albuminuria*, Edinburgh, 1888, p. 116.
[4] *Loc. cit.* [5] "Versuche zur Chemie des Eiweissharns," Diss., Berlin, 1876.

latter found no globulin at all in 13 out of 41 cases of renal albuminuria, which is contrary to everybody's else experience, to show how untrustworthy his investigations are. Rosenstein observes that Führy-Snethlage[1] also demonstrated the falsity of my statement; but as a matter of fact the values obtained by the latter, which the writer shall presently give, represent a complete confirmation of his assertion. One of the cases mentioned (XIII.–XV., Smits) was complicated with vesical catarrh and must be excluded, as globulin (and nucleo-albumin) are increased in the urine in that condition (see p. 20). In 2 cases of chronic nephritis he obtained an "albumin quotient" of 15.0 and 11.1, while in 3 cases of uncomplicated amyloid disease or amyloid nephritis he obtained only 3.6, 1.06, and 3.6—that is to say, the quotient was almost five times as great in chronic diffuse nephritis as in amyloid disease. According to J. Strauss,[2] the globulin in a case of parenchymatous nephritis complicated with amyloid disease made up 94 per cent. of the entire albumin content; the "albumin quotient" was only 0.06! In addition to globulin he also found nucleo-albumin. Finally G. Rem Picci[3] was able to confirm my assertion that *comparatively* more globulin is found in amyloid disease of the kidneys than in other *chronic* renal diseases.

The albumin may temporarily be reduced to an insignificant quantity or even disappear altogether, to make its appearance again after a short interval. It has already been mentioned that albumin may be absent. This occurs not only, as was formerly believed, in cases in which only the medullary substance is diseased while the glomeruli escape, but it has been also observed in cases in which the latter were found to present signs of pronounced amyloid degeneration.

Judging from the investigations by Bartels, Dickinson, Fleischer, and Rosenstein at our disposal, the *urea* and the other urinary constituents in the main present nothing that is characteristic. The proportions of these constituents probably vary in accordance with the different states of digestion and metabolism, so that the quantity excreted may be at times normal and at others diminished. The former is the case when digestion and assimilation are adequate and when there is a *copious discharge of urine;* the latter when, as not infrequently happens, diarrhea and dropsy are present and the quantity of urine is diminished.

In regard to the *uric acid*, Dickinson says that it is sometimes excreted in normal quantities, but is frequently diminished or may be absent. The excretion of *sulphuric* and *phosphoric acids* in the urine was found by Fleischer,[4] in a case examined with due regard for the quantity of nourishment taken, to be both relatively and absolutely less than under normal conditions.

It would be difficult to give an explanation for the urinary changes which are regarded as characteristic, if for no other reason, because these changes may be altogether absent notwithstanding the presence of amyloid disease, although such a thing happens only in a small number of cases.

One cause for the increased excretion of water in the urine has been sought in a greater permeability of the degenerated glomerular vessels, or in the diminished absorption of water in the medullary substance. The tendency to diarrhea in amyloid disease of the intestinal blood-

[1] "Over het Vorkomen van Paraglobuline in Urine," Leiden, 1875.
[2] Inaug. Diss., Strassburg, 1895.
[3] *Il Policlinico*, 1898.
[4] *Deutsch. Arch. f. klin. Med.*, xxix., p. 187.

vessels would appear to argue in favor of the vessel walls being more permeable than under normal conditions (Senator[1]). The diminished absorption in the medullary substance may possibly be due to the degeneration of the uriniferous tubules. Others have attempted to explain the increase in the quantity of urine by the heightening of the blood-pressure brought about in the healthy glomerular vessels because of the obstruction of the degenerated coils which have become completely impermeable. But there is no doubt that the kidneys as well as other organs are capable of compensating for the loss of parenchyma by increased work on the part of the surviving essential tissue, although it is very doubtful whether this increased amount of work can be kept up beyond the normal limit for any length of time without any additional help—in other words, whether an overcompensation develops. In indurative nephritis we see an overcompensation so far as the excretion of water is concerned; but, as the writer has explained elsewhere (see p. 282), this result is accomplished by the co-operation in compensatory work of the renal parenchyma and the hypertrophied heart. As cardiac hypertrophy is usually absent in amyloid disease, the increased work performed by the healthy parenchyma might possibly explain the occurrence of a normal quantity of urine, but would hardly suffice to explain an increase above the normal.

The behavior of the *albuminuria* is also difficult to explain, for, although it is quite easy to understand that the degenerated glomerular vessels are more pervious to albumin than normally, the fact that, notwithstanding the presence of degeneration of these vessels, albuminuria may be almost absent baffles comprehension. As regards the relative *increase of globulin in the urine*—*i. e.*, the reduction of the "albumin quotient"—it may be explained by the greater permeability of the vessels (see p. 20). Csatáry has called attention, and probably with reason, to the changes in the blood-plasma as a cause for the variations in the albumin quotient; but our knowledge of this subject, and especially of the behavior of the blood-plasma in amyloid disease, is still very limited. All that we know is that, as Mya and Vizeglio[2] have shown in various diseases, the percentage of globulin as compared to the serin may be greatly increased; and, moreover, it appears from the investigations of v. Limbeck[3] that the relation of globulin to serin undergoes a change when albuminous fluids escape from the blood; particularly the globulin of the serum appears to increase when the albumin loss is diminished. If these factors have any influence on the albumin quotient in the urine they would appear to show that the permeability of the vessels involved in amyloid disease is increased. Finally, it should be remembered that in the tests for globulin which have been made up to this time no account was taken of the possible presence of any *nucleo-albumin*, although it is quite conceivable that the altered epithelial cells might give up part of their albumin to the urine in the form

[1] *Virchow's Archiv*, lx.

[2] *Rivista clin.*, 1888, iv.

[3] *Prager med. Woch.*, 1893, No. 3.

of nucleo-albumin, and thus *apparently* increase the globulin percentage (see p. 21).

All other symptoms that are usually observed belong not to amyloid degeneration of the kidneys, but either to the associated amyloid disease of other organs, to the causal conditions, to the general cachexia, or, finally, to various complications.

Those organic changes and symptoms that are peculiar to diffuse renal disease, particularly the various forms of Bright's disease—*cardiac hypertrophy*, *albuminuric retinitis*, and *uremia*—are exceedingly rare in amyloid disease of the kidneys, and probably do not depend on that condition at all, but on other associated processes.

Cardiac hypertrophy, as Traube already observed, sometimes occurs in so-called amyloid contracted kidney. In 83 cases of amyloid degeneration, in some of which the kidneys were not affected, Dickinson found the heart hypertrophied in 6, while E. Wagner observed hypertrophy of the left side of the heart only 10 times among his 256 cases; and it is probable, though not certain, as he himself says, that renal atrophy was present at the same time; while it does not appear from Dickinson's statements whether in the 6 cases of cardiac hypertrophy amyloid contraction of the kidneys was really present. For it appears *à priori* quite possible that cardiac hypertrophy might occur with amyloid degeneration in the absence of contracted kidney. According to the usual belief, which has much in its favor, the cachexia that usually attends amyloid disease counteracts the development of cardiac hypertrophy, so that, if the latter is present, it is a sign that amyloid disease is secondary and has been a late development.

But cardiac hypertrophy occurs in other conditions besides contracted kidney and valvular lesions, particularly in chronic "parenchymatous" nephritis (see p. 239), to which amyloid degeneration may be added from one cause or another, since parenchymatous nephritis as a matter of fact is very frequently complicated with amyloid degeneration. Or there may develop as the result of syphilis, for example, arteriosclerosis with cardiac hypertrophy, and later, amyloid disease in the sclerotic kidney, also under the influence of syphilis or some other etiologic factor.

That this is possible is proved by the 2 cases which the writer here reports, and which show that cardiac hypertrophy may occur with other renal affections accompanied by amyloid disease as well as with the typical amyloid contracted kidney.

Robert E., tipstaff, formerly trumpeter, thirty-three years of age, admitted on the 18th of March, 1880, says that he was perfectly healthy until eight days ago, when he noticed a swelling of the feet. The swelling extended rapidly to the scrotum, hands, and forearms, so that three days later, on the 15th of March, he had to give up his work. He admits alcoholic abuse, but denies syphilitic infection and knows of no other cause for his disease except exposure to cold.

Well-built man in fairly good state of nutrition, with edema of the face, legs, scrotum, and penis, and a slight cyanosis. No eruption, no glandular swelling, some dyspnea, no fever. The fingers are somewhat clubbed, the cardiac impulse is not palpable, the boundaries of the dulness are normal; the first sound in the apical region is somewhat impure. Elsewhere over the heart muffled but pure sounds without accentuation; heard also over the carotids. There is slight bron-

chitis, otherwise the lungs are normal. Pulse 76, regular, tension not increased; arterial walls not thickened. Abdomen greatly distended, but ascites not positively demonstrable. The upper limit of the liver dulness is in the fifth interspace; the lower margin cannot be positively determined. The splenic dulness is not increased. The urine is somewhat turbid and presents a bloody sheen; contains a large percentage of albumin; in the sediment numerous leukocytes, some distinctly recognizable renal epithelial cells, many in a state of fatty degeneration, fatty granular cells, pale and finely granular casts, a few isolated short and broad, coarsely granular casts, and finally, a few washed-out red blood-cells.

Diagnosis: Chronic parenchymatous nephritis.

The condition as a whole at first underwent little change. The quantity of urine varied between 580 and 1250 c.c. (18–40 oz.); the specific gravity between 1016 and 1018. The percentage of albumin was always high; the admixture of blood variable but never very great. The eye-grounds were normal.

On the 8th of April a pronounced uremic attack developed, preceded by headache. This was followed by an increase in the cyanosis. A similar attack occurred again on the 10th of April. The sputum, which until that time had been mucous, presented an *admixture of blood*, although no disease focus could be found in the lungs. During the last days fever developed and the temperature ranged between 37.7° and 38.8° C. (99.8° and 102° F.). Death occurred on the 27th of April.

Autopsy on the 28th of April. (Abstract.) Marked emaciation; considerable anasarca. The abdomen contained several liters (quarts) of a clear yellowish fluid; the left pleural cavity about ½ liter of slightly turbid fluid; a few adhesions. The *heart* on the whole greatly enlarged, completely filling the pericardium. Length from the origin of the aorta to the apex 14 cm.; the greatest width 13 cm. The apex is formed solely by the left ventricle. The cavities of the heart are fairly wide and filled with large quantities of clotted blood. The thickness of the wall of the left ventricle is 2 cm.; the papillary muscles are thick and well rounded; the thickness of the wall of the right ventricle is 0.75 cm. The muscle is pale. The *lungs* are distended; the alveoli large. The tissues are saturated with edematous fluid. The bronchial mucous membrane is reddened, covered with purulent mucus, and the lower right lobe contains small isolated bronchopneumonic foci. The *spleen* is enlarged; 14 cm. in length, 10 cm. in width; flaccid, and pale red in color; and the capsule is wrinkled. The *mesenteric glands* are swollen, and grayish red in color. *Both kidneys are greatly enlarged*, the dimensions on either side being 14 x 8 x 4.8 cm. The capsules are hyperemic, in places adherent, and cannot be stripped without bringing some of the parenchyma along with them. The surface is finely granular; the general color clay-like, with red, brown, and yellow linear and punctiform markings. The cortex is enlarged, also of a clay color, and contrasts with the prune-colored columns of the medullary substance. The glomeruli are large.

The *liver* is greatly enlarged; the capsule slightly thickened, presents slight retractions and bands of cicatricial tissue. The lobular outlines on the cut surface are blurred, and the color pale brown. The *stomach* is dilated and pale. The *intestines* are greatly distended. The *aorta* is uniformly pale, elastic, and soft. The greatest diameter is found at the arch, where it is 5.3 cm. At the junction with the descending portion it is also 5.3 cm. The liver, spleen, and kidneys give a distinct amyloid reaction.

Anatomic Diagnosis: Chronic amyloid parenchymatous nephritis with cardiac hypertrophy, amyloid of the liver and spleen, perinephritis, etc. (Lues?)

Karl R., forty-nine years of age, innkeeper, formerly gardener; admitted 20th of September, 1879, in a semi-unconscious condition. Said by his wife to have suffered from convulsions in youth, but to have been healthy until three years previously. At that time he began to complain of palpitation and dyspnea, said to be caused by fatty heart. These symptoms subsided somewhat after a course of treatment at Carlsbad. Toward the end of 1878 the patient had an "attack of syncope" which left his locomotion slightly impaired. A similar attack occurred in April, 1879, accompanied, according to the physician's statement, by right-sided hemiplegia and hemiopia. At that time the urine, on repeated examination, was found to be free from albumin. Another attack with aphasia occurred on the day before admission. The patient is said to have drunk a great deal of beer in former, but not in recent years, although he complained very much of

thirst. His marriage has been a childless one, but infection is said never to have taken place.

Strongly built, obese man, very bald; no eruption, no edema, no glandular swelling. Lies restless in bed and mutters to himself unintelligibly. The right pupil is somewhat larger than the left, and in both the reaction to light is imperfect. There is paresis of the upper and lower branches of the facial and of the extremities on the right side. Tapping the cranium on the left side appears to give pain. Cutaneous and tendon reflexes are distinct. The apex beat is in the sixth interspace, somewhat outside of the nipple line. The heart dulness is difficult to determine on account of the heavy covering of fat. There are no murmurs. The second aortic sound is ringing. The pulse is 88. Both radial arteries, as well as the temporal, are greatly thickened and tortuous. The urine obtained by catheter was slightly bloody, and that obtained later was of high color, fairly clear, with a specific gravity of 1031, faintly alkaline, and contained a small percentage of albumin; the scanty sediment contained a few very long, very pale casts, quite a number of pus corpuscles and triple phosphates. Otherwise the condition presents nothing interesting.

Diagnosis: Arteriosclerosis; hypertrophy and dilatation of the left ventricle. Cerebral hemorrhage into the internal capsule on the left side. Death occurred on the 14th of October.

Autopsy on the 15th of October. (Abstract.) The dura mater in its anterior third is slightly adherent, both on its external and internal surfaces. The pia presents a marked milky turbidity and is thickened along the vertex and to the left of the median line. The vessels at the base, as well as the artery of the Sylvian fissure, especially on the left side, are extremely thickened. The left half of the centrum ovale is bluish, attenuated, fluctuating, and forms the roof of a cavity the size of a goose egg, which is filled with black coagula, and has destroyed the posterior third of the striate body and the outer portion of the posterior half of the optic thalamus, extending on the outer side to the mantle of white matter, posteriorly as far as the entrance to the inferior cornu, and downward as far as the pons. On the right side in the white substance, immediately above the posterior end of the optic thalamus, is a region as large as an almond, of an ochre-yellow color, not extending into the depths of the tissue, corresponding in position to a slight depression of the external surface of the cortex. The *pericardium* as well as the heart, especially its right half, is buried in fat. The heart is large; the thickness of the wall of the left ventricle 2.4, of the right 0.5 cm. The valvular apparatus is normal; the papillary muscles are round. The entire course of the *aorta* is marked by heavy deposits on the intima. The circumference immediately above the valves is 8 cm., that of the pulmonary is 7 cm. The size of the *liver* is normal; its surface smooth. The *spleen* is rather diminished in size and its capsule is wrinkled; the splenic pulp is firm. *Both kidneys* are large and present an abnormally developed fatty capsule. The capsule on the whole is readily stripped. The left kidney measures 13 x 5, the right 11 x 4.5 cm. The surface presents slight depressions in places. The cut surface is yellowish in color; the cortex of normal width, with large glomeruli. The arteries in the boundary zone are thickened and gape. The left kidney presents at its upper extremity, near the anterior border, a deep cicatricial retraction, extending into the cortex, over which the capsule is thickened and adherent. On microscopic examination a few glomeruli are found to be obliterated, and yield a distinct amyloid reaction with iodin, and in greater numbers with methyl-violet. Others are atrophic, with thickened capsules, and do not give the reaction; many of the straight uriniferous tubules contain casts. In the stroma a few isolated minute collections of round cells are seen, usually arranged around the glomeruli. The intima of the arteries is distinctly thickened. In the liver and spleen no amyloid change is demonstrable.

The second case is remarkable for the comparatively good state of nutrition, which is perhaps due to the fact that the amyloid disease was not very far advanced and was confined to the kidneys, and not even very extensive in those organs.

The reason that cardiac hypertrophy has not been found more

frequently in association with amyloid disease of the kidneys may be simply that the kidneys were not always examined for the condition unless their appearance aroused suspicion of amyloid disease, or unless amyloid degeneration was obviously present in other organs.

A final question which calls for further investigation and explanation is whether, under the influence of amyloid disease and the cachexia usually associated with it, an already developed cardiac hypertrophy may undergo involution and even give place to atrophy with or without dilatation.

The infrequency of albuminuric retinitis is only in part explained by the fact that it is rare in the forms of nephritis without contraction, and amyloid kidneys rarely become distinctly contracted. Other causes must be operative; for although Litten found retinitis present in about 20 per cent. of all cases of chronic parenchymatous nephritis, he saw it only twice among several hundred cases of amyloid degeneration.

Uremia also, as has been mentioned, rarely develops in amyloid disease, at least so far as *acute eclamptic* attacks are concerned; but the assertion of many authors that uremia never occurs with amyloid contracted kidney is incorrect, as the first of the two cases just reported, among others, demonstrates. The infrequency of acute uremia is explained by many authors by the fact that the urine is usually not diminished in amyloid disease, but rather shows a tendency to increase, so that there is no danger of retention of urinary constituents, and besides, owing to the insufficient nutrition of the patients, the nitrogenous excrementitious products are less abundant, and in part washed out of the blood by the dropsical effusions and by diarrhea. But, as the writer has already remarked, there are many cases in which the quantity of urine is not increased, and dropsical effusions and diarrhea are capable only to a limited extent of acting vicariously as eliminators of the specific and especially harmful urinary constituents. Other symptoms belonging to *chronic uremia*, such as headache, mental hebetude, vomiting, and possibly in some cases also diarrhea, are not so very rare; hence, without denying the contributory action of some other causes, the writer is inclined to believe that the infrequency of acute uremic attacks is partly due to the diminished irritability of the central nervous system in a protracted disease.

Among the symptoms due to other causes besides the degeneration of the kidneys, *dropsy* occupies the most important place. Although not a constant, it is a very frequent, accompaniment of amyloid disease, whether the kidneys participate in the morbid process or not. E. Wagner found in his postmortem investigations that it occurs in half of all the cases in which syphilis is the cause of the disease, barely in one-third of the cases of amyloid disease secondary to phthisis, and in one-quarter of the cases secondary to some affection of the bones. Judging from clinical observation, it seems to the writer, on the contrary, that dropsy is rarer in amyloid disease secondary to syphilis than in the form which follows phthisis. Possibly the reason for this is that the symptoms pointing to amyloid disease, especially the cachexia, are

less pronounced in syphilis, so that the syphilitic form of amyloid disease is oftener diagnosed post mortem than during life, which was also Wagner's theory.

When the kidneys participate in the amyloid degeneration, the dropsical fluid not infrequently presents an opalescent, milky appearance, such as is sometimes observed in the effusions of non-indurative nephritis (see p. 234).

The cause of the dropsy is no doubt correctly sought in the cachexia; for the effusions in the rare cases of *simple* amyloid degeneration not complicated with inflammatory processes, in regard to their distribution, do not resemble true renal dropsy, but rather the cachectic form (or "*hydrops cachecticus*")—that is to say, many cases present only a flaccid edema of the lower extremities, and only the severer cases edema of the upper extremities as well. Of the serous membranes, the peritoneum is most frequently involved, probably owing to amyloid disease of the abdominal organs—the liver, spleen, and intestines—and the associated circulatory disturbances. Effusions in the other cavities, however, also occur, although less frequently. The dropsy is usually very obstinate, probably because the cachexia persists and is very difficult to remove.

Diarrhea is quite frequent. Like the dropsy, it may be present when the kidneys are not involved in the disease, being dependent on various affections of the intestine; but in many cases, as has been mentioned already, of uremic origin. In simple amyloid disease of the intestinal mucous membrane profuse and obstinate diarrhea is said by Traube[1] to occur; the stools resembling café au lait and containing very few if any pus corpuscles. When simple or tuberculous intestinal ulcers are present, either alone or with amyloid degeneration, blood and pus may also be found in the stools, and in simple catarrh the alvine discharges may contain mucus.

Numerous other disturbances produced by the *basal disease*, as well as *complications* depending on the same, occur in the course of amyloid disease and may cause temporary or permanent *fever*, which is not a feature of amyloid degeneration itself.

The general *state of the nutrition* is usually bad, as the writer has already said in speaking of the etiology; the impairment is due to the causes of the disease; the complexion is pale; there is great loss of strength. Exceptional cases are observed, rarely, however, especially those in which the amyloid disease develops secondarily to *syphilis*, in which the digestive organs are but slightly involved or escape altogether.

All that is known of the *blood-changes* is that, as in all advanced cases of cachexia and anemia, the specific gravity and the percentage of albumin are lower than normal. [In its hemoglobin and number of red corpuscles the blood is of the secondary anemic type.—Ed.]

[1] *Gesammelte Beiträge zur Path. u. Phys.*, iii., 1878, p. 445.

COURSE, DURATION, AND TERMINATION.

An insidious onset and a chronic course are the invariable rule in renal as well as in other forms of amyloid disease. The duration of the renal disease cannot be determined with certainty, because the early stages very frequently, if not always, are unattended by any characteristic symptoms, especially albuminuria. The latter may, as the writer has said, be absent altogether or disappear periodically, and unquestionably is not present at the very beginning of the degenerative process, but develops only when a considerable portion of the kidneys has become involved. If the duration of the disease is counted from the first appearance of albuminuria, the course may be relatively short, as the observations of Bull [1] and Johannessen [2] tend to show, in which death occurred within a few months or, at most, a year; according to one observation of Johannessen's, it occurred as early as seventeen days after the first appearance of albumin. On the other hand, there are much slower cases, extending over several years, examples of which are found in the writings of several authors, and to which the writer himself can add some with a duration of three to five years. One case of fifteen years' duration, probably the longest known up to the present time, was observed by E. Wagner. The writer is inclined, however, to agree with Bull that the cases which last more than a year usually belong to the category of so-called amyloid contracted kidney, in which the amyloid disease represents a later development in the course of a chronic inflammatory process, and in which the duration, at least so far as the kidneys, share in the degeneration is concerned, is very difficult to determine, because the albuminuria, having been present before, cannot be used as a starting-point for the calculation.

The course and duration are greatly influenced by the kind and the course of the primary disease and the extent to which other organs are involved in the amyloid process. In this respect phthisis appears to be especially ominous, particularly when the intestinal canal is the seat of either tuberculous or amyloid disease and the strength is undermined by severe intestinal and digestive disturbances. Other pulmonary conditions (as bronchiectasis) and bone suppurations are somewhat more favorable, and syphilis more favorable still—*i. e.*, cases due to these diseases have a longer duration.

The termination also depends primarily on the underlying disease and also on the extent of the amyloid degeneration in the body. When it is confined to the kidneys, life does not appear to be in especial danger, since the function of the organ on the whole suffers little disturbance. If, therefore, the basal disease is curable and there is a possibility that the cause of the amyloid degeneration may in time be removed, as in bone or joint disease or in syphilis, there is a prospect that the amyloid disease also may come to a *standstill;* and if the kidneys alone have been involved and not too extensively, *functional recovery* may take place. Complete recovery in the anatomic sense is

[1] *Nordik med. Arkiv*, x., 1878, No. 23. [2] *Norsk. Mag. for Lägevid*, 1880, ix., p. 131.

hardly conceivable, as Virchow[1] correctly remarks; for even if the conversion of the amyloid into hyaline substance, which Litten achieved experimentally, were to take place clinically, such a change could not be called a *restitutio in integrum*.

At all events, by far the most frequent termination in those cases which clinically present obvious signs of amyloid in the kidneys and other organs is death.

DIAGNOSIS.

Amyloid disease of the kidney cannot always be diagnosticated. The diagnosis is possible only in those cases which present the above-mentioned urinary changes that are regarded as characteristic (p. 320), and even then the diagnosis is positive only if one of the recognized causal factors is present and the morbid changes and symptoms make it possible to demonstrate positively or with a great degree of probability the presence of amyloid degeneration in other organs, especially the spleen, liver, and intestine. If the case, in addition, presents *edema* of the cachectic variety, the diagnosis is practically assured; but if one or the other of these four diagnostic points is lacking, the diagnosis is proportionately more uncertain and cannot be regarded as more than probable.

The urinary changes that are regarded as characteristic may by themselves give rise to confusion with other conditions. If the urine is dark and scanty, the condition may be mistaken for *renal congestion*, the differential diagnosis from which has already been discussed on page 153; if it is pale and abundant, for *indurative nephritis* or contracted kidney, especially when the condition develops on a syphilitic basis, since that disease enters into the etiology of both renal diseases. In such doubtful cases the condition of the remaining organs must be taken into consideration; cardiac hypertrophy, hard and tense arteries, albuminuric retinitis, hemorrhages, and uremia are against amyloid disease, while the above-mentioned splenic, hepatic, and intestinal signs, and obstinate dropsy are in favor of that condition. *Amyloid contracted kidney* may be surmised when the two groups of symptoms are combined, and the etiology is in favor of amyloid degeneration.

Non-indurative chronic "parenchymatous" nephritis is distinguished by the urinary findings; the urine is turbid and contains a fairly large proportion of morphologic constituents. The disease frequently occurs in association with amyloid degeneration, and in such cases the latter can only be inferred from the etiologic factors.

PROGNOSIS.

The prognosis of amyloid degeneration is on the whole unfavorable, as it is an incurable disease developing on a cachectic basis. The prognosis depends mainly on the primary disease, which determines both the course and the termination, and secondarily on the degree to which the

[1] *Berlin. klin. Woch.*, 1885, p. 813.

amyloid process has involved the other organs, especially the state of the bowel and of the digestive apparatus as a whole. General factors, such as the strength and nutrition, fever, and the like, also have a certain influence on the prognosis.

As the nutrition is often quite well preserved in amyloid disease secondary to syphilis, the prognosis in that form is relatively the best.

TREATMENT.

In the main the *prophylaxis* of amyloid disease coincides in every respect with the actual *treatment*. Everything that is calculated to cure or, at least, improve the underlying disease is also calculated to prevent the occurrence of amyloid degeneration, and, if that condition has already developed, to arrest its further progress. Among the diseases which ordinarily lead to amyloid degeneration, syphilis is the one that is most amenable to successful treatment, and less frequently than others produces a marked cachexia. Antisyphilitic treatment has the most successes to its credit, particularly the administration of *iodin preparations*, both because amyloid disease develops only during the advanced stages of syphilis, when mercurial treatment is not suitable, and because vigorous mercurial treatment in itself produces anemia and cachexia, and is therefore calculated to assist in the development of amyloid degeneration.

In addition to all the special remedial measures demanded by the treatment of the basal disease, the nutrition and strength of the patient require the most careful attention. *Invigorating hygienic* and *dietetic measures*, good food, fresh air, baths, massage, and the like, best accomplish this purpose, in addition to *tonics*, and contribute not a little toward the improvement of the patient's condition and the prolongation of life, if not to a cure of the disease.

Among the drugs that may be recommended, besides the iodin preparations (potassium iodid, sodium iodid, iodipin, and the like), that are worth trying, even when the amyloid disease does not rest on a syphilitic basis, may be mentioned ferrum iodatum saccharatum, or the syrup of the iodid of iron, arsenic, alone or in combination with quinin (as, for example: ℞ Quin. muriat., 5.0 (1¼ dr.); acidi arsenosi, 0.03 (½ gr.); extracti gentianæ, q. s. ut ft. pil. No. lx. S.—Two pills three times daily, and more for an adult); sodium cacodylate, 0.1 (2 gr.), several times a day by the mouth or 0.05 (1 gr.) once a day hypodermically, or atoxyl hypodermically, 0.05 to 0.2 (1 to 3 gr.)—or the arsenical and chalybeate waters of Roucegno, Levico (by the spoonful with Seltzer water); Mittelbad in somewhat larger quantities; quinin preparations, cod-liver oil, etc. It is needless to add that the state of the stomach must be carefully looked after when these remedies are used.

It is worth mentioning for the benefit of future investigators that Davidsohn succeeded, by inoculating mice with blood-serum obtained from animals with amyloid disease, in immunizing them against otherwise certainly fatal doses of staphylococcus bouillon.

FATTY DEGENERATION OF THE KIDNEY.

(Lipomatosis Renum.)

LITERATURE.—Rayer, *loc. cit.*, iii., p. 614. Rokitansky, *Zeits. der Wien. Aerzte*, 1859, No. 32, and *Lehrb. der path. Anat.*, 1861, iii., p. 345. Godard, "Recherches sur la substitution graiseusse du rein," Paris, 1859. Habershon, *Med.-Chi. Trans.*, l., p. 87. H. Senator, "Albuminurie," *loc. cit.*, p. 91. D. Hansemann, *Virchow's Archiv*, cxlviii. V. Linstow in *Zülzer-Oberländer's klin. Handb. der Harn- u. Sexualorgane*, Leipzig, 1894, ii., p. 99, and the Literature on Lipuria in this volume, p. 66.

There are three ways besides the new formation of fatty tissue or lipomatosis in which fat may be produced in organs that normally are devoid of that tissue: (1) by *fatty infiltration;* (2) by *fatty degeneration* (fatty metamorphosis); and (3) by *fat-embolism.*

1. The occurrence of **fatty infiltration,** which is found as a physiologic condition in the kidneys of many animals, was long regarded as doubtful in the case of man, or, at least, exceedingly rare. Hansemann, however, believes that it does occur not so very infrequently in man, especially in certain morbid conditions, such as *diabetes mellitus* and *obesity*, as well as in many cases of *poisoning with phosphorus, arsenic*, and *corrosive sublimate.* He also found the renal epithelium infiltrated with fat in a variety of other diseases, and even in an otherwise perfectly healthy man, who had lost his life a few days previously by a fracture of the skull. In this connection the so-called "*nephritis of pregnancy*," in which the fatty condition of the kidneys is believed by Leyden and Hiller to be due to fatty infiltration, may also be mentioned (see p. 217).

Pathologically, kidneys the seat of *fatty infiltration* resemble, so far as their external appearance is concerned, kidneys with *fatty degeneration*, which will be presently described. On microscopic examination the epithelial cells appear filled with fatty granules, which are found chiefly at the base of the cells; but after they have been treated with alcohol, which extracts the fat, the cells appear entirely normal. Nor does the remaining renal tissue in the absence of complication present anything abnormal.

Fatty infiltration of the kidneys does not give rise to any special symptoms.

2. **Fatty degeneration**[1] (fatty metamorphosis) is the result of all those conditions in which the supply of oxygenated blood to the tissues is interfered with without being entirely abolished. Such a state of affairs may be brought about by an insufficient supply of an otherwise normal blood or by some abnormality in the blood.

Deficient blood-supply to the kidneys, and the resulting *anemia*, have already been discussed (p. 161), and it was pointed out in that

[1] Contrary to the older view, the term "fatty degeneration" or fatty metamorphosis signifies not only a conversion of the cell protoplasm into fat, but also the appearance of fat or bodies similar to fat (myelin) within the cells, with a simultaneous alteration and usually deterioration of both function and substance. *Cf.* Rosenfeld, *Centralbl. f. inn. Med.*, 1901, No. 6; *Münch. med. Woch.*, 1902, No. 1. Kaiserling and Orgler, *Virchow's Archiv*, clxvii.

connection that it is the result either of a purely *local circulatory disturbance* or is a part of a *general anemia*. Among the diseases accompanied by general anemia, *pernicious anemia* is the one that most frequently leads to fatty degeneration of the organs, and especially of the kidneys. It is probable that other causes besides anemia are operative; for instance, the defective condition of the blood itself. Fatty degeneration less intense in character but, on the other hand, more frequent, is to be observed in advanced cases of pulmonary phthisis and in cachexia due to other causes; it is therefore often found with *amyloid degeneration* (see p. 319), although in that condition a local interference with the circulation may be present from the amyloid degeneration of the blood-vessels. The fatty change observed in the epithelium as well as in the stroma—that is, in the lymph vessels—along with inflammatory conditions (see p. 320), is probably to be attributed to the nutritive disturbances of the tissues that attend the inflammation.

The *change in composition of the blood* which leads to fatty degeneration is in all probability also due to the interference with oxygenation processes by a *poison* or an *infection* or by *overheating* (Litten[1]) of the body, because the red blood-cells lose their property of taking up oxygen in the normal way and giving it up to the tissues. Among the poisons, the most important by far is *phosphorus*, after which may be mentioned others with a similar action, such as *arsenic*, *antimony*, *corrosive sublimate*, *chromic acid*, *aloin*, *cantharidin*, and a number of others that produce a condition intermediate between degeneration and parenchymatous inflammation. Parenchymatous inflammation itself may lead to fatty degeneration through an intermediate stage of cloudy swelling; and it is accordingly the rule in parenchymatous inflammation to find both conditions, albuminous as well as fatty turbidity of the cells, especially of the epithelial lining of the uriniferous tubules. The poisons at the head of the list, especially phosphorus and arsenic, however, cause a fatty degeneration without any preliminary stage of albuminous turbidity, and these intoxications are therefore regarded as the type of a pure fatty degeneration. Among the *infectious processes*, septic and septicopyemic infections are the ones that lead to fatty degeneration usually associated with inflammatory changes. Here may be classed also *acute yellow atrophy of the liver* and *acute fatty degeneration of the newborn*.

In a typical case of fatty degeneration the kidney is large, pale yellow in color, and doughy to the touch, and the capsule strips readily. On the cut surface the cortex is broader than normal, of a grayish-yellow, opaque appearance, interrupted by scattered linear and punctiform red markings. The medullary substance also, although less pale than the cortex, appears somewhat paler than normal. Microscopically the epithelium of the tubules in the cortical substance, the convoluted as well as the straight, and the epithelium of Henle's loops appear in a state of fatty degeneration and even disintegration, so that free granular fat is found in the lumen of the tubules, the walls of which have

[1] *Virchow's Archiv*, 1877, lxx., p. 10.

in places lost their epithelial covering. The glomeruli are usually normal and rarely present signs of fatty degeneration; in many places the interstitial capillaries are also fatty and surrounded by small hemorrhages.

Fatty degeneration due to intoxication or infection is often accompanied by hyperemia and hemorrhages, as well as more profound inflammatory changes.

The *symptoms* that are directly caused by the fatty degeneration of the kidneys vary according to the intensity of the process and the destruction of epithelium. In severe and fulgurant typical cases, such as occur after phosphorus-poisoning and acute yellow atrophy, the urine becomes scanty, dark, and turbid, and contains a moderate or a very small quantity of albumin as well as albumoses ("peptone"); the sediment consists of fatty epithelial cells, fatty granules, hyaline and fatty granular casts, with a few red blood-cells and leukocytes. Other abnormal constituents, such as leucin and tyrosin, lactic acid, etc., are also found in the above-named disease; they are not, however, to be regarded as directly caused by the fatty degeneration of the kidneys, but rather the expression of other more deep-seated metabolic disturbances.

The albumin probably consists of serum-albumin, globulin, and nucleo-albumin, the last two probably in relatively larger proportions, as it is to be assumed that they are derived from the disintegrated epithelial cells. Part of the albumin is derived from the blood, more especially from the glomerular vessels and the interstitial vascular or lymphatic system, from which it readily escapes into the uriniferous tubules after they have lost their epithelial lining. In spite of the apparent integrity of the glomerular vessels, albumin and blood may escape into Bowman's capsules in phosphorus-poisoning, as the writer has proved by experiments of his own.[1]

When the fatty degeneration and destruction of epithelial cells are less rapid and complete, the above-described urinary changes are correspondingly less marked, and in cases characterized by a chronic development, such as are seen in pernicious anemia, etc., the urine either presents no characteristic changes whatever or may be somewhat diminished in quantity, of a high specific gravity, and contain more or less albumin and a few casts or fatty granular cells. How much of this is to be charged to the fatty change and how much to other disturbances that are usually present, such as cardiac weakness, profound metabolic changes, and the like, is difficult to say. That such disturbances usually contribute their part is demonstrated by the frequent increase of indican and uric acid and the occurrence of leucin and tyrosin and other abnormal constituents in pernicious anemia.

The *course*, *duration*, and *prognosis* of fatty degeneration of the kidneys depend chiefly on the causes and on the extent to which other organs, especially those concerned in hematopoiesis, are involved. There is always some danger to life, which may be enhanced by the profound disturbance of the renal function. On the other hand, it would appear that once the immediate danger to life has been removed,

[1] *Albuminurie*, 2d ed., 1890, pp. 46 and 94.

the epithelium rapidly and completely tends to regenerate, as may be inferred by the rapid return of the urine to its normal condition in cases that end in recovery.

The *treatment* of fatty degeneration consists primarily in combating the causes of the condition and the cardiac weakness that is usually present at the same time. The measures directed immediately to the correction of the fatty change in the kidneys are of only secondary importance; in fulgurant cases it may be advisable to give the patient copious draughts of some carbonated water, and to introduce fluids in other ways by colonic injections, infusion, and transfusion, in the hope of flushing out the kidneys and uriniferous tubules and freeing them from the obstruction of tissue débris and coagula—procedures that may also prove useful in other ways, especially by improving the function of the heart.

3. **Fat-embolism** of the kidneys may occur under circumstances already mentioned as causative of hematogenous *lipuria* (p. 67). On the whole the condition is very rare, and the disturbances that it produces are insignificant, if they are present at all, since the greater portion of the fat circulating free in the blood-stream is arrested in the capillaries of the lungs, and the symptoms thus produced may be so intense as to overshadow all other symptoms, especially such as might be created by the entrance of fat-droplets into the kidneys.

A priori, extensive fat-embolism of the glomerular vessels might be supposed to cause a diminution in the quantity of the urine; but as embolism of the pulmonary vessels, which, as the writer has said, is always the most prominent feature, also leads to congestion and diminution of the quantity of urine, no conclusions can be drawn from such an event clinically as to the condition of the kidneys. Nothing but the demonstration of fat in the urine, when all other sources could be excluded, would justify the assumption of fat-embolism of the kidneys, provided some cause, such as fracture of a bone, were present.

It is needless to say after the above remarks that the condition requires no special treatment.

These fatty changes are not to be confounded with the condition in which there is an excess of fat around the kidneys, beginning in the fatty capsule. This condition always develops when a large portion of the kidney is destroyed, provided no other factors are present to prevent the proliferation of fat and to favor emaciation. Excess of fat around the kidney is therefore found most frequently when one kidney has become atrophied from local causes that do not disturb the general nutrition; as, for example, when a kidney is destroyed as the result of obstruction of the ureter by a calculus. In some cases of extreme atrophy of the renal parenchyma, the proliferation of fat, beginning in the fatty capsule, attains such a degree that the kidneys are replaced by a large lump of fat, to which the ureters, as well as the renal arteries and veins, are attached like pedicles, and in the interior of which a few remains of the organs are found.

PYELITIS AND PYELONEPHRITIS.

LITERATURE.—Rayer, *loc. cit.*, iii., pp. 1 to 243. Basham, *Lancet*, January, 1860. Oppolzer, *Wien. Spitalszeit.*, 1860, Nos. 17 and 18. Dickinson, *Med.-Chi. Trans.*, lvi., p. 223. *Virchow's Geschwülste*, 1863, i., p. 247. Litten, *Virchow's Archiv*, 1876, lxvi. Lancereaux in *Dict. encycl. des sc. méd. par Dechambre*, 3d Ser., iii., p. 221. Ebstein, *Deutsch. Arch. f. klin. Med.*, 1878, xxiii., and 1882, xxxi. Aufrecht, "Die diffuse Nephritis," Berlin, 1879. E. Wagner in *v. Ziemssen's Handb., loc. cit.*, p. 309. Albarran, "Etude sur les reins des urinaires," Paris, 1889. Guyon, *Ann. des mal. des organes génit.-urinaux*, 1891, pp. 257 and 521. M. B. Schmidt and L. Aschoff, "Die Pyelo-nephritis in anatomischer und ätiologischer Beziehung," Jena, 1893. R. Savor, *Wien. klin. Woch.*, 1894, Nos. 4 and 5. Küster, in *Deutsch. Chi.*, Lieferung 52, Stuttgart, 1896. Guyon's *Klin. Vorlesung über die Krankh. der Harnwege*, translated by Kraus and Zuckerkandl, 2 vols., Wien, 1897. P. Güterbock, *Die chi. Krankh. der Harnorgane*, iv., 1898. J. Israel, *Chi. Klin.*, etc., chapters iv. to vi. Dsirne in *Casper's and Lohnstein's Monatsbl. f. Urologie*, 1902, vii. See also the Literature on Hydronephrosis in this volume.

Rayer was the first to describe *pyelitis*—*i. e.*, inflammation of the pelvis of the kidney and of the calices—as a special affection, and to show that most of the cases described by the older authors as suppuration of the kidney and renal calculus were in reality cases of inflammation of the pelvis of the kidney. (See Suppurative Inflammation of the Kidneys, page 301.) He was also aware that the inflammation of the pelvis of the kidney very frequently spreads to the renal parenchyma, and that inversely the inflammation may also descend and spread from the renal substance to the pelvis of the kidney, although the latter sequence of events is more infrequent. The association of inflammation of the pelvis of the kidney and of the calices with inflammation of the kidney substance he called *pyelonephritis*.

In the last-mentioned form, that in which a descending spread of the inflammation from the kidney substance to the pelvis takes place, which is in the main a rare combination, pyelitis is usually insignificant and sinks into the background before the antecedent and causal renal affection. In the other class of cases, however, in which the inflammation spreads in the opposite, *ascending*, direction, from the pelvis to the kidneys, the nephritis, the so-called *ascending nephritis*, is in every respect a very important complication.

Pyelitis very frequently involves the corresponding *ureter*, and inflammation of that structure, or *ureteritis*, cannot be clearly distinguished from the same process in the pelvis.

ETIOLOGY AND PATHOGENESIS.

The commonest causes of pyelitis are:

1. *Mechanical irritation by foreign bodies*, among which *concretions* are by far the most important (*pyelitis calculosa*). It is needless to say that large or hard and pointed concretions are most likely to set up irritation, either by becoming wedged fast or by injuring the mucous membrane; but smaller concretions in the form of gravel may also act as mechanical irritants in the smaller ducts of the calices or in the pelvis of the kidney if they accumulate in sufficient quantities and

remain *in situ* long enough. It is doubtful whether the chemical nature of the concretions has any effect on the production of inflammation of the mucous membrane; although in cases of so-called phosphatic calculi, which are found in decomposed alkaline urine and contain in their interior the germs of fermentation and putrefaction, the latter may be the direct cause of the inflammation. *Tumors*, such as carcinoma and tuberculosis, more rarely act as causes, and still more rarely large and small *parasites*, such as echinococcus, strongylus, and amebæ.[1] Ollivier[2] thought himself justified in regarding *blood-clots* as the cause of an inflammation which he described under the name of "pyelonephritis hæmatofibrinosa"; he observed this condition in a man, seventy-four years of age, with widespread atheromatosis, especially of the renal vessels.

[Of course, in the cases where the calculus or other irritant has damaged the pelvis, micro-organisms of various kinds can more readily localize, as they find here a *locus minoris resistentiæ*.—ED.]

2. Inflammation of the lower portions of the urinary passages, especially of the bladder, often involves *by extension* the pelvis of the kidney and the kidney itself.

The causes of inflammation of these deeper portions of the urinary system, particularly of *cystitis*, are therefore of equal importance in the etiology of pyelitis and pyelonephritis. The extension of the inflammatory process, as has been explained in connection with suppurative nephritis (p. 303), is favored by *stagnation of the urine;* hence, an ascending inflammation derived from the bladder is particularly apt to develop when the possible causes of inflammation are combined with urinary retention. Cystitis from whatever cause, if it is combined with urinary retention lasting for some time, is almost certain to produce an ascending pyelitis. The complication is accordingly observed most frequently in chronic vesical catarrh due to calculus, to catheterism, or to any other cause, particularly in old men with prostatic enlargement, and in cystitis associated with paralysis of the bladder (*ischemia paralytica*).

As regards cystitis due to *parasitic* causes, it is stated by Rovsing[3] that only the pyogenic bacteria which decompose urea, especially the various kinds of Staphylococcus pyogenes, are capable of producing a purulent inflammation, as the ammonium which is set free during decomposition destroys the epithelium and allows the bacteria to make their way into the tissues of the mucous membrane. The bacteria that do not decompose urea, especially the Bacterium coli, which is frequently present, are said to produce only bacteriuria or a superficial inflammation of the mucous membrane (*cystitis epithelialis*). These parasites are probably capable, without the assistance of stagnation, by their unaided motility to make their way upward, but in these cases also urinary stag-

[1] "Amöburie," *Weekbl. for het Nederl. Tijdschr. v. Geneesk.*, 1895, cited in *Virchow's Jahrsber.*, 1895, ii., p. 210.

[2] *Arch. de phys. norm. et path.*, 1873, 1.

[3] *Casper's and Lohnstein's Monatsber. über die Gessammtl. auf dem Gebiet der Krankh. der Harn- u. Sexualorgane*, 1898, p. 505.

nation greatly favors the extension of the inflammatory process. In addition, as the writer has already remarked (p. 303), L. Lewin and Goldschmidt [1] maintain that under certain circumstances active opening of the vesical orifice of the ureters may permit the passage of material from the bladder into the ureters and further up to the kidneys, urinary tubules, lymph spaces, and blood-vessels.

[In this connection see the article by Sampson, already referred to on page 304.—Ed.]

3. Certain drugs that have a *specific action* on the deepest portions of the renal parenchyma and on the *mucous membrane* of the urinary passages (pelvis of the kidney and bladder) may produce a pyelitis in addition to an irritation of the kidneys and of the bladder. These drugs, which are known as *irritating diuretics*, include certain *balsams*, *ethereal oils*, and *tar preparations* (turpentine, copaiba, balsam of Peru, cubeb, mustard, sandal-wood oil, cantharides, etc.).

Many *specific organisms of infections and their toxins* appear to have a similar specific action on the pelvis of the kidney, for that structure is often distinctly attacked in cases of small-pox, dysentery, cerebrospinal meningitis, and especially cholera. In the latter disease the extreme venous congestion is no doubt operative as well as the toxin (see p. 210). According to C. Posner and Arth. Lewin,[2] such causes of inflammation (bacteria and toxins) may also be derived from the intestine when that structure is the seat of disease or merely fecal obstruction, and may make their way into the blood and from there into the pelvis of the kidney.

4. In *venous congestion* of the kidney, whether it be the result of general or of local causes, catarrh of the pelvis is not infrequent. To this category belongs the pyelitis frequently observed in *patients with cardiac disease* with disturbance of compensation, and especially the pyelitis met with during *pregnancy*.[3] The pyelitis that accompanies *movable kidney* is probably in part due to the displacement of the kidney and the mechanical interference with the circulation caused by the kinking of the ureter. It is probable that the resisting power of the mucous membrane is reduced by the congestion, which thus relatively intensifies the virulence of the causal micro-organisms that enter the kidneys from the blood or from the deeper urinary passages or their immediate neighborhood (intestine).

5. Pyelitis may undoubtedly be produced by *traumatism—i. e.*, external violence; but, owing to the well-protected position of the pelvis of the kidney, this cause is exceedingly rare.

6. The possibility of *exposure to cold* being the cause of pyelitis cannot be altogether discarded, although a certain degree of skepticism in regard to cold as a cause of disease is quite proper. After an extensive experience the writer considers it absolutely certain that chilling of the abdomen by exposure to a draught, especially in women during

[1] *Verhandl. der phys. Ges. zu Berlin*, Oct., 1897, and *Virchow's Archiv*, cxxxiv.
[2] *Centralbl. f. die Krankh. der Harn- u. Sexualorgane*, 1896, vii.
[3] See C. B. Reed, *Philada. Med. Jour.*, Dec. 9, 1899.

menstruation, and more rarely in men, may produce cystitis, and thus afford an opportunity for the development of a pyelitis.

7. Occasionally pyelitis, as has been stated in the introductory paragraph, is a *concomitant* or *sequel of inflammatory* or *other diseases of the renal parenchyma*, be it that the same cause acts on both portions of the urinary apparatus (the uropoietic and the uriniferous), or that the inflammation extends downward from the parenchyma to the mucous membrane.

8. Finally, that *inflammation in neighboring structures*, especially purulent and ulcerative processes, may sometimes extend so as to involve the pelvis of the kidney requires no special explanation.

As the commonest among the causes here enumerated rarely occur in children, it is readily understood why pyelitis and its sequel (pyelonephritis) are most frequent in *mature and advanced age*. The *male sex* is oftener affected than the female, but only in a very small degree.

PATHOLOGIC ANATOMY.

Unilateral pyelitis and pyelonephritis are much more common than the bilateral form. This is particularly true of calculous pyelitis, although the ascending inflammation derived from the bladder does not always spread to both sides, as might be supposed; either it attacks the pelvis of only one kidney or one much more severely than the other. It is impossible to give any cause for such an occurrence which probably depends on purely local conditions.

In the mildest form of inflammation, the catarrhal, the pelvis of the kidney in recent cases presents the well-known changes of acute inflammation of the mucous membrane—*i. e.*, the membrane is reddened, swollen, and covered with mucus containing blood-corpuscles and desquamated epithelial cells of various ages, and in addition—depending on the cause and variety—other foreign materials, such as parts of concretions (crystals of urates, oxalates, or phosphates, microparasites, and the like). Blood is also found mixed with the material, either as the result of minute injuries to the mucous membrane by sharp concretions, or of severe infections and intoxications, which lead to extravasations on account of the blood-changes and the injury to the blood-vessels, and finally in hemorrhagic diathesis due to other causes; as, for instance, scurvy.

In *chronic catarrh* the red discoloration is less pronounced, just as in the case of other mucous membranes; the color is rather bluish red or brownish red, and in places intensified by the presence of brownish or slate-colored spots, representing the remains of former hemorrhages. The mucous membrane is traversed by greatly enlarged and tortuous veins, covered with a thick, rather purulent secretion, and is increased in thickness; the submucous tissue, and ultimately the entire wall of the pelvis of the kidney, become infiltrated with serum or seropus and are increased in thickness. Sometimes the mucous membrane of the pelvis, though more particularly that of the ureter, contains *cysts* varying

in size from that of a poppy-seed to that of a pea, or even smaller cysts, recognizable only with the microscope, filled with a pale serous or a thick colloid material of a yellowish-brown color (*pyelitis* and *ureteritis cystica*). These cysts are attributed partly to the retention of catarrhal secretions and of the contents of follicles (Virchow, Litten), and partly to fatty degeneration and mucoid softening of the papillary proliferations which are formed in cases of chronic inflammation (Ebstein). According to Pisenti,[1] v. Kahlden,[2] and others, the cyst formation is due to a special sporozoön. Small gray lymphatic nodules, probably swollen and resembling *lymphoid follicles* (Chiari,[3] Przewoski[4]), are observed in chronic catarrh (*pyelitis granulosa*). Finally, in very rare cases, especially of tuberculous inflammation, a kind of horny change of the epithelium may lead to the formation of glistening, white scales and the production of *cholesteatoma-like structures*.

Superficial and deep *ulcers* are more common in chronic than in acute pyelitis. The ulcers may extend as far as the external boundary of the pelvis of the kidney, and in rare cases may even break through and lead to severe inflammation in the neighborhood, infiltration with urine, burrowing abscesses, and other similar complications.

The catarrhal inflammation frequently becomes complicated by the formation of a *diphtheric* membrane if, as the result of putrefaction or fermentation, the urine undergoes ammoniacal decomposition. It is rare as a primary condition, but may occur in severe infectious diseases, especially septicopyemic processes, in which case it is no doubt directly due to the infectious germs which are brought to the mucous membrane either by the blood or by the urinary stream. A *simple fibrinous* (*croupous*) *pyelitis* may be the expression of a very intense acute inflammation of the mucous membrane due to the ingestion of the above-mentioned drugs which possess a specific action on the mucous membrane of the urinary passages, especially cantharides. (See Fibrinuria, p. 42.)

If drainage from the pelvis of the kidney is obstructed by some impediment in the kidney itself, or further down in the ureter or at some still lower point, and the obstruction continues for any length of time, distention of the pelvis, and later of the calices and of the entire kidney, takes place, resulting finally in atrophy of the tissue and conversion of the viscus into a sac filled with a more or less serous or purulent material (*hydronephrosis* and *pyonephrosis*). The pressure of the stagnating fluid and the resulting interference with the circulation may, when reinforced by ulcerations which result from the irritation of foreign bodies (concretions) and decomposed urine, lead to gangrenous sloughing of the calices and destruction of even the entire pelvis.

Besides undergoing complete atrophy as the result of the severe and long-continued pressure by the pelvis and calices, the renal parenchyma may even become the seat of various kinds of inflammatory processes, such as parenchymatous changes, or more particularly *purulent inflammation* and *chronic interstitial nephritis*.

[1] *Centralbl. f. allg. Path.*, v., 1894.
[2] *Ziegler's Beitrag zur path. Anat.*, xvi., 1894.
[3] *Prager med. Woch.*, 1888.
[4] *Virchow's Archiv*, cxvi., 1889, p. 116.

Suppurative inflammation of the kidney, beginning in the pelvis (*pyelonephritis suppurativa*), as above explained (p. 303), leads to the formation of larger or smaller abscesses, and is caused by the entrance of pyogenic organisms from the pelvis and calices directly into the collecting tubules and higher up into the uriniferous tubules, and later into the interstitial tissue and the lymph spaces. The microscope shows the uriniferous tubules filled with microparasites, and the epithelium, at first swollen and turbid or opaque, later in a condition of disintegration. The interstitial tissue contains small purulent foci, which appear as yellowish dots and stripes, first in the medullary and later in the cortical substance, coalesce as the tissue breaks down, and form larger or smaller abscesses.

Chronic interstitial nephritis is very apt to follow pyelitis, especially when congestion is present, but may also develop without that condition if the irritation (by concretions or by the bacteria which are the cause of the pyelitis) continues. It may also accompany abscess formation.

Aufrecht and Albarran have demonstrated that as a result of the stagnation the uriniferous tubules become dilated, the epithelium swells, and casts are formed; these events are followed by interstitial inflammation which eventually leads to connective-tissue proliferation and induration. In pronounced cases of renal contraction the organ is very much diminished in size, but the surface has few or no irregularities—is, in fact, almost smooth. The capsule strips readily; the parenchyma is firm, of a grayish-yellow color, interrupted occasionally by bluish-red punctiform and linear markings. The diminution in the width of the cortical as well as of the medullary substance is fairly uniform; the pelvis and calices are dilated, as are also the ureters, or, more rarely, only one ureter if the urinary stagnation begins in the bladder. In contrast to what occurs in hematogenous contraction of the kidney, the proliferation of connective tissue is not confined chiefly to the cortex, but appears also in the medullary substance, being very well developed, especially in the boundary zone, and obliterating more or less completely both urinary tubules and glomeruli.

In the ascending form of inflammation caused by inflammatory irritation, particularly of bacterial origin, small necrotic foci form in the renal tissue, which later break down into pus, become demarcated from the rest of the tissue and surrounded by a fibrous capsule.[1] These as well as the before-mentioned interstitial inflammatory processes lead to contraction of the kidney and to the formation of cicatrices and cysts of varying sizes. The contents of the encapsulated abscesses undergo absorption and inspissation, or sometimes even calcification.

Not infrequently many different changes are present in the kidneys at the same time, being usually much more pronounced in one than in the other. Thus, there may be dilatation of the pelvis and calices, going on to a certain degree of *pyo-* or *hydronephrosis*, *necrosis*, *suppuration*, and *abscesses* of various sizes, *parenchymatous nephritis*, and *interstitial inflammation*. *Amyloid degeneration*, both in the affected and in the

[1] S. O. Brucauff in *Virchow's Archiv*, clxvi.

healthy kidney, may develop as a final complication in not a few of the cases.

Among the *sequelæ* of pyelonephritis when, as is commonly the case, it is unilateral may be mentioned compensatory hypertrophy of the other kidney, and in rare cases hypertrophy of the heart. Pyelonephritis may, like other suppurations in the kidney, lead to pyemic infection or to suppuration elsewhere, either by extension to the neighborhood or by rupture and escape of the pus from the pelvis of the kidney or from the renal parenchyma itself (see p. 308).

It is evident from the etiology of pyelitis that the corresponding ureter is usually also involved in the inflammatory process; but in rare cases it is found to be intact, notwithstanding the fact that the inflammation has spread from the bladder and must have passed through the ureter on its way to the kidney.

SYMPTOMATOLOGY.

The *descending* form of pyelitis, which usually represents a concomitant of some other renal disease, as well as the form which develops in the wake of severe and especially infectious general diseases, does not, as a rule, reveal itself by symptoms, because any disturbances to which it may give rise are disguised by the symptoms of the original disease.

In the same way, *ascending* pyelitis derived from the bladder does not always produce symptoms, because, if the inflammation spreads very slowly, the already existing symptoms of the vesical affection, and especially the condition of the urine, do not suffer any considerable change as the result of the secondary development of pyelitis.

The most characteristic symptom-complex is observed in the acute inflammations due to primary irritation of the pelvis of the kidney, as by calculi or irritating diuretics, and those acute and chronic cases which lead to intense congestion in the pelvis of the kidney. The most important phenomena are:

1. **Urinary Changes.**—In acute cases the urine is diminished in quantity, usually contains mucus, pus, and quite frequently blood, and, if the inflammation is due to the presence of concretions, some crystalline constituents of the latter, especially uric acid. In cases of fibrinous or diphtheric nephritis (see p. 340) coagulated fibrinous masses from the pelvis or in the shape of casts of the ureter, or flocculent tissue shreds the remains of the necrotic mucous membrane, may be found in the urine. Accordingly, the microscope reveals the presence of blood, mucus, and pus corpuscles, epithelium from the pelvis, crystals of uric acid or calcium oxalate, fibrin, coagulated tissue elements, and, in rare cases, when the inflammation is due to other causes, such as parasites or tumors, the characteristic products of these conditions.

Frequent micturition often accompanies the onset of an acute pyelitis, probably from the reflex irritation of the bladder or as the result of abdominal pressure (bearing down).

In very acute pyelitis or during an acute exacerbation of a chronic pyelitis, even when the affection is unilateral and the other kidney is quite normal, complete *anuria* sometimes develops. It is supposed that this is due to a reflex effect on the other kidney or its arteries (see p. 162). In bilateral pyelitis, or when one of the kidneys is already diseased and secretes little or nothing and an acute pyelitis develops on the other side, the quantity of urine, of course, undergoes great diminution. Anuria may develop, and if it persists for any length of time, uremia.

In *chronic* pyelitis and pyelonephritis, diminution of the urine is rare; the excretion is more likely to be increased to twice or even three times the normal quantity. This increase is probably due to the diminished absorption of water from the urine in the medullary substance and, in addition, to compensatory hypertrophy of the sound portions of the affected kidney and of the healthy kidney, as well as, in many cases, to cardiac hypertrophy. In accordance with the quantity, the *specific gravity* is normal or, quite frequently, diminished; the *reaction* is feebly acid unless the urine is decomposed, as is the case particularly in ascending pyelitis derived from the bladder with urinary stagnation, when the reaction is neutral or alkaline. In the latter case the odor is intensely urinous (ammoniacal). Sometimes the urine contains hydrogen sulphid. It is always more or less *turbid* from the presence of mucus or pus, and not infrequently of blood and other constituents, the admixture of which, as in the case of the acute form, is connected with the cause of the pyelitis or with the decomposition of the urine. Decomposed urine, owing to the action of the ammonia on the pus, is tough and gelatinous, draws out in threads, and is filtered with great difficulty.

The *filtrate* in cases of simple pyelitis without involvement of the renal parenchyma contains very little *albumin*, which is derived from the admixture of mucus and pus. Once the renal parenchyma becomes involved, as in pyelonephritis, the percentage of albumin increases, particularly in its relation to the number of pus corpuscles (see p. 19). As may be inferred by analogy to what occurs in cystitis, the albumin in pyelitis and pyelonephritis consists of serum-albumin, globulin, and nucleo-albumin.

The *sediment* may be scanty or abundant, and settles to the bottom of the tube in a layer of varying thickness. The most constant constituents are *pus corpuscles* and *epithelial cells* in a more or less perfect state of preservation or, when the urine is decomposed, more or less disintegrated, and with many free nuclei; in addition the sediment contains a variable proportion of *blood-corpuscles*.

The *epithelial cells* are often arranged like the tiles on a roof, and are caudate and club-shaped, or long drawn out and spindle-shaped. The assumption that these forms of epithelium are peculiar to the pelvis of the kidney is not correct, as forms in every respect similar are found in the ureter and bladder. It is nevertheless true that the arrangement of caudate and club-shaped cells after the fashion of roof tiles is more frequently observed in pyelitis than in cystitis. The implication

of the kidneys is indicated by the finding of epithelium from the urinary tubules and by the various forms of *tube casts* as well as mononuclear leukocytes.

The urine further contains *microparasites* which may be the cause or merely by-products of the urinary decomposition, or rarely may be the causal micro-organisms of the primary disease (see Etiology, p. 336), and crystals, either like the microparasites, the result of decomposition (so-called triple phosphates), or in some way related to the causal processes, just as in acute pyelitis; and, finally, certain other rarer findings, to which reference has also been made.

Variations in the composition of the urine represent a frequent phenomenon, especially in unilateral chronic pyelitis. Whenever the drainage of the diseased pelvis of the kidney is obstructed by a concretion, a blood-clot or a plug of mucus, which obstructs the corresponding ureter, the urine loses its abnormal characters, and appears clear and free from albumin because it is derived solely from the healthy kidney, at once regaining its former appearance, however, as soon as the obstruction has been washed down into the bladder. Obstruction is accompanied by swelling of the kidney and a variety of subjective symptoms, that always disappear when drainage is restored. Such a change in the composition of the urine and in the subjective symptoms may be repeated a number of times.

In bilateral pyelitis, or when only one kidney is present, complete anuria may develop under such circumstances, and if it continues may lead to uremic intoxication.

2. **Pain** in the lumbar regions is a constant attendant upon *acute* pyelitis, and if a stone or other foreign body has become wedged fast in the ureter, may go on to the severest and most intense kind of *renal colic*. The pain then radiates along the ureters to the bladder or urethra, or to the testicles or perineum, or even into the thigh of the affected side or upward into the back as far as the shoulder. Any sudden movement of the body—coughing, sneezing, or even drawing a deep breath—aggravates the pain, which in true renal colic is attended in addition by a number of reflex phenomena, such as chills and vomiting.

In the *chronic* form there is entire freedom from severe pain so long as the excretion is freely discharged from the diseased pelvis; at most the patient may complain of a dull sense of pressure in the corresponding side. But whenever retention takes place and the kidney becomes swollen, pain may develop on account of the distention of the renal capsule and of the nerves that enter the kidney, the pain disappearing again as soon as the excretion is evacuated.

3. **Swelling of the kidney** occurs in acute and more frequently in chronic pyelitis, as already mentioned, from obstruction of the ureters and stagnation of the renal secretion. The condition is called *hydro-* or *pyonephrosis* according as the secretion is serous or purulent. The size of the tumor produced in this way depends on the length of time during which the urinary passages have been obstructed and the excretory activity of the kidneys abolished; it may be so large as to cause

a visible bulging in the corresponding lumbar and abdominal regions. On bimanual palpation and percussion the size can usually, although not always, be accurately determined, and unless the tumor is small, fluctuation is more or less distinct. The writer has already stated that as the obstruction is removed the swelling either collapses and disappears or becomes smaller, while at the same time the subjective symptoms which it produces subside, and that this alternate appearance and disappearance of all the symptoms may be repeated several times.

4. *Fever* is usually present in acute pyelitis, although it does not always attain a high degree. When the affection begins with typical renal colic the scene usually opens with chilliness, or even violent chill followed by fever and sweating. These febrile attacks are due to the irritation of the mucous membrane of the ureter by the foreign body, and are analogous to other forms of fever produced by mechanical irritation of sensitive mucous membranes, such as the urethra, the bile ducts, the Eustachian tube, and to the attacks known as "catheter fever." They must not be mistaken for *remittent* or *intermittent fever*, which may develop later in the disease and in chronic pyelitis from absorption of the purulent urine, and occurs regularly when urinary stagnation continues for any length of time and when the pyelitis goes on to purulent pyelonephritis; in these cases it often takes on the character of hectic fever.

Generally speaking, the gravity of the condition is increased whenever the *kidneys participate* in the inflammatory process, especially when, as frequently happens, *multiple abscesses* develop in the kidney. In such cases the general condition is more profoundly affected than in simple pyelitis, and unless the abscesses, as happens occasionally, are entirely shut off, the urine contains more albumin and pus and is more scanty because the other kidney, which originally had not been affected, usually succumbs in the course of the disease either to parenchymatous nephritis or to amyloid degeneration, and compensatory hypertrophy therefore fails to develop altogether or, at least, to a sufficient degree. Gradually the signs of chronic uremia or, if the decomposition and stagnation of the urine is protracted, the intoxication known as *ammoniemia* develops (p. 107) and the patient dies. In rare cases the pus may, as has been mentioned in connection with purulent inflammation of the kidneys, rupture and escape in various directions; in the most favorable cases directly or by way of other organs toward the exterior; in unfavorable cases toward the interior, in which case the fatal termination is hastened.

COURSE, DURATION, AND TERMINATION.

Acute pyelitis, being due to the action of a single temporary inflammatory irritant, such as stone or irritating diuretics, ends in recovery in a short time under proper treatment—*i. e.*, in a few days or, at most, one or two weeks. The form which develops after an acute infectious disease depends entirely on the course of the former; and finally the

course and termination of pyelitis due to secondary extension from the bladder depend on the vesical infection.

All *chronic* forms present great variations in their course between improvement and the reverse; complete recovery is exceptional. The changeability is due in part to the constant repetition of the causal factors at varying intervals, as, for instance, in calculus formations; in part to the varying degree of urinary stagnation and pus retention, and in part to unknown causes, as is so frequently the case in chronic inflammations. Unless the disease is speedily brought to an end by severe suppuration, uremia, or ammoniemia, the duration of simple unilateral pyelitis is practically unlimited. Thus, in women particularly, catarrhal or mild suppurative pyelitis may last for years and with varying intensity and few symptoms, which only at times become more pronounced, and without any profound disturbance of the general health.

Severe suppuration and involvement of the parenchyma of one or both kidneys, of course, hasten the advent of death, which may, in addition to the causes already mentioned, be brought on by severe hemorrhage from the diseased portions, or rupture with infiltration of urine, suppuration, and the like.

DIAGNOSIS.

The chief diagnostic signs for the recognition of chronic as well as of acute pyelitis are found in the urine, the admixture of mucus or pus with or without blood being the most important. But such a condition is also found in the urine in diseases of the urinary passages below the pelvis of the kidney, in the ureters, bladder, and urethra, and pus may get into the urine from the renal parenchyma or from sources altogether outside of the urinary tract, which may evacuate their contents into it, and pus thus become mixed with the urine. Disease outside of the urinary passages, such as suppuration in the immediate or more remote neighborhood—as, for instance, in the prostate gland and the adnexa of the uterus—are, as a rule, readily excluded by means of other symptoms. As regards diseases of the urinary apparatus itself, the affections of the urethra—inflammation and ulcers—may be recognized by the fact that the pus makes its appearance independently of micturition, either spontaneously or when the urethra is compressed or "milked." Suppuration of the ureters as an independent condition is extremely rare, and for practical purposes has the same significance as pyelitis, from which it cannot and need not be distinguished.

In ordinary cases, therefore, all that is required in diagnosis is the exclusion of affections of the *bladder*, such as inflammation and ulceration, and of the *kidneys*. The absence of any *interference with micturition* is against a bladder affection and in favor of pyelitis, while its presence does not absolutely justify the exclusion of pyelitis. The composition of the urine when the kidneys are otherwise healthy affords no positive diagnostic points between pyelitis and cystitis. In both conditions the percentage of albumin is small as compared to the sediment,

although it is probably somewhat larger in pyelitis than in cystitis. (See Albuminuria Spuria, p. 19.) The sediment may have exactly the same composition in both conditions. The presence of *large club-shaped, caudate, squamous epithelial cells, arranged like the tiles on a roof,* is rather in favor of pyelitis, but is also, although not so frequently, observed in cystitis. The reaction of the urine in pyelitis is usually acid; in *chronic* (suppurative) cystitis it is usually alkaline or, at least, neutral. More important from a diagnostic point of view is the character of the *pain,* whether it is limited to the region of the kidneys or radiates along the ureters; and even more important is the presence of a *swelling in the lumbar region* whenever it is found by a careful and thorough examination that it is undoubtedly a swelling of the kidney. If the swelling occurs at the same time as other phenomena characteristic of pyelitis, or shortly after their appearance, the diagnosis of pyelitis may be made with the greatest confidence. In order to achieve still greater certainty in such cases, the procedure advised by v. Bergmann,[1] and *exploratory puncture* and *exploratory injection* may be resorted to; v. Bergmann's procedure consists in thoroughly washing out the bladder and then exerting pressure on the tumor, to determine whether the pressure causes pus to flow from the catheter. Exploratory injection and exploratory puncture have already been sufficiently discussed in connection with purulent inflammation of the kidneys (see p. 310).

The most positive information is, of course, afforded by cystoscopy, which enables the observer to see the flow of the purulent secretion from the ureter, in bilateral conditions from both ureters, and at the same time to examine the condition of the bladder, and especially to determine the existence of a vesical affection *in addition* to a possible unilateral or bilateral pyelitis—in other words, to determine the existence of *cystopyelitis,* the recognition of which without the aid of cystoscopy presents very great difficulties.

[Help is also afforded by a cystoscopic inspection of the orifice of the ureter—*i. e.*, by ureteral meatoscopy. The pouting, swollen, and reddened lips of the ureter at its opening into the bladder often give evidence of inflammation in the pelvis and ureter itself. (*Cf.* Fenwick.)

Catheterization of the ureters would also be of great service, although where there is already an infected bladder and a questionable ureter and pelvis of the kidney, the danger of spreading the trouble upward, and thus producing an ascending pyelitis, ought not to be forgotten.—Ed.]

The distinction between pyelitis and the ordinary *inflammations of the kidney* is in the main not very difficult. In the latter the percentage of albumin is higher, and the sediment contains casts, renal epithelium, and mononuclear leukocytes, to say nothing of symptoms such as dropsy and the like. The former, on the other hand, is characterized by a low percentage of albumin with a sediment containing (multinuclear) pus corpuscles and squamous epithelium. The association of these urinary peculiarities points to *pyelonephritis.* With *indurative nephritis* (*contracted kidney*) chronic pyelitis may have in common an increase in the

[1] *Berlin. klin. Woch.*, 1885, p. 767.

quantity of urine and a low percentage of albumin; but the changes in the vascular apparatus and in the eye-grounds are wanting; and, on the other hand a purulent or mucopurulent sediment is not found in contracted kidney. If the latter is present along with signs of contracted kidney, however, vesical disease can be excluded, and the diagnosis of a combination of the two conditions is justifiable.

Finally, in doubtful cases a distinct lowering of the molecular concentration of the urine, and of the excretion of sugar after the administration of phloridzin, and a marked delay in the excretion of methylene-blue would be in favor of a renal affection (compare p. 237).

The distinction of purulent pyelonephritis from other forms of *renal suppuration* in which the purulent contents may be evacuated into the pelvis of the kidney is more likely to be made by the history than by the objective symptoms.

The rare forms of *croupous* and *diphtheric* pyelitis may be surmised when the characteristic membranes, pseudomembranes, and tissue fragments appear in the urine, and all the other circumstances in the case point to disease of the pelvis of the kidney. The *cause* of the pyelitis, the recognition of which is of great importance from the standpoint of prognosis and treatment, may sometimes be determined by the history, the examination of urine, and the demonstration of concretions and of micro- and macroparasites.

PROGNOSIS.

The prognosis of pyelitis varies according to the etiology and the clinical course. Acute pyelitis, the causes of which are of a temporary nature or can be readily removed, usually has a favorable prognosis; if the causes cannot be removed it goes on to the chronic form, in which the prospect of complete recovery is inherently less favorable and the sequelæ of which may become a direct menace to life, as has been remarked under the head of Symptomatology and in discussing the course and termination. Urinary stagnation and ammoniacal decomposition affect the prognosis unfavorably in any case of pyelitis and pyelonephritis.

TREATMENT.

The things that ought to be done or, rather, left undone to *prevent* the development of pyelitis and pyelonephritis may be deduced from the etiology. To be brief, every drug should be avoided that irritates the mucous membrane of the urinary passages, whether it be introduced directly from the outside through the urethra, by way of the blood and lymph stream, endermatically, or when administered in any other way. The strictest asepsis must be observed with the introduction of catheters, sounds, or other instruments into the urethra or bladder; inflammations of these structures, particularly of an infectious nature (gonorrheal), must be subjected to most careful treatment; if irritating remedies, such as the above-mentioned irritating diuretics, must be employed they

should be used with the greatest caution; and finally foreign bodies should be removed whenever possible.

The *treatment* of *acute pyelitis* and of *acute exacerbations of chronic pyelitis*—unless they represent a subordinate feature of a severe constitutional disease, when they are practically to be disregarded—like the prophylaxis, has for its principal object to remove the cause whenever possible. If this has been done, all that is necessary in most cases is to guard the patient against exposure to cold, keep him warm, and prescribe a bland diet, particularly the avoidance of stimulating beverages. Among the drinks that may be recommended here in addition to milk and almond milk, which is justly popular, and decoctions or emulsions of hemp-seed, linseed, and poppy-seed, are especially alkaline and alkaline saline waters (Seltzers, Fachinger, Bilin, Vichy, Evian, Wildunger, Helenenquelle, Salzbrunner, Kronenquelle, Ems, Giesshübler, Gleichenberger, and the like), because they stimulate diuresis, increase the quantity of and dilute the urine, and at the same time render the action either neutral or alkaline, thereby liquefying the tenacious mucous or mucopurulent secretion and causing it to be cast off, besides favorably influencing a number of other causes, such as gravel and calculi. Moderate pain may be relieved by compresses to the lumbar region, or warm baths, or by the administration of potassium bromid in doses of 0.5 to 1 gm. (8–15 gr.) every two or three hours, or the very efficacious powdered nutmeg (*Semen myristicæ*), a knife-pointful several times a day. If the pain is severe, particularly in renal colic due to the passage of a stone, opiates or morphin are indispensable, and are best administered either subcutaneously or in the form of suppositories.

In *chronic pyelitis*, in addition to the drugs and remedial procedures called for to satisfy the *causul indication*, astringents and agents which, in addition to an astringent, also possess a certain *specific* action on the urinary passages and *antiparasitic* properties must be employed. All such remedies, if they are successfully used, have in common that they restore the acid reaction of the urine when it has become neutral or alkaline from decomposition. For this reason some of these remedies, unless they have a favorable action on the uratic sediment itself—as, for instance, urotropin—are to be used only with great caution in that form of pyelitis which is based on a uric acid diathesis and associated with the discharge of concretions formed in acid urine; they may be used only when the urine is decomposed and the local treatment of the bladder does not appear to be adequate. Under any other circumstances the alkaline waters and other remedies referred to in the section on Calculus Formation are indicated in this condition.

The *exclusively astringent* remedies, such as tannin, gallic acid, alum, and lead acetate, which in large doses also develop antiparasitic properties, are at the present time, for good reasons, less commonly used than formerly, because their continued use—and unless they are used continuously they have no value whatever—is not well borne, and in the case of lead acetate may cause toxic phenomena. In obstinate cases, however, when all other remedies fail, they are worth trying, especially

lead acetate in combination with opium, which causes it to be tolerated better and for a greater length of time (lead acetate and powdered opium, āā 2 gm. (30 gr.); licorice juice, enough to make 30 pills; S.: one or two pills three or four times a day). *Lime water* is also credited with an astringent action; it is best administered with milk (equal parts), to be taken a cupful at a time, and is recommended especially in the so-called uric acid diathesis with gravel and calculus formation when the urine is acid and not decomposed. Between the astringent remedies and the other class are the *foliæ uvæ ursi* or *foliæ bucco*, of which a decoction should be made in the strength of 20 to 30 gm. (5 dr.–1 oz.) in one-third to one-half liter of water, to be taken as a beverage through the day. The former acts by virtue of the tannin and *arbutin*, the latter being converted in the body into hydroquinone, although part of the benefit is due to the incidental ingestion of fluid. *Arbutin*, which has been recommended as a substitute, in the dose of 3 to 4 gm. (45–60 gr.) a day, either in powder or in solution, is well borne for a considerable period, but is not equal in efficacy to bearberry tea.

Among the numerous remedies recommended for their *antiseptic action*, *urotropin* and *salol*, in doses of 0.3 to 0.5 gm. (5–8 gr.), in capsules, every two to four hours, deserve to be mentioned before all others. Salol also possesses some analgesic properties. *Formin* (*hexamethylenetetramin*) is said to act like urotropin and should be given in doses of 0.5 to 0.6 gm. (8–10 gr.), well diluted in water, several times a day. Instead of salol, *salicylic acid*, 0.2 to 0.5 gm. (3–7 gr.), in wafers or capsules, several times a day, may be recommended, but only for a short time. Next in importance are *methylene-blue*, in the dose of 0.1 gm. (1½ gr.), in capsules, every two or three hours, or subcutaneously once a day; and *camphoric acid*, in doses of 0.5 to 1 gm. (8–15 gr.), in capsules, every three or four hours. The last-mentioned drug cannot be given long at a time, because it soon causes digestive disturbances. [Boric acid in capsules, 0.3 gm. (5 gr.) at a dose, is sometimes of benefit.—Ed.]

In addition to these remedies numerous others are recommended and may be tried in obstinate cases, because they occasionally act when those enumerated above leave one in the lurch. Such remedies are *fluid extract of tar*, one teaspoonful two or three times a day, or in combination with salol and tannin in the form of *urosterile* tablets, 6 to 10 a day; the *ethereal oils* and the so-called *balsams*, among which *oil of turpentine*, 5 to 10 drops in milk or in capsules, several times a day, is the most efficient; East India *oil of santal*, which is to be used in the same way, and *salosantal* (a solution of salol in oil of santal), in the dose of 0.3 gm. (5 gr.), in capsules, five times a day, which, however, is not so well borne in the long run as *copaiba balsam* or *Peruvian balsam*; the latter may also be given in somewhat larger doses. Finally *enterol*, in capsules of 0.25 gm. (4 gr.) each, of which 10 or 12 are to be taken during the day, has been recommended.

To correct *ammoniacal decomposition* of the urine, *potassium chlorate*,

in the dose of 0.3 gm. (5 gr.), several times a day, sometimes renders very good service and may be tried along with the other remedies.

As a rule, however, and always when the decomposition is very great, the internal remedies must be supplemented or replaced by local treatment—*i. e.*, irrigation of the bladder or even of the pelvis of the kidney. Irrigation of the pelvis of the kidney, which was first recommended by Casper,[1] requires great skill and caution; it has, however, proved of signal value in a few cases. When the condition is so obstinate and severe, however, the only hope of cure or improvement usually lies in *surgical intervention*—opening of the pus cavity by nephrotomy, or resection of the diseased portion of the kidney, or extirpation of the entire kidney (nephrectomy). For the indications for these and other procedures, as well as the technic, the student is referred to text-books on surgery. In regard to nephrectomy, it may be recalled, however, that before deciding on the operation, it must be ascertained with absolute certainty that the other kidney is present and capable of performing its function.

In order to determine this point, the ureters are catheterized after the method of L. Casper and P. Fr. Richter,[2] in which the urine is collected for several minutes from both ureters simultaneously and tested for its molecular concentration, the percentage of nitrogen, and the quantity of sugar excreted after the injection of phloridzin. [The freezing-point of the blood is also determined.—Ed.] Phloridzin, in the dose of 0.005 gm., is injected under the skin a quarter- or half-hour before the examination. When the kidneys are healthy, the values obtained from the two organs are identical or practically so; the greater the functional impairment of one of the kidneys, the smaller the corresponding values. It is needless to say that the general state of nutrition, the strength of the patient, the force of the heart, and all other factors must be carefully weighed, just as in the case of any other major operation.

If for any reason the case is inoperable, L. Weber[3] advises the administration of creosote, in doses of 0.2 to 0.3 (4–5 minims), three times a day, in order to guard against the danger of pyemic fever.

HYDRONEPHROSIS AND PYONEPHROSIS.

Literature.—Fr. A. Walter, *Einige Krankh. der Niere u. Harnblase*, Berlin, 1800. Johnson, *Med.-Chi. Trans.*, July, 1816. Chopart, *Traité des mal. des voies urin*, 1st ed., Paris, 1821, ii., p. 124. König, *Krankh. der Nieren*, Leipsic, 1826, p. 152. Rayer, *loc. cit.*, iii., p. 476. R. Virchow, *Ges. Abhandl.*, 1856, p. 874, and *Die krankhaften Geschwülste*, i., 1863, p. 267. Boogard, *Nederlan. Tydschr. voor Geneesk*, 1857. Th. O. Heusinger, *Ein Fall von angeborener Blasenniere*, Marbourg, 1862. Roberts, *On Urinary and Renal Diseases*, London, 1872, p. 474. Kussmaul, *Würzburg. med. Zeits.*, iv., 1863. Henninger, "De l'hydronephrose ou hydropisie du rein," *Thèse*, Strassburg, 1862. Heller, *Deutsch. Arch. f. klin. Med.*, v., 1869. Friedreich, *Virchow's Archiv*, lxix. Nicaise, *Gaz. méd. de Paris*, 1874, p. 542. J. Englisch, *Zeits. der Gesellschaft der Aerzte in Wien*, 1875, p. 47; *Deutsch. Zeits. f. Chi.*, xi., 1879; and *Jahrb. der Kinderheilk.*, 1875, viii. G. Simon, *Chirurgie der Nieren*,

[1] *Therap. Monatshefte*, October, 1895.
[2] *Functionelle Nierendiagnostik*, Berlin and Wien, 1901.
[3] *N. Y. Med. Rec.*, Nov. 25, 1893.

1876, ii., p. 176. L. Landau, *Die Wanderniere der Frauen*, Berlin, 1881, p. 82, and *Berlin. klin. Woch.*, November 19, 1888. J. Cohnheim, *Allg. Path.*, 2d ed., ii., p. 400. Hansemann, *Virchow's Archiv*, 1888, cxii., 3. Terrier and Baudoin, *De l'hydronephrose intermittente*, Paris, 1892. Baudoin, *Gaz. hebdom.*, 1892, Nos. 6 and 7. Tuffier, *Bull. et mém. de la Soc. de chi.*, 1893, p. 685, and *Ann. des mal. des organes gén.-urin*, 1894, p. 17. Navarro, "Contribution à l'étude de l'hydronephrose," *Thèse*, Paris, 1894. E. Küster, *Deutsch. med. Woch.*, 1888, Nos. 19 and 22. See also the Literature accompanying Pyelitis.

Hydronephrosis is the term applied since Rayer's time to dilatation of the pelvis of the kidney and of the calices from obstruction to the flow of urine, going on to atrophy of the parenchyma and conversion of the kidney into a sac filled with a watery or thin, mucoid material. By *pyonephrosis*, a term proposed by Roberts, is meant a cyst-like distention of the kidney with purulent contents. Intermediate forms also occur, as the fluid, without being distinctly purulent, sometimes contains pus corpuscles and presents a mixed, mucopurulent appearance. Hydronephrosis also not infrequently becomes converted into pyonephrosis; and conversely, although much more rarely, the purulent material may apparently, by the breaking down of pus corpuscles under the influence of a continued secretion, become converted into a mucoid or seromucoid fluid—*i. e.*, the pyonephrosis becomes a hydronephrosis. E. Küster has proposed the term "*Sackniere*" or "*cystonephrosis*" for these intermediary forms which merge imperceptibly one into the other.

The first description of a tumor of this kind appears to have been given by Nic. Tulp,[1] in 1674. Ruysch described a case as "*expansio renis*" or "*hernia renalis*"; Peter Frank and Walter described the affection later as "*hydropsia renum*" or "*renalis*," and Johnson as "*dystensio hydrorenalis*."

ETIOLOGY AND PATHOGENESIS.

The obstruction which leads to *hydronephrosis* may be situated in any portion of the urinary passages from the calices to the external urinary meatus. *Bilateral hydronephrosis* develops when both ureters are impermeable, or when the obstruction is situated in the bladder or in the urethra. In the latter case the bladder and ureters, of course, become distended by the stagnating urine. *Partial hydronephrosis* develops after occlusion of only one or of several calices (Fenger,[2] Rayer, Chopart); but it is more frequently observed in cases of congenital fission or reduplication of one ureter when one of the portions is impermeable (such cases have been reported by Englisch), and in cases of horseshoe kidney with occlusion of one of the two ureters.

Congenital hydronephrosis, either unilateral or bilateral, may occur as the result of some intra-uterine obstruction. As the secretion of urine begins in the fourth fetal month, the hydronephrosis may become very great and cause an obstacle to labor if the obstruction develops early in pregnancy. In bilateral hydronephrosis the fetus usually dies before term.

[1] *Observationes méd. Amstelodami*, ii., p. 168.
[2] *Nord. méd. Ark.*, v., 1873, No. 12.

These *congenital obstructions* may be due to developmental errors or to intra-uterine inflammatory processes causing impermeability of the urinary passages. Thus, deficiency or congenital stenosis or kinking of one ureter has been observed (by Weigert),[1] as well as abnormal insertions, especially insertion at the upper, instead of at the lower, portion of the pelvis (G. Simon); the presence of *valves* in the ureter, which do not always cause disturbances during intra-uterine life, but develop into an impediment to the flow of urine some time after birth; and finally *constriction* or compression of the ureter by peritoneal bands or by a supernumerary abnormal artery (Kussmaul, Rokitansky). Among the rarer causes of stagnation may be mentioned *obstruction of the bladder*, either on the side of the ureter or that of the urethra, and impermeability of the latter from the presence of adhesions or from external pressure (Englisch, Knöpfelmacher[2]). Finally atresia of the hymen may, by causing an accumulation of the secretions (hematometra), and by the pressure exerted by the distended structures (uterus and vagina) on the lower urinary passages, become a cause of urinary stagnation and its consequences.

The *acquired* causes of hydronephrosis may be either of a gross mechanical nature, such as occlusion by foreign bodies, kinking, tumors, valve formation, or compression from without, or may depend on *inflammatory swelling and cohesion of the mucous membrane* in the narrower portions of the urinary passages (calices, pelvis, ureter, and urethra), or on *connective-tissue adhesions* with the surrounding structures, or finally on a combination of gross mechanical and inflammatory conditions.

Simple *traumatic* hydronephrosis, due to the action of some external violence on the lumbar region, a blow or a fall, has been observed in a very few cases (P. Wagner[3]). The ureter is injured by the traumatism, or becomes occluded by a blood-clot or compressed by a perirenal extravasation or exudate, or finally a concretion already present may be rendered movable and become wedged fast in the canal.

The commonest obstructions are *renal calculi* that have become wedged in one or both ureters, and *pelvic*, and more rarely abdominal, *tumors* (a large splenic tumor, for instance). These tumors may cause occlusion either by simple pressure from without, as in the case of new growths of the uterus or prostate, or by invading the ureters or encroaching on their orifices in the bladder.

Besides the already mentioned condition of hematometra, a *uterus* enlarged from pregnancy or altered by pathologic changes or by displacement may indirectly cause, or at least favor, the development of an external impediment to the flow of urine, and thus lead to the production of hydronephrosis. Finally, as Landau has shown, *floating kidney* is a frequent cause of hydronephrosis, which in such cases is at

[1] *Berlin. klin. Woch.*, 1876, p. 234, and *Virchow's Archiv*, lxx., 1877.
[2] *Jahrb. f. Kinderh.*, xli.
[3] "Ueber traumatische Hydronephrose," *Berlin. Klin.*, No. 72, 1894, and *Centralbl. f. die Harn- u. Sexualorgane*, 1896, No. 1.

first and for a long time intermittent, but may later become permanent (see p. 139).

It should be mentioned that hydronephrosis from causes other than wandering kidney not infrequently is intermittent and variable as to size, because the impediment may from time to time be nearly or wholly overcome and the contents of the sac be nearly completely drained off. This diminution or complete disappearance of the swelling occurs when, for example, an occluding foreign body, especially a urinary calculus or a blood-clot, becomes temporarily loosened or washed away, to be again wedged fast or replaced by another: or when the ureters or calices become temporarily occluded by inflammatory swelling or the accumulation of mucus, or when a tumor that obstructs the flow undergoes softening and disintegration, etc. But even without such changes it is possible, as Krakauer[1] has pointed out, that when the ureter at its insertion forms an acute angle with the pelvis, the changes in the pressure of the accumulated fluid may cause a temporary evacuation, and it is probable that changes in the position of the body are not without some influence. Another mechanism which has been pointed out by E. Küster consists in the displacement of the mucous membrane of the pelvis of the kidney, which is quite movable on its foundation, over the opening of the ureter, as the result of inflammatory swelling; or, according to Hansemann, the first portion of the ureter may be dragged upon and form an acute angle with the pelvis, so that the upper edge is converted into a valve, and thus produces an impediment that is capable of being overcome, and is, therefore, temporary. J. Israel[2] regards insufficiency of the musculature of the pelvis and calices, which accompanies inflammatory conditions and increases with the distention of the pelvis, as a possible factor; but it is probably of no great importance.

In short, even when there are coarse impediments, especially congenital valves or an oblique position of the ureter, the interference with the flow may vary from time to time in accordance with varying conditions of pressure and traction, or these conditions of pressure and traction may even be the first cause of the obstruction. In this way might be explained those forms of hydronephrosis in which the autopsy, whether during life at surgical operations or in the cadaver, fails to reveal any mechanical impediment. Finally it is conceivable that hydronephrosis might develop or persist even after the removal of its cause, such as a calculus, for instance.

In order that hydronephrosis may attain its full development, it is necessary, according to Cohnheim, that there be either a very gradually developing impediment or a temporary resistance to the outflow of urine, alternating with intervals of freedom; because, when the occlusion takes place suddenly, the circulation in the kidneys is profoundly affected, first in the papillæ and in those portions of the pyramids and cortex surrounded by the calices, especially the columns of Bertini. As

[1] "Hydronephrose," *Diss.*, Berlin, 1881.
[2] *Berlin. klin. Woch.*, 1888, p. 364, Discussion.

the pressure increases, the secretion in the renal parenchyma rapidly diminishes and finally gives out altogether, and the kidney atrophies. When, on the other hand, the obstruction to the flow of urine is *gradual and interrupted from time to time*, the secretion in the corresponding kidney is never abolished altogether; and when the obstruction is intermittent large masses of fluid may accumulate behind the obstruction and be evacuated in a copious stream when the latter is removed.

There are, however, exceptions to this rule; for in the first place hydronephrosis may form after *sudden* occlusion of the ureters, and, on the other hand, when the occlusion develops slowly and does not become quite complete, the compensatory activity of individual portions of the kidney may still cause the urine to flow in variable quantities either into the dilated pelvis of the kidney or dilated cavities that form within the medullary substance. This condition is distinguished by Guyon, Tuffier, and others from true hydronephrosis under the name of "*uronephrosis.*"

It appears that these different modes of termination depend on individual conditions permitting the development of a collateral circulation in the kidneys, especially the cortical substance. The kidney normally consists of three zones: (1) one which is exclusively supplied by the capsular arteries; (2) one which is supplied by the latter and the terminal branches of the renal arteries; (3) one which is supplied chiefly by the latter, supplemented only by very slight anastomoses with the arteries of the pelvis of the kidney and of the ureter. When this latter region is occluded, the first two become distended at its expense (Lindemann [1]).

No *age* is exempt from hydronephrosis. The writer has already said that it may originate before birth and be *congenital*. In such a case, if the children are not stillborn or die soon after birth, the hydronephrosis may continue to increase. *Acquired* hydronephrosis rarely develops immediately after birth, and when it does, appears to be due to uric acid infarcts of the newborn, which under certain circumstances may cause a partial or total hydronephrosis directly or by forming the nucleus for subsequent deposition and the formation of calculi. Hydronephrosis is encountered much more frequently in later life than in childhood, because as the years go by the causes, such as tendency to calculus formation, tumors, and inflammation in the urinary passages or their immediate neighborhood, tend to multiply; and in the *female sex* particularly because obstructions that originate from the uterus and wandering kidney predominate during the period of sexual maturity and middle age. The latter circumstances explain the greater frequency of hydronephrosis in the female sex in general, and particularly during adolescence and middle age, whereas in men it is more apt to develop on the threshold of old age.

As a rule, hydronephrosis is *unilateral*, rarely *bilateral*. Among 52 cases, Roberts found 32 of unilateral and 20 of bilateral hydronephrosis. Unilateral nephrosis is somewhat more common on the right than

[1] *Zeits. f. klin. Med.*, xxxiv., 1898.

on the left side; and when the disease is bilateral, one kidney is usually more affected than the other.

Pyonephrosis in the great majority of cases develops secondarily to pyelitis, with coincident impediment to the flow of urine of some duration, as has already been explained elsewhere (p. 340). A rare modus consists in the entrance of pus organisms into a hydronephrotic sac, usually by way of the urinary passages, so that the pyonephrosis in this case also may be said to be *urogenetic*. The infection may, however, be carried by metastasis—in other words, it may be hematogenous, as mentioned above (p. 303); and finally an abscess in a kidney from some other cause, that cannot evacuate, may attain such a size as to convert the kidney into a pus sac after a large part of the parenchyma has been destroyed.

PATHOLOGIC ANATOMY.

In moderate grades of hydronephrosis only the pelvis of the kidney and the calices are visibly involved in the dilatation, which, however, may amount to several times the normal volume. The papillæ present a variable degree of flattening, the veins in the medullary substance are fuller than normal, but the renal parenchyma, both macroscopically and microscopically, presents nothing, or practically nothing, abnormal. In the more severe grades, in which the pressure of the accumulated fluid causes gradually increasing destruction, first of the medullary and then of the cortical substance, the kidney in cases of total hydronephrosis finally becomes converted into a sac filled with fluid, which may attain or even exceed the size of a man's head and fill one entire half of the abdominal cavity. Peter Frank asserts that his son found in the cadaver of a man a hydronephrotic kidney containing not less than 60 pounds of fluid!

Such enormous hydronephrotic sacs, the origin of which is nearly always to be found in the ureters, usually have an irregular, ovoid outline, interrupted by localized prominences, and gradually become smaller as the ureter is approached. The prominences correspond to the dilated calices which are situated upon the outer portions of the sac and communicate with the interior by means of wide, neck-shaped openings. The interior of the sac accordingly represents a multilocular cavity, the septa of which may or may not be in a good state of preservation, or may have disappeared, or may eventually be represented by narrow bands. The papillæ are quite flat, or recognizable only as small flat elevations, or they may be entirely destroyed by necrosis (Friedreich). The medullary substance has disappeared and the width of the cortex is reduced to one or a few millimeters.

The suprarenal capsule is often found unchanged on the outer surface of the sac.

In cases of *partial* hydronephrosis the same changes are found in portions of the kidney corresponding to the calices which have undergone saccular dilatation and which may be entirely cut off from the pelvis of the kidney or communicate only by very narrow openings.

On *microscopic* examination it is seen that the wall of the sac consists of the thickened renal capsule, on the inner surface of which a variable thickness of intact cortical substance is found in places. The latter often presents the changes of chronic indurative nephritis, the uriniferous tubules being separated by broad bands of connective tissue which compress or constrict them and thus lead to the formation of small cysts. The capsules of the glomeruli are at first dilated and contain an albuminous fluid which compresses the vascular coils until they also become obliterated and fuse with the capsule to form a spheric mass of connective tissue. (See Pyelitis, p. 345.)

At first the *pelvis of the kidney* presents its normal structure, particularly the mucous membrane and the muscularis, but later the tissues are more or less completely destroyed, and finally the wall of the pelvis as well as that of the calices consists merely of thickened connective tissue.

The character of the *hydronephrotic fluid* varies with the duration of the hydronephrosis and the completeness of the obstruction to the entrance of urine into the sac. So long as urine is secreted, even to a very slight extent, and can make its way into the sac, the contents are composed of a pale, very much diluted urine containing some albumin and an admixture of mucus or possibly blood. As the stagnation increases and the urinary secretion diminishes, the character of the fluid becomes altered; owing to the increased excretion from the distended mucous membrane of the pelvis of the kidney and of the calices, it becomes more and more turbid and contains more mucus, with a corresponding diminution of specific urinary constituents. Finally, when the mucous membrane becomes atrophic and has ceased to secrete, the fluid assumes a more serous character, probably as the expression of a simple transudation.

Precipitation of urinary salts, urates, phosphates, and oxalates in microscopic or macroscopic quantities not infrequently takes place in the fluid, which may also contain epithelium from the calices or from the pelvis of the kidney, and a variable quantity of leukocytes and red blood-cells. *Cholesterin crystals* have also been found (Schetelig[1]); and as chemical constituents in addition to urea, which is rarely absent, and then only during the latest stages, sometimes uric acid and so-called mucin and metalbumin or paralbumin.

Kehrer[2] found *gas* in a hydronephrotic sac and believed it to be carbon dioxid which had been generated from the acid urine and the alkaline transudate.

When the cause of the hydronephrosis is not seated in the pelvis or in the calices, the *ureter*, depending on the seat of the obstruction, may be partially or totally distended to the thickness of the thumb or of the small intestine, and either the whole or individual segments of the canal may be tortuous or kinked. Below the obstruction the ureter may be more or less narrowed.

In *unilateral hydronephrosis* the unaffected kidney often undergoes

[1] *Arch. f. Gynäk.*, i. [2] *Ibid.*, 1881, xviii., p. 371.

compensatory hypertrophy (see p. 163). In other cases it may be diseased and present the changes observed in a kidney when the function of its fellow is suddenly interrupted (p. 156); or it may be completely atrophied as the result of some disease that has preceded the hydronephrosis on the other side (Rosenstein, Hansemann).

As regards changes in the other organs, it should be mentioned that *cardiac hypertrophy* is sometimes found as a compensatory process. Its development depends on the degree of functional disturbance in the kidneys, the state of nutrition, and probably also the age of the patient.

Pyonephrosis, when it is not secondary to hydronephrosis, is usually not attended by so extensive a dilatation, and the surface of the sac is more irregular, presenting bosses and large irregular elevations. The walls of the sac are, as a rule, thicker and not infrequently contain small purulent foci. Microscopically there are found, in addition to the remains of renal parenchyma, more marked signs of inflammation, either of recent date or of considerable standing. More often than in hydronephrosis the cavity contains projecting ledges and dividing walls which cut it up into a number of chambers and smaller cavities and recesses.

The contents consist of a mixture of pus and urinary constituents, the former predominating at times, and at other times the latter. The pus frequently undergoes decomposition, and fatty acids and ammonium salts are formed. Not infrequently the fluid contains an admixture of fresh or recently decomposed blood or hemoglobin, and very commonly the contents are of the consistence of mortar and composed of calcium carbonate, triple phosphates, detritus, and bacteria, with possibly some cholesterin plates.

SYMPTOMATOLOGY.

The most important, and in many cases the only, symptom of hydronephrosis is the *swelling of the kidney*. Partial hydronephrosis and total hydronephrosis of limited extent may therefore run their course without giving rise to any symptoms, and if the remaining renal parenchyma is healthy and performs its function properly, there may be a total absence of morbid phenomena of any kind.

Depending on the completeness of the impediment, the length of time that it has been present, and whether it is permanent or can be overcome, the tumor may be larger or smaller, the size may be constant or it may vary from time to time (*periodic* or *intermittent hydronephrosis*). If the tumor is large, the lumbar region on the corresponding side, and later the corresponding half of the abdomen, bulges, the neighboring organs are displaced, and the same symptoms and phenomena develop as in the case of any other swelling of the body. If the hydronephrosis develops in a movable kidney, the lower portion of the abdomen at first becomes the chief seat of distention and the enlargement suggests an ovarian tumor; in other cases the enlargement at first affects the upper portions of the abdomen, one or the other hypochondrium, and extends downward during the subsequent course.

Bilateral hydronephrosis obviously causes enlargement of the entire abdomen. The enlargement begins at the loins and extends forward, giving the body a barrel-shape. In acquired—*i. e.*, not congenital—hydronephrosis one side is almost always more distended than the other, because extensive bilateral hydronephrosis is inconsistent with life for any length of time.

The tumor can be quite readily grasped with the two hands applied at the same time, the one to the lumbar region behind, the other to the abdomen in front—*bimanual palpation*—and separated from the neighboring organs, particularly when the patient is in the knee-elbow position. The tumor yields the so-called "*ballottement rénal.*" Under favorable conditions it is possible to feel the individual irregularities and localized enlargements of the sac. On *percussion* the tumor, unless the bowel is interposed, yields dulness; in rare cases a tympanitic note has been observed from the presence of *gas within the tumor* (Kehrer). The tumor is almost always movable with respiration, and this phenomenon is most marked when the hydronephrosis develops within a movable kidney. Only very large tumors that cause an extreme distention of the abdomen and force the diaphragm far upward fail to present movement with respiration, because of the diminished respiratory excursion. Quite frequently *fluctuation* may be detected unless a heavy pad of fat and a very tense abdominal wall are interposed and interfere with detection of the sign, or the walls of the tumor itself are too thick.

In itself hydronephrosis usually causes only a moderate degree of *pain* unless it has developed in a displaced kidney. In the latter case pain is both frequent and severe, being caused by the traction on neighboring organs. When, after evacuation takes place, the fluid suddenly reaccumulates in excessive quantities, severe pains with every sign of renal colic or a "gastric crisis"[1] may occur, probably owing to the distention of the renal capsule. Except for these conditions the patients complain only of a feeling of tension and fulness and the distress incident to displacement of the neighboring organs and consequent interference with the functions of the body, such as dyspnea, constipation, and the like.

The *composition* and the *quantity of the urine* are very variable. Often there is no deviation from the normal if the affected kidney or the hydronephrotic portion of it is shut off and its contents do not reach the bladder, while the other kidney, or in partial hydronephrosis the part that is not affected, performs its function normally. Again, *oliguria* or even complete *anuria* may be present in bilateral hydronephrosis, which, it is true, is rarely observed for any length of time after birth, or in unilateral hydronephrosis when the other kidney is shut off or for any reason has ceased to secrete, a condition which, of course, cannot last long without bringing on uremia and death.

On the other hand, when the hydronephrosis is incompletely or only temporarily shut off and the other kidney is quite healthy, *polyuria* and *pollakiuria* may be observed *either continuously for a considerable time or periodically;* when, after copious accumulation of fluid, the impediment

[1] *Cf.* Renvers, *Berlin. klin. Woch.*, 1888, p. 1069.

is suddenly overcome, the contents of the sac become added to the urine supplied by the other kidney. Permanent polyuria is probably due to the fact that while there is a sufficiency of effective cortical parenchyma left in the diseased kidney, absorption in the more or less atrophied medullary substance is diminished, to which are added the effect of compensatory hypertrophy of the sound kidney and, under certain circumstances, also of the heart (see p. 163). From time to time the quantity of urine may diminish (*oliguria*) whenever the impediment is reinforced or renewed and thus interferes with the flow of urine.

This *variability in the excretion of urine* from a normal condition to polyuria or oliguria or even complete anuria with the corresponding changes in the signs due to the tumor itself, such as size and sensitiveness, is very characteristic of hydronephrosis.

The *composition of the urine* itself is also variable and depends on whether the hydronephrotic sac is permanently or temporarily closed, and whether the remaining parenchyma as well as the other kidney is healthy or has also been attacked by disease. Thus, the urine may at times be normal, at other times turbid from the presence of mucus, pus, or blood. It may contain morphologic elements indicating the implication of the mucous membrane of the urinary passages or even of the renal parenchyma—*i. e.*, leukocytes, squamous epithelium or renal epithelium, and casts; or it may contain crystalline elements, particularly uric acid, often in quantities appreciable by the naked eye, whenever the gravel or concretions which form the impediment to the urine have been washed out.

Fever may occur when the hydronephrosis develops rapidly as the result of sudden obstruction, and may be accompanied by pain from the tension of the renal capsule; it is then probably reflex in character, caused in part by the distention and in part or chiefly by the irritation of the foreign body wedged fast in the urinary passages. (See Pyelitis, p. 345.) When the hydronephrosis develops gradually there is usually no fever, and it occurs only, as not infrequently happens, when suppuration is added—that is, when the hydronephrosis becomes converted into a pyonephrosis.

The *general condition* of the patient is not much affected by unilateral hydronephrosis except when the condition develops suddenly or the fluid after evacuation reaccumulates rapidly, when, as has been remarked, there may be temporary febrile movements, otherwise the general condition depends on the nature of the primary disease or of the obstruction. In the case of a malignant tumor, such as cancer of the bladder, the general condition is, of course, bad; on the other hand, it may be quite good when the cause of the obstruction, which in that case is usually temporary, is a movable kidney or the wedging fast of a stone.

When unilateral hydronephrosis becomes complicated by the formation of an impediment in the other kidney, or when the function of the second kidney is disturbed by other diseases and oliguria or anuria develops, *acute* or *chronic uremia* supervenes and may bring on death.

Another danger lurks in the *rupture of a hydronephrotic sac*, either

as the result of an injury or simply excessive tension of the sac (J. W. Taylor[1]). Such a condition is always attended by intense pain and collapse, but the immediate danger to life may be dissipated by absorption of the fluid.

In *pyonephrosis* the *local* symptoms are on the whole the same as in hydronephrosis, but the pain is more pronounced, while on the other hand the enlargement is usually less conspicuous, because the tumor, as has been remarked (p. 358), does not attain so great a volume as in the case of hydronephrosis, and because it is drawn deeper into the body by adhesions with neighboring organs. The *general condition* is not so good as in hydronephrosis, and fever is both more common and more marked than in the latter condition. The character of the fever varies; it may be continuous, intermittent or remittent, or of a distinctly septicopyemic type.

The composition of the *urine* may be quite as variable in pyonephrosis as in hydronephrosis; if the sac drains freely into the bladder the urine will contain more pus or the purulent and decomposed contents of the bladder.

COURSE, TERMINATION, AND PROGNOSIS.

Once hydronephrosis has developed it usually progresses very slowly, lasting for many years, and often becoming stationary for a considerable interval; the size varies, periodically increasing and decreasing, or the swelling disappears altogether (intermittent hydronephrosis), the changes depending altogether on the behavior of the obstruction; the latter again is dependent on the primary disease. If the primary disease is capable of cure or improvement, as, for example, calculus or movable kidney, the hydronephrosis may terminate in more or less complete recovery unless it has lasted too long and the parenchyma has suffered too much damage. If the obstruction is caused by an incurable disease, such as, for example, carcinoma of the bladder, the hydronephrosis, as a rule, persists until death is brought on by the primary disease; but even under such circumstances temporary improvement of variable duration is not altogether impossible, for the tumor may soften and break down and drainage be thus restored.

Hydronephrosis may itself become the immediate cause of death, as has been mentioned, through the occurrence of rupture; or it may indirectly bring on death by uremia if the other kidney is also diseased or incapable of functionating or in the course of time also becomes the seat of hydronephrosis. In the latter case (*acquired bilateral hydronephrosis*) death occurs very early unless the flow from the kidney, which until that time had been healthy, is at once restored.

In *congenital bilateral hydronephrosis* death occurs very soon after birth or the child is stillborn.

The course of *pyonephrosis* is somewhat more rapid, corresponding to the greater severity of the disturbances. In other respects it depends

[1] *Lancet*, October 4, 1884.

on the same conditions that determine the course of hydronephrosis, and left to itself is more apt to terminate in death. Sometimes partial recovery takes place by the formation of a *fistula* after spontaneous rupture toward the surface, or after operative interference.

The *prognosis* of bilateral hydronephrosis is accordingly unfavorable under all circumstances. In unilateral hydronephrosis it depends, so far as danger to life and duration of life are concerned, on the nature of the obstruction that has caused the hydronephrosis and on the condition of the other kidney. If the latter is healthy, or its function only slightly impaired, and if life is not jeopardized by the process which has caused the urinary stagnation, hydronephrosis may exist for years and be compatible with a fair measure of health. The prognosis of pyonephrosis in general is distinctly more unfavorable, as follows from what has been said. Owing to the progress in renal surgery, however, the prospect of cure or improvement both in hydronephrosis and in pyonephrosis is now very much better than formerly.

DIAGNOSIS.

The chief requirement for positive diagnosis of hydronephrosis is the demonstration of a *renal swelling*. The diagnosis of partial hydronephrosis, unless, as in exceptional cases, it causes a large tumor, cannot, therefore, be made at all; and a small total hydronephrosis that does not cause any demonstrable tumor can be recognized only under especially favorable circumstances by certain other diagnostic points. Among the latter are: 1. The *demonstration of a cause* that has led or may lead to occlusion of a ureter, such as calculi, a tumor of the bladder, swelling or displacement of the uterus, and the like, especially when there are also periodic painful sensations or a sense of pressure in the corresponding lumbar region, oliguria, anuria, and uremic phenomena alternating with polyuria. 2. The *cystoscopic* proof of the absence of any discharge of urine from the ureter. The latter is of the greatest diagnostic significance under all circumstances, whether there is a tumor or not, and even when the presence of a tumor evidently belonging to the kidney has been demonstrated. For other tumors having their starting-point in the kidney may simulate a hydronephrosis, and it is just for these cases that the proof of the failure of urine to flow from a corresponding ureter is important in the diagnosis, since it would require the conjunction of very unusual and special circumstances for the ureter to be made impermeable by a renal swelling not dependent upon hydronephrosis. [The ureteral catheter may show no flow of urine from the one kidney, or a ureteral sound may reveal the existence of an obstruction. Kelly has even been able to demonstrate the presence of a calculus in the ureter by the impression made upon wax placed on the tip of the exploring ureteral sound.—Ed.]

When a tumor is present, it must be shown that it belongs to the kidney and contains fluid. This is done by bimanual palpation in the

dorsal and in the lateral position, and by rectal and vaginal examination, preferably under full anesthesia.

It is usually stated as characteristic of *renal tumors* that they push the intestines, especially the colon, before them, and therefore do not obscure the percussion note in the abdomen to the same extent as tumors of the liver, spleen, or ovaries. This sign is of little value in the case of large tumors, because the position of the corresponding section of the bowel, especially the colon, is very variable and depends largely on the length of the mesentery (the mesocolon) and the presence of adhesions. Nor is the sign known as "*ballottement rênal*" absolutely conclusive, and the fact that the tumor shows less mobility with respiration than tumors of the liver or spleen has only a subordinate value, because, as has been mentioned, renal tumors may also follow the respiratory movements, although possibly not quite so completely. It is of some importance that in the case of renal tumors a space formed by the bowel can often be demonstrated between the liver and kidney or between the spleen and kidney by means of palpation and percussion, but even this is not a constant finding. *Inflation* of the stomach and bowels with air may assist in the diagnosis, because the procedure obscures tumors of the kidney, while tumors of the liver and spleen, on the contrary, are brought more prominently into the foreground.

The distinction from *ovarian tumors* may be made by the fact that the latter, unlike renal tumors, develop from the true pelvis upward and are connected with the uterus.

The presence of *fluid* within the tumor may be demonstrated by *fluctuation* and by means of *puncture*, and sometimes by the fact that *palpation causes the tumor to collapse* because its contents are discharged into the ureter. The latter sign is quite characteristic of renal tumor, and in itself strongly suggests hydronephrosis, because other sac-like tumors containing fluid, such as renal cysts and echinococcus, can rarely be made to evacuate their contents in the same way by palpation.

The information obtained by means of *puncture* may be very valuable but is not absolutely conclusive, even if urine or a fluid resembling urine, even one with *acid reaction* and containing urea, uric acid, and casts, is obtained. For while it is a strong point in favor of renal tumor, it may occur in cystic kidney (*q. v.*) as well as in hydronephrosis, and in exceptional cases in ovarian tumors possessing an open connection with the urinary passages. In another way exploratory puncture may decide the diagnosis by bringing to light characteristic constituents of other tumors, such as hooklets of echinococcus and cylindric cells in ovarian tumors. The procedure is not quite free from danger, because there is some risk of fluid, the noxious or harmless nature of which cannot well be determined beforehand, getting into the peritoneal cavity and giving rise to inflammation or suppurative processes. The attempt should always be made to perform the puncture extraperitoneally—that is, from the back or side—and it is, of course, needless to say with the observance of the strictest asepsis.

[It is a wise precaution when the sac is tensely distended with fluid,

if exploratory puncture is made, to use a rather fine needle and also to withdraw enough fluid to lessen appreciably the tension within the sac. This will lessen the danger of rupture of the sac at the point of puncture and also the danger of leakage. Should sudden diminution in the size of the sac follow the exploratory puncture, and general abdominal pain with collapse develop, immediate laparotomy might be indicated, with washing out of the abdominal cavity, repair of the wound in the sac, and such operative treatment in the way of drainage or removal of the hydronephrosis as seemed indicated by the condition of the kidney and the nature of the obstructive cause.—ED.]

It is unnecessary to enumerate all the tumors that may occur in the abdominal cavity and may possibly give rise to confusion with hydronephrosis, for the diagnosis must never be based on a single sign, no matter how valuable it may be; in every case all the aid obtainable from the *history* and the *objective signs* must be utilized to the fullest extent. To review briefly, the most important historic data are the presence of a cause and the mode of development of the disease; the most important objective findings are the demonstration of a tumor connected with or belonging to the kidney and containing fluid, and, above all, the cystoscopic proof that one ureter is impermeable.

Cardiac hypertrophy, in the absence of its ordinary causes, has some confirmatory weight in the diagnosis.

Practically the same rules apply to the *diagnosis of pyonephrosis.* The appearance of pus in the urine when a renal tumor is present is in favor of pyonephrosis and against hydronephrosis. Another sign in favor of the former is intermittent fever. Cardiac hypertrophy is probably extremely rare in pyonephrosis, and would therefore turn the scale in favor of hydronephrosis.

TREATMENT.

By appropriate measures directed *against the cause*, hydro- as well as pyonephrosis can be *prevented*, and by the same means the disease can be completely removed or improved or brought to a standstill after it has once developed. From the nature of the case, causal treatment is most successful in cases due to calculus, movable kidney, and displacement of the uterus which are susceptible of improvement, and from stricture of the urethra from any removable cause, but is less successful in the case of inaccessible and malignant tumors and malformations.

If the causal indication cannot be satisfied or the measures adopted fail, the only resort remaining is operative treatment. Such an operation in the case of *hydronephrosis*, however, is justifiable only in the case of large tumors which cause a great deal of distress; in the case of smaller ones it is enough to guard the tumor against traumatic injury, to see to it that the bowels are kept open, and to avoid anything that might cause disease of the other kidney. In addition *gentle massage* might be used with great caution in the hope of bringing about a reduction of the tumor. To escape the tension of the abdominal muscles,

massage is best performed in a warm bath. *Pyonephrosis* always requires surgical intervention provided the diagnosis is absolutely positive.

The operative procedures are: 1. *Puncture* and drainage, if necessary with *aspiration*. Like the exploratory puncture, it should be done extraperitoneally if possible, and, as the effect is almost always only temporary, it should be resorted to only for the immediate removal of severe symptoms, as, for instance, during pregnancy and when for some reason a radical operation cannot be performed. In very exceptional cases of hydronephrosis a single evacuation by puncture has been known to effect a permanent cure. The injection of tincture of iodin, carbolic acid solution, and the like, after the sac has been evacuated by means of puncture, which has been recommended by some authorities for the purpose of inducing inflammatory adhesions, is uncertain in its results and not without danger. It is rarely practised at the present time. 2. *Incision of the hydro- or pyonephrotic sac and the formation of a fistula or nephrotomy*, which was first recommended by G. Simon, appears to be the most advisable procedure in most cases and comparatively the least dangerous, because any functionating parenchyma remaining in the diseased kidney is thereby preserved. It also makes it possible to remove any obstructions that may be present, through the fistular opening, and a final argument in its favor is that in some cases permanent cure has been observed with closing of the fistula, perhaps after total destruction of the renal parenchyma. 3. *Nephrectomy* is never to be considered until after nephrotomy has been performed, and if the remaining kidney is absolutely healthy or, at least, retains an adequate degree of functional power. The method of testing the functional power of the kidney has been described in the preceding section (p. 351). 4. *Ligation of the renal vessels en bloc*, recommended by Nicolai,[1] is said to be followed by contraction and obliteration of the renal tissue. The same caution with regard to the condition of the other kidney applies to this procedure. 5. *Resection of the kidney* might be indicated if a *partial hydro- or pyonephrosis*, which otherwise would probably have escaped detection, is accidentally discovered during an operation performed for some other purpose.

For further details in regard to these operations and their technic, the student is referred to text-books on surgery.

CYSTIC KIDNEY.

LITERATURE.—Hawkins, "Case of Aqueous Encysted Tumor," in *Med.-Chi. Trans.*, 1833, p. 175. R. Bright, "Memoir on Abdominal Tumors," in *Guy's Hosp. Rep.*, 1839, No. 8, p. 208. Rayer, *loc. cit.*, iii., pp. 507 and 544. Adamkiewicz, "De renum in foetu hypertrophia," *Diss.*, Berlin, 1843. Cruveilhier, *Traité d'anath. path. gén.*, iii., p. 380. Rokitansky, *Lehrb. der path. Anat.*, iii., p. 338. Lever, *Path. Soc. Trans.*, 1848–49, p. 74. Bouchacourt, *Gaz. méd. de Paris*, 1843, p. 65, and *Gaz. des hôp.*, 1853, p. 107. Lancereaux, *Bull. de la soc. anat.*, 1865, p. 333. Beckmann, *Virchow's Archiv*, 1856, ix., and 1857, xi. Förster, *Spec. path. Anat.*, p. 357. Virchow, *Ges. Abhandl.*, pp. 837 and 864. *Die krankhaften Geschwülste*, i., p. 270, and iii., p. 93, and *Berlin. klin. Woch.*, 1892, p. 105. J. Simon, *Zeits. f. rat. Med.*, vi., p. 244, and *Med.-Chi. Trans.*, xxx., p. 141. Erichsen, *Vir-*

[1] *Münch. med. Woch.*, 1895, No. 40 (Physiol. Verein in Kiel).

chow's Archiv, xxxi., p. 371. H. Hertz, *ibid.*, xxxiii., p. 233. Koster, *Nederland. Arch. for Geneesk*, ii., p. 779, and iii., p. 103, and *Dublin Quar. Jour.*, xi., vi., p. 256. J. Klein, *Virchow's Archiv*, xxxvii., p. 504. Laveran, *Gaz. hebdom. de méd. et de chi.*, 1876, Nos. 48 and 49. Sturm, *Arch. der Heilk.*, xvi. E. Klebs, *Path. Anat.*, 1876, i., p. 658. Brigidi and Severi, *Lo Sperimentale*, 1880, xlvi., p. 1. Courbis, "Contribution à l'étude des kystes du foie et des reins," *Thèse*, Paris 1877. Strübing, *Deutsch. Arch. f. klin. Med.*, 1891, xxix., and in *Zülzer-Oberländer's klin. Handb. der Harn- u. Sexualorgane*, 1894, ii., p. 170. Chotinsky, "Ueber Cystennieren," *Diss.*, Bonn, 1882. Thorn, "Beitrag zur Genese der Cystenniere," *Diss.*, Bonn, 1882. Leichtenstern, *Deutsch. med. Woch.*, 1884, No. 51. Lejars, "Du gros rein polykystique de l'adulte," *Thèse*, Paris, 1888. Sabourin, *Arch. de physiol. norm. et path.*, xiv., p. 229, Philippson, *Virchow's Archiv*, cxi., 1888, p. 549. Arnold in *Ziegler's Beiträge zur path. Anat.*, etc., 1890, vii. Kiderlen, *Jahrb. der Hamburger Krankenhäuser*, 1890, i. Terburgh, "Ueber Leber- und Nierencysten," *Diss.*, Freiburg, 1891. C. Ewald, *Berlin. klin. Woch.*, 1892, No. 1. B. Stiller, *ibid.*, No. 10, and *Verhandl. des VIII. Cong. f. inn. Med.*, 1888. Nauwerck-Hufschmidt in *Ziegler's Beiträge zur path. Anat.*, etc., 1892, xii. v. Kahlden, *ibid.*, 1893, xiii., and 1894, xv. F. Singer, "Ein Fall von Hydrops renum cysticus," *Diss.*, Griefswald, 1894. A. Depage, "Contribution à l'étude du rein kystique." *Ann. de la soc. Belge de chi.*, 1895, No. 5. A. v. Mutach, *Virchow's Archiv*, cxlii., 1895, p. 46. Bensaude, *Bull. de la soc. anat. de Paris*, February, 1896. Bar, *Progrès méd.*, 1899, No. 4. Brindeau and Mazé, *ibid.* P. Jacob and Davidsohn *Charité-Ann.*, 1900, xxv. A. M. Luzzatto, *La degenerazione cistica dei reni*, Venezia, 1900.

Cysts occur in the kidneys and, more rarely, in the fatty capsule in which the kidneys are embedded and in the surrounding tissue under a great variety of circumstances, vary in number and size, and may be unilateral or bilateral, congenital or acquired.

The most familiar examples, because the most frequent, are the cysts that occur in *chronic* and *especially indurative nephritis* (p. 267). They are formed from dilated uriniferous tubules or Malpighian corpuscles by retention of the contents or possibly by colloid conversion of the epithelial cells, and are therefore to be regarded essentially as *retention cysts*. They have no special significance either as sequelæ or as complications of the form of nephritis referred to.

Parasitic cysts, on the other hand, such as echinococcus and cysticercus, represent a more independent disease, and will be found among the entozoa of the kidneys.

Among *genuine* neoplasms, *dermoid cysts*, which, it is true, are exceedingly rare in the kidneys, should receive the first mention. The writer has only been able to find 2 cases of the disease in the literature, 1 by Paget[1] and 1 by Marchand.[2] They have no practical interest.

The cysts which occur in the *renal capsule and surrounding tissue* are divided by K. Hoffman[3] into cysts formed by the degeneration of lymph glands, retroperitoneal cysts lined with squamous or ciliated epithelial cells, cysts of the fibrous capsule, which may or may not communicate with the pelvis of the kidney, and finally cysts due to stagnation of lymph.

Polycystic Degeneration of the Kidney.—In this condition, which is distinctly more important than those referred to above, the

[1] *Lectures on Surg. Path.*, ii., p. 84.
[2] *Bericht der oberhessischen Gesellschaft f. Natur- u. Heilk.*, 1882.
[3] Diss., Königsberg, 1895.

kidneys are completely *honeycombed with large and small cysts*, causing a *cystic degeneration* of the organs, sometimes attended by considerable increase in size (*hydrops renum cysticus*, "conglomerated cyst formation of the kidneys"). Again the credit must be awarded to Rayer for having been the first to separate the condition from other cystic formations or similar pathologic conditions of the kidneys, such as parasitic cysts and hydronephrosis, with which the condition was confounded by the older physicians (Bonet, Plater, Morgagni, Sandifort, etc.). Rayer has given us an accurate naked-eye description of cystic degeneration and has also discussed its clinical significance, but has not vouchsafed any opinion in regard to its causes. Later investigators have added to the literature and have devoted especial attention to an explanation of its mode of origin.

ETIOLOGY AND PATHOLOGIC ANATOMY.

Cystic kidneys have been seen in fetuses during the second half of intra-uterine life and in mature infants immediately after birth, hence there is no doubt that they may be *congenital*. They also occur in adults, usually in mature life. The cases of the second category are on the whole rare. Whether the cysts in adults are always *acquired* or whether they are in part congenital is difficult to decide. It is quite conceivable that the congenital cyst might remain stationary for a certain length of time without producing any appreciable enlargement, and in later years undergo a rapid or gradual enlargement and cause death. Steiner[1] observed cystic degeneration of the kidneys in several members of the same family, and Höhne[2] reports the case of a woman, forty-nine years old, and her twenty-year-old daughter both afflicted with cystic renal degeneration, observations which seem to indicate the existence of *hereditary* predisposition.

A little more than half of the cases of cystic kidneys observed in adults occurred in *men*, and most frequently in the *fifth decade of life*, the number decreasing from that time on to old age. Before the third decade cystic kidney is exceedingly rare, and Luzzatto found only two cases out of 187 that developed between the tenth and twentieth years of life, both in males.

Almost always, particularly in cases that are unquestionably congenital and belong to the fetal period or the very earliest stage of infancy, both kidneys are attacked by the cystic degeneration, although not to the same extent. In Lejars' statistics the affection was found to be unilateral only once in 60 cases, and Luzzatto states that he found the disease unilateral in 41 out of 226 cases.

The affected viscus appears either to be composed of several large cysts or it looks as if it were covered or riddled with innumerable vesicles of various sizes, so that the transverse section presents the appearance of a comb of honey. In the latter case the kidney retains its normal shape; in the former it may have the shape of a bunch of

[1] *Berlin. klin. Woch.*, 1899, Nos. 32 and 41. [2] *Deutsch. med. Woch.*, 1896, No. 47.

grapes, some of the berries of which are larger than others. In both cases the kidney is enlarged and heavier than normal. Congenital cystic kidneys have been seen as large as an infant's head and weighing as much as 1 kg. (2 pounds) and even larger ones, weighing as much as 1½ kg. (3 pounds) in adults. Fetal cystic kidney often proves an obstacle to delivery.

The cysts may be thin-walled, translucent, of a yellowish color, and filled with a clear yellowish fluid, or the walls may be of firmer consistence and the contents a sanguinolent, brownish and more viscid material. They may be unilocular, or the interior may be divided like a fan by septum-like projections from the wall or by bands which cross from side to side.

The cyst wall consists of fibrous connective tissue, which in many cases is covered on its inner aspect by a layer of flat polygonal cells and more rarely by cylindric cells. This layer of cells sometimes becomes separated from the wall and floats free in the interior of the cavity. In other cases no such covering can be discovered. Sometimes the epithelial cells lining the inner surface are identical in appearance with the epithelium of the uriniferous tubules. The septa between the individual cysts vary in thickness and frequently contain normal or even hypertrophied renal parenchyma, congregated in islands or strips that are separated from one another by connective tissue of varying density with a large-meshed areolar arrangement. The meshes of this connective tissue which develops frequently around the uriniferous tubules (circumcanalicular), contain still recognizable dilated uriniferous tubules and in places glomeruli in a fair state of preservation, sometimes with distinct capsules, also the remains of uriniferous tubules or solid cords of tissue containing nuclei, probably metamorphosed uriniferous tubules.

The contents of the cysts, even in the same kidney, are not uniform. They may be clear and thin, almost as colorless as water or the color of lemon; they may be mucoid or milky, or they may be tenacious and colloid, more or less reddish or dark-red or chocolate-colored from the admixture of blood-pigment. The odor is usually urinous or ammoniacal, the reaction neutral or alkaline. In addition to albumin (serum-albumin, globulin) the fluid contains urinary constituents, particularly urea, sometimes in very notable quantities (6 per cent. in Strübing's case, for instance); it also contains uric acid either in solution or in crystals, as well as crystals of calcium oxalate, cholesterin, and spheres in the form of rosettes or resembling leucin, which were first described by Beckmann and Förster, and are said to consist of an albuminous or colloid substance; red blood-cells and leukocytes, fatty granules, pigmented epithelial and other cells, and detritus. Not infrequently renal concretions have been found in the cysts or in the urinary passages (pelvis, ureters).

Cysts are found frequently in the *mucous membrane of the pelvis of the kidney and of the ureters*, and *also in the liver*, as well as in the kidneys. Among 60 cases collected by Lejars, such cysts were found in the liver 17 times, and according to Luzzatto in 19.1 per cent. Con-

genital cystic kidney is besides associated with all kinds of malformations in the region of the genito-urinary apparatus, such as atresia of the prepuce or the urethra, absence of the bladder, occlusion of the ureters, absence or occlusion of the pelvis of the kidney, double vagina or uterus, or of other organs, such as hydrocephalocele, cleft palate, supernumerary fingers and toes, club-foot, absence of limbs, and the like.

Various theories have been advanced in regard to the *mode of origin* of cysts. Many assert that *congenital* cystic kidney is an altogether different condition from the cystic condition of *adults*. (See Luzzatto, p. 57.) But the manner in which cyst formation takes place is as uncertain for one variety as it is for the other.

Passing over the older and quite untenable explanations, cystic kidneys may now be regarded as *retention cysts* or as tumor-like *new formations*.

As regards the formation of cysts by retention, which Virchow in particular adopts, the obstruction to the evacuation of urine and the subsequent stagnation may be due to a (fetal) inflammation with occlusion of the lower urinary passages or to defective development (arrested or maldevelopment) of the kidneys.

In most cases the obstruction is not to be sought for in the larger urinary passages from the pelvis of the kidney downward, because an obstruction in that situation would lead to *hydronephrosis* and not to cystic kidney, unless possibly in very exceptional cases in which the hydronephrosis develops early in fetal life and in which the youngest imperfectly developed glomeruli in the peripheral portions of the cortex become distended by the stagnation instead of, like the older fully formed glomeruli, becoming contracted and obliterated (v. Mutach).

As a matter of fact, no obstruction is found in the larger urinary passages in the majority of cases, and it must therefore be sought higher up toward the kidneys. This obstruction was at first supposed by Virchow to consist in a stoppage of the collecting tubules by concretions, uric acid and calcareous infarcts; but more recently he has adopted the view that it consists in *atresia of the papillæ*, completely interrupting the openings of the collecting tubules into the calices in many places. Atresia of the papillæ he believes to be due to inflammatory adhesions—that is, to an *embryonal papillary nephritis* or *pyelonephritis*—resulting in the formation of connective tissue with complete destruction of the tubules in the papillæ. Proliferation of the connective tissue has been repeatedly observed; but v. Mutach points out that it cannot always be regarded as the product of an interstitial inflammation, as it may owe its origin to an earlier period and represent the effect of *arrested development at the fetal stage*, or the effect of stagnation.

Nor has proliferation in the interstitial connective tissue or atresia of the papillæ been found in every case, for which reason many authorities, especially Koster, Klebs, and Ribbert, are inclined to regard mechanical obstructions due to *faulty development* as the cause of stagnation, a theory which finds a certain support in the frequent association of other malformations with cystic kidneys, and in the fact that cystic

kidneys have been observed in children of the same mother (Virchow and others). Koster believes that since, according to Kupfer, the uriniferous tubules develop independently of the pelvis of the kidney, an arrest of development might conceivably prevent connection from being established between them; but this explanation does not apply to those cases in which the tubules unquestionably do communicate with the pelvis of the kidney and with the ureter. On the other hand, Klebs believes that the cause is to be found in a congenital non-inflammatory occlusion of the urinary passages, which may be situated in any part of the same, either in the papillæ, with or without obliteration of the pelvis of the kidney, or further down. Ribbert[1] starts with the fact that the kidney develops from two separate anlagen, the urinary portion, from which the urinary cortex and the glomeruli are formed, and the portion which forms the straight uriniferous tubules. That part, then, which connects the separate anlagen and is destined to develop into the system of convoluted tubules, so it is said, fails to develop. The glomeruli which continue to grow independently form one group of cysts, while another takes its origin from the extremities of the collecting tubules.

In *adults* cystic kidney, according to the observations of Thorn, Leichtenstern, and Arnold, at least in part, unquestionably depends on *retention, the result of chronic inflammatory* processes in the region of the pelvis of the kidney, the calices, and the medullary substance, leading to distention and cystic degeneration of the uriniferous tubules. The cause of the inflammation or stagnation may be quite remote and may even consist in congenital malformation, such as the presence of valves or a kink at the orifice of the ureter in the pelvis of the kidney. The *beginnings of the theory that cysts represent a tumor-like new formation* date back to John Simon, Sturm, and Sabourin, who thought that the cysts were formed by a proliferation of the epithelium of the uriniferous tubules. In a more definite fashion Brigidi and Severi later regarded proliferation of all the epithelial cells with secondary colloid degeneration as the cause of genuine *hydrops renum cysticus* in contradistinction to the smaller cysts, which they thought were due to extravasations of blood into the capsules of the glomeruli. Philippson also found a proliferation of the epithelial cells, going on to the formation of sprouts and papillomata, as well as circular proliferation in the membrana propria of the uriniferous tubules; and quite recently Nauwerck and Hufschmid, v. Kahlden, Singer, and Kozowsky[2] explicitly advanced the view that cysts are not formed from uriniferous tubules distended by retention, but from atypical proliferation of glands in originally normal or malformed kidneys, and are therefore to be regarded as *adenocystomata*, just like the hepatic cysts which are found in association with them in many cases.

The writer should also mention v. Mutach's discovery of islands of *hyaline cartilage* within the stroma of a congenital renal cyst, which

[1] *Verhandl. der Deutsch. Path. Ges.*, ii., 1899, p. 187.
[2] *Petersburg. med. Woch.*, 1897, No. 27.

seems to speak in favor of the tumor-like new formation theory, and find its analogue in the much more frequent occurrence of such islands of cartilage in adenoma of the testicles which develop so close to the kidneys.

D. v. Hansemann[1] refers all cystic kidneys to intra-uterine inflammatory occlusion of the tubules (after Virchow), and accordingly uses the term pseudotumors to designate cystic kidneys.

SYMPTOMS, COURSE, AND TERMINATION.

Clinically, *fetal* cystic kidneys are practically interesting in only one respect—that is, in connection with *labor*—as the enlargement of the body due to the renal tumor interferes with delivery and necessitates various procedures which may cause the death of the fetus, if it has not been already destroyed.

If a child with congenital cystic kidney is born alive, it usually dies in a short time, either from asphyxia, owing to the high position of the diaphragm and the encroachment on the space that should be occupied by heart and lung, or from other disturbances due to some additional malformations.

In the case of *adults*, particularly when there is only one cystic kidney, there is often a total absence of any symptoms referable to a kidney disease until death occurs from some other cause. A goodly number of such cases has been reported, in which the renal affection was not discovered until the autopsy. In another group of cases, while symptoms pointing to disease of the urinary apparatus or of the kidneys in particular may be present, they are not characteristic of any definite disease and are very often inconstant and extremely variable.

The most important symptom pointing to disease of the kidney is a *swelling of the kidneys*, which, however, except in relatively rare cases, is not sufficiently marked to be discovered during life. In Lejars' collection, such a swelling was present in only 18 out of 62 cases. The mechanical disturbances caused by the swelling are the same as those which are produced by other kinds of renal enlargement, especially that of hydronephrosis, which indeed shows the greatest resemblance to cystic kidney, and to the description of which (p. 358) the reader is accordingly referred. But in contradistinction to hydronephrosis, the swelling of cystic kidney is much more frequently bilateral, and fluctuation is more rarely detected. In a few instances it was possible to recognize by palpation individual cysts of the tumor which were apparently more prominent than the rest. *Pain*, varying in degree from a slight feeling of pressure to violent cramps, may be present or absent. In isolated cases there were severe paroxysms of pain, resembling renal colic, which were perhaps the expression of a sudden increase in size or a recrudescence of the process. (Compare the Clinical History on p. 373.)

There are no continued observations extending over any considerable period of time in regard to the *behavior of the urine*, because the affection

[1] *Zeits. f. klin. Med.*, xliv., 1902.

is not usually treated until it has reached an advanced stage. Judging from the available reports, the urine appears to be exceedingly variable. It has been found entirely normal as regards quantity and composition, or scanty and of a low specific gravity, frequently neutral or alkaline in reaction. In other cases it was said to be abundant, with or without albumin, frequently containing blood, and, what is especially characteristic, the above-described rosets or bodies resembling leucin (see p. 368).

Edema is also observed occasionally, and finally symptoms of *cardiac hypertrophy*, so that many patients at certain periods of their disease present the picture of a *chronic interstitial nephritis* with polyuria or albuminuria, which is explained by the compensatory hypertrophy of the remaining parenchyma and of the heart. When this compensation fails to take place or is inadequate, the signs of *uremic intoxication* are more or less distinct. The symptoms may be acute, eclamptic in character or chronic, consisting in headache, mental hebetude, vomiting, or other digestive disturbances.

Among other symptoms not directly referable to the renal affection should be mentioned the *bronzing of the skin* which has been observed in a few instances, and in the cases characterized by associated *cysts in the liver*, swelling of that organ, and the presence of a watery material, demonstrated by the detection of fluctuation and by exploratory puncture.

The *general condition* may remain undisturbed for a long time and until death, or there may be a general deterioration lasting a variable length of time and sometimes going on to pronounced cachexia, especially when chronic uremic conditions are associated with digestive disturbances. *Fever* is not observed in most cases; but it appears that it may occur periodically, perhaps in connection with the above-mentioned attacks resembling renal colic. The conversion of the cystic contents into pus, which has been observed not so very infrequently, may also cause fever.

The *beginning* of cystic degeneration of the kidneys is quite imperceptible, and the *course* is exceedingly chronic and extends over years. Lejars relates the case of a woman, who for fifteen years before death felt in both lumbar regions pain probably referable to the disease, which was then just beginning; and in the following case of the writer's own observation, signs of kidney disease were first noticed twenty years before death and continued with variations until toward the end of life. It would appear from this observation and a few other cases found in the literature, as might be assumed *à priori*, that the course lacks uniformity and is interrupted by the variable rate of growth and the occasional renewal of growth or arrest of the cysts.

Ultimately the disease always ends in death; but as the writer has already remarked, death is not always the immediate result of the condition, being often due to some intercurrent disease or secondary affection indirectly due to the kidney disease, such as cardiac hypertrophy, arteriosclerosis, and resulting hemorrhages. Death is not infrequently brought about by *uremia*, more often the chronic than the acute form, and finally

death has been observed as the result of *septicopyemic infection* after suppuration of the cystic contents.

The writer reports the following case of *renal and hepatic cysts*, which in many respects is exceedingly interesting.

K., hack driver, forty-three years of age, admitted to my clinic on the 7th of October, 1891. Is said to have had intermittent fever as a child twelve years of age and gonorrhea at twenty. In 1871 he contracted inflammation of the kidneys after catching a severe cold, having gotten into a severe perspiration from lifting heavy pieces of baggage on a truck during cold, wet weather and then being drenched as he sat on his box. A few hours later he had a chill, followed by fever, and violent pain in both lumbar regions and in the vertebral column. The urine became bloody and scanty. The legs were swollen up to the knees; also the eyelids. He had a feeling as if he had a lump of lead in the region of the kidneys, and quick movements caused him violent pain in the same region. He recovered in eight weeks. Since then he has been having four times every year an attack of "cold fever," with violent pain in the region of the kidneys, and dark, turbid urine. In August of this year (about six weeks ago) the patient had a stroke, during which he fell from his box. He became speechless and the *left* side of his body was paralyzed. Paralysis and loss of speed improved after three days, and four weeks later he was able to resume his occupation. His present disease began two weeks ago, on the 14th of September, again with pain in the region of the kidneys, and nocturnal fever. The urine became brownish red, turbid, and threw down a heavy sediment. He complained of a sense of pain in the loins and pain in the left side of the head.

Status præsens.—7th of October.—Medium-sized man, large-boned, with flaccid muscles, moderate covering of fat, grayish-yellow complexion and slightly reddened cheeks. The back is covered with numerous acne pustules, and a number of pigmented spots are seen on the chest. Both knees present various superficial scars said to have resulted from ulcers. Both ankles are slightly edematous and painful on pressure, the lower eyelids somewhat puffy.

The thorax is well built and the movements are good. The apex beat is faintly visible, and palpable in the fifth interspace between the mammillary and the parasternal lines. The outlines of the cardiac dulness are apparently somewhat smaller than normal. The heart sounds everywhere weak but pure. The sounds over the carotid are also normal. The boundaries of the lungs in front are somewhat lower than normal; behind, over the lower chest, there are signs of a moderate effusion, above which moist râles are heard; otherwise the lungs present nothing remarkable.

Tongue and pharynx are normal. The abdomen is slightly distended. The spleen is palpable for the width of three or four fingers below the walls of the thorax.

The patient is obliged to evacuate urine frequently, and the act is attended by painful sensations in the region of the bladder, which is also sensitive to pressure. Examination per rectum reveals nothing abnormal.

The patient can go about, and, except for a weakness of the left arm, presents nothing abnormal as regards the nervous system.

The quantity of the urine is greatly diminished, barely 400 c.c. in twenty-four hours; it is dark red in color, contains blood, has a specific gravity of 1020, and on microscopic examination reveals red blood-cells, a few leukocytes, and numerous bacteria. The pulse is 80, regular, of moderate tension; the artery is thickened and hard. There is no fever.

October 8th.—After taking calomel (two doses of 0.3 gm. (5 gr.) each) the patient vomited several times. The quantity of urine is only 200 c.c., and the appearance is the same as yesterday's.

October 9th.—Patient sleeps tolerably well, yet complains of violent pain in the region of the kidneys. Repeated vomiting of watery, dark-green masses.

October 10th.—The patient, who until yesterday could go about with comfort, was during the night unable to get up when he had a desire to go to stool. His consciousness is now perfectly clear; he complains of weakness in the legs and heaviness of the tongue. Movement has become entirely abolished in both lower extremities, except for slight traces at the ankle joint and in the toes. There are

no contractures; the patellar reflexes, which were present before, are absent; the cremasteric reflexes are distinct, as are also the gluteal reflexes. Sensation is apparently undisturbed. Pressure on the muscles and nerve trunks is not painful. The arms are normal except for a slight feeling of formication on movement. The speech is somewhat thick, but the movement of the tongue is normal, nor is any abnormality discoverable in the domain of any of the other cerebral nerves nor in the pupils. The quantity of urine to-day is barely 50 c.c. The patient vomits frequently. The temperature during the entire time varied between 36.2° and 37.3° C. (97.1° and 99.1° F.). Death occurred suddenly during the afternoon.

A positive diagnosis was not made, but tumor (carcinoma) of the kidney was surmised.

The *autopsy* was performed on the 11th of October. The following is taken from the notes:

The *surface of the brain* is not flattened. The arachnoid is intact; the vessels, especially the arteries of the fissure of Sylvius, are greatly thickened and covered with yellow spots. The ventricles are moderately dilated and contain a clear watery fluid. In the right hemisphere, chiefly in the anterior portion of the lenticular nucleus, there is a cyst as large as a pigeon's egg, with thin, smooth, reddish-brown walls and containing a reddish-brown watery fluid. The *medulla oblongata* appears normal to the naked eye, as does also the *spinal cord*, the caliber of which is somewhat small. The *heart* is large, especially the left ventricle. The *lungs* are edematous. *Edema of the glottis* is present. The *aorta* presents a fairly well-marked brawny degeneration on its inner surface. The *spleen* is enlarged to twice its size, slightly indurated, and contains numerous large follicles. *Both kidneys* are enlarged, each one representing a tumor the size of an infant's head, consisting entirely of cysts even up to the size of a man's fist. In the right kidney the cysts contain in part a clear watery, in part a clear brownish, fluid, while others are filled with pus. The *ureters* are intact. The *bladder* is almost empty and presents signs of mild chronic catarrh. The liver is large and presents on its surface numerous cysts, ranging in size from that of a millet seed to that of a cherry stone.

Anatomic Diagnosis.—Encephalomalacia; cyst of the right hemisphere; cystic kidney; cystic liver; catarrhal cystitis; hypertrophy of the heart.

In addition to the peculiarities of this case that have already been referred to—namely, the association of renal and hepatic cysts (the cyst in the brain was unquestionably a so-called apoplectic cyst) and the attacks of renal colic with hematuria—attention should be called to the cardiac hypertrophy, for which in this case arteriosclerosis is probably more responsible than the loss of renal parenchyma, and the absence of any sign of tumor during life, notwithstanding the great enlargement of the kidneys.

Finally, the writer will give a short account of a second case, in which a positive diagnosis could be made during life.

The case was that of a lady, sixty years of age, who a few years previously had developed signs of *diabetes insipidus* (polyuria with urine of very low specific gravity and free from albumin; nervous symptoms, headache, etc.), to which were gradually superadded symptoms pointing to Basedow's disease (slight exophthalmos, tachycardia, and tremor of the hands). The urine became slightly albuminous, and contracted kidney was thought to be present.

On examination a distinct tumor was discovered in the region of the right kidney, while the left was not distinctly enlarged. The cardiac dulness was moderately increased in both directions, but there were no other pronounced signs of cardiac hypertrophy. The urine, which was pale and somewhat more copious than normal, contained a moderate quantity of albumin and deposited a scanty sediment containing the above-mentioned rosets, and granules and small crystals of hemoglobin. A brother of the patient is said to have died of "contracted kidney."

DIAGNOSIS.

The diagnosis of cystic degeneration of the kidneys in adults is a most difficult task, and should be attempted only when there is a bilateral swelling obviously referable to the kidneys, with local prominences on its surface, the contents of which are clearly shown by the presence of fluctuation or the results of puncture to be fluid, associated with periodic hematuria or a symptom-complex like that of contracted kidney —and this is a very rare conjunction. In any case of *bilateral* tumor of the kidney, however, one should think of renal cyst, especially when the contents of the tumor are fluid, and positive or probable indications of a *hereditary* or *family* predisposition are discovered or ascertained. The finding of the above-mentioned *rosets* or *leucin-like bodies* in the urine in such a case is sufficiently characteristic to clinch the diagnosis.

Of those tumors which possess the greatest similarity to cystic tumors and might give rise to confusion, *echinococcus* can be excluded with the least difficulty, because its occurrence in both kidneys is exceedingly rare; if there is any doubt, it may be promptly dispelled by the demonstration of hooklets or the characteristic membrane in the fluid obtained by exploratory puncture. *Carcinoma* of the kidneys when primary is also rarely bilateral. It may, however, present a picture in every respect similar to that of cystic degeneration, but may be excluded if the heart is hypertrophied and the urine is like that of contracted kidney. The same is true of *soft sarcomata* and *strumous tumors* of the kidneys. *Hydronephrosis* and *pyonephrosis* may give rise to confusion, and can be excluded only by the demonstration of a cause and by variations in the behavior of the urine as regards quantity and composition during a considerable period of observations. In addition, however, all other means available for the diagnosis of the presence of a tumor within the kidney must be utilized. (See Hydronephrosis, p. 351.)

Unilateral cysts of the kidney obviously present even greater difficulties, and a probable diagnosis can only be made when all the symptoms enumerated as characteristic of the bilateral affection are present at the same time. A valuable support for the diagnosis, but one that is only rarely available, is the finding of *cysts in the liver*, if necessary by means of exploratory puncture.

Congenital renal cysts can probably never be distinguished from congenital hydronephrosis.

PROGNOSIS AND TREATMENT.

Bilateral cystic kidneys represent a disease of the kidneys that is not susceptible of treatment, and the prognosis as regards recovery is therefore absolutely unfavorable. The prognosis is also unfavorable as regards life, once the disease has been recognized, because by that time it is already far advanced; the renal parenchyma has been very largely destroyed, and death usually occurs early and sometimes quite unexpectedly.

The prognosis of *unilateral* renal cysts and the treatment depend

chiefly on the condition of the other kidney. In this respect, what the writer has said about hydronephrosis applies equally in the case of unilateral cystic degeneration, both as to the prognosis and the treatment, especially as recognition of both conditions is rarely possible until they are revealed by an operative autopsy or postmortem demonstration. In some cases another condition, such as ovarian tumor, for example, is diagnosticated instead. In any case, if cystic kidney is diagnosticated or discovered in the course of an operation performed for some other reason, any procedure except evacuation of the sac—which is usually very large—by puncture or incision is to be deprecated.

If operation is contra-indicated, the treatment consists solely in guarding the patient against any injury that might cause rupture of the tumor, and relieving his distress as much as possible by symptomatic treatment.

NEOPLASMS OF THE KIDNEY.

Although nearly every kind of new growth may occur in the kidneys, only a few of them have any practical interest. It is to these that our attention will be particularly devoted.

TUBERCULOSIS OF THE KIDNEYS.

LITERATURE.—Howship, *A Practical Treatise on the Symptoms, etc., of Some of the Most Important Complaints that Affect the Excretion of the Urine*, London, 1823. F. A. v. Ammon in *Rust's Magazin f. die gesammte Heilk.*, xl., p. 500. Rayer, *loc. cit.*, iii., p. 618. Rilliet and Barthez, *Traité des maladies des enfants*, 2d ed., iii., p. 852. Dufour, "Etude sur la tuberculose des organes génito-urinaires," *Thèse*, Paris, 1854. Fuchs, *De tuberculosi system. uropoietici*, Königsberg, 1856. W. Müller in *Virchow's Archiv*, 1859, xvii., p. 205. A. Schmidtlein, *Ueber die Diagnose der Phthisis tuberculosa der Harnwege*, Erlangen, 1862. Kussmaul, *Würzburger phys. med. Zeits.*, 1863, iv. Mosler, *Arch. der Heilk.*, 1863, p. 209. S. Rosenstein, *Berlin. klin. Woch.*, 1865, No. 21. C. E. E. Hoffmann, *Deutsch. Arch. f. klin. Med.*, 1867, iii., p. 67. Challan, *Bull. de la soc. anat.*, 1869, p. 161. Klob, *Oesterreichische Zeits. f. prakt. Heilk.*, xiv., p. 9. Th. Schmidt, *St. Bartholomew's Hosp. Rep.*, London, 1872, viii. J. Arnold, *Virchow's Archiv.*, lxxxiii., 1881. H. Heiberg, *Norsk. Mag. for Lägerid.*, vol. 3, vi., 1877, pp. 111 and 147. S. Rosenstein, *Centralbl. f. die med. Wissenschaft*, 1883, p. 65. Babes, *Progrès méd.*, 1883, No. 3. E. Frerichs, *Beitrag zur Lehre von der Tuberculose*, Marburg, 1882. Steinthal, *Virchow's Archiv*, c., 1885. Benda, *Berlin. klin. Woch.*, 1884, No. 12. Durand-Fardel, "Contribution à l'étude de la tuberculose du rein," *Thèse*, Paris, 1886. Oppenheim, "Zur Kenntniss der Urogenital-Tuberculose," *Diss.*, Göttingen, 1889. Cayla, *Gaz. des hôp.*, 1888, No. 15. Coffin, *ibid.*, 1890, No. 49. J. Israel, *Deutsch. med. Woch.*, 1890, No. 31; *ibid.*, 1896, No. 22, and *Chirurg. klin der Nierenkrankh.*, Berlin, 1901, chap. viii. Baumgarten, *Zeits. f. klin. Med.*, 1886, x. Hauser, *Deutsch. Arch. f. klin. Med.*, xl. Cornil and Brault, *Études sur la pathologie du rein*, Paris, 1884, p. 300. Albarran, *Gaz. méd. de Paris*, 1891, No. 25. P. Gredig, "Beitrag zur Kenntniss der Nierentuberculose," *Diss.*, Zürich, 1892. Tuffier, *Arch. gén. de méd.*, May and June, 1892. Camargo, *Revue méd. de la Suisse Romande*, 1892, No. 10. E. Vigneron, "De l'intervention chirurgicale de la tuberculose du rein," *Thèse*, Paris, 1893, and *Ann. des mal. génito-urin.*, 1893, p. 689. Facklam, *Arch. f. klin. Chi.*, 1893, p. 715. Pasquier, "Contribution à l'étude de la tuberculose rénale," *Thèse*, Paris, 1894. Palet, "Des résultats immédiats et éloignés de la néphrectomie dans la tuberculose rénale," *Thèse*, Lyon, 1893. Borrel, *Tuberculose expér. du rein. Ann. de l'Institut Pasteur*, February, 1894. Orth, *Nachrichten der königl. Wissenschaften zu Göttingen. Math.-phys. Classe*, 1895, i. E. Meyer, *Virchow's Archiv*, 1895, cxli., p. 414. E. Küster, "Die chi. Krankh. der Niere." *Deutsch. Chi.*, lii. 3. L. Casper, *Berlin. klin. Woch.*, 1896, No. 17. B. Goldberg,

Centralbl. f. die Krankh. der Harn- u. Sexualorgane, 1897, viii., and *Berlin. klin. Woch.*, 1899, No. 5. P. Güterbock, *Die chi. Krankh. der Harnorgane*, vol. iv., 1898, chap. viii. J. Schnürer, "Die primre Nierentuberculose," *Sammelreferat, Centralbl. f. die Grenzgebeite der Med. u. Chi.*, ii., 1899, Nos. 12–14. F. König, "Die chirurg. Behandlung. der Nierentuberculose," *Deutsch. med. Woch.*, 1900, No. 7. König and Pels-Leusden, "Die Tuberculose der Niere," *Deutsch. Zeits. f. Chi.*, lv. A. Pousson, "Rapport sur la valeur de l'intervention chirurg. dans la tuberculose rénale," *Con. interna. de Méd.*, Bordeaux, 1900. Noble and Balcock, "Eine neue Methode der Diagnose bei Tuberculose der Nieren," *Centralbl. f. Gynäk.*, 1900, No. 12.

Tuberculous diseases of the kidneys were described by Morgagni and some other authors who flourished even before his time, under various titles, such as atheromatous cyst, struma, and scrofulous tumors, and were probably included in the same category with other diseases. Baillie[1] also mentions the occurrence of "tubercles" in the kidney, resembling in all respects the ordinary pulmonary tubercles. Gaspar L. Bayle[2] was the first to give a full description of the disease, which was later called "caseous nephritis," and he emphatically expressed the view that the lesions are identical with tuberculous deposits, a view which was later attacked in many quarters, and has only recently met with general acceptation through R. Koch's discovery of the specific bacillus common to both processes. The chief credit of defining the disease in such a way as to make it recognizable and of differentiating it from other renal affections belongs to Howship, and later v. Ammon and Rayer, although absolute certainty in diagnosis has only been made possible by the more recent achievements of bacteriology and by cystoscopy.

ETIOLOGY AND PATHOGENESIS.

The cause of tuberculous disease—Koch's bacillus—may enter the kidneys in various ways: (1) by way of the blood-vessels—*i. e.*, *hematogenous* infection; (2) by propagation from the urinary passages, representing the *urogenetic* or *ascending* form; and finally (3) by extension from neighboring tissues, especially the suprarenal capsules—*i. e.*, "by contiguity"; this is the rarest mode of invasion.

When the bacilli reach the kidneys through the blood-channels, they not only enter the glomeruli, but may also escape from the latter and enter the uriniferous tubules, and thus produce the so-called "excretion tuberculosis" (Ausscheidungstuberculose) of the kidneys (Cohnheim). It is probable, however, that the bacilli cannot escape into the uriniferous tubules except when the glomeruli are diseased, or when their structure has previously been injured in some way (E. Meyer[3]).

The form of tuberculosis which develops by ascension along the urinary passages or by continuity is undoubtedly *secondary*. Yet cases occur in which the kidneys alone are attacked by tuberculosis, or, at

[1] *A Series of Engravings to Illustrate the Morbid Anatomy*, etc., London, 1799–1812, cited by Rayer.

[2] "Remarques sur les tuberculoses," in *Jour. de Méd.*, etc., by Leroux, Corvisart and Boyer, vi., p. 26.

[3] *Cf.* Biedl and Kraus, "On the Excretion of Micro-organisms Through the Kidneys," *Arch. f. exp. Path.*, etc., xxxvii.

least, are unquestionably attacked earlier than other portions of the *genito-urinary apparatus;* these cases are often designated *primary renal tuberculosis*, although it is very questionable whether a primary renal tuberculosis, in the strict sense of the term, ever occurs. Owing to the protected position of the kidneys, it is *à priori* most improbable that the tubercle bacilli should avoid the usual ports of entry and reach the kidneys directly. It is more than probable that even those tubercles which are apparently isolated and are not produced by immediate extension trace their origin to a focus somewhere in the body which may be hidden and difficult to discover—as, for instance, in some lymph gland —and from which the hematogenous infection of the kidneys has developed by *metastasis*. Strictly speaking, therefore, every case of renal tuberculosis is probably secondary.

It is true, however, that tuberculosis of the kidneys may be the first manifestation of the disease in the *uropoietic system*—in other words, it may be *primary* and spread by descending to the urinary passages. As Steinthal and Baumgarten have shown, descending tuberculosis is, in fact, the most frequent form, a statement which is also supported by the information gained during operations. J. Israel states that among his operative cases of renal and vesical tuberculosis, tuberculosis of the kidneys was the primary disease in 40.9 per cent.

In regard to the influence of *age* and *sex*, there is a distinct difference between acute *miliary tuberculosis* and chronic tuberculosis in the form of *caseous inflammation*. The former, in the first place, represents a concomitant of general miliary tuberculosis and, like that disease, is relatively more frequent during *childhood* than later in life; the period between first dentition and the fifth year being apparently the period of greatest incidence. In the second place, eruption of miliary tubercles often occurs secondarily to chronic tuberculosis of the kidneys. The latter, so-called "*nephrophthisis*," on the other hand, is found overwhelmingly more frequently during middle mature age, and is more common in men than in women. In regard to the sexual differences, a great discrepancy is observed in the statements of different authors, according as their statistics are based on the results of autopsy or the findings during operations. Operations are performed much more rarely in the ascending, urogenetic form, on account of the distinctly less favorable prognosis, than in cases of so-called primary renal tuberculosis, and the former is more frequent in men, so that in the statistics based on operations the female sex shows the greatest incidence (J. Israel). In children up to the fourteenth year of life the male sex, according to Hamill,[1] furnishes the greatest number of cases. Among 46 cases he found 32 were boys. A preponderance in favor of the female sex in general was observed by v. Krsywicki and Gredig.

As regards *age*, the greatest number of cases is observed during the third and fourth decades; the second and fifth decades come next, and show approximately equal frequency; while last in respect to frequency are the first and sixth decades. Dietrich found tuberculosis of the

[1] *Contributions from the Wm. Pepper Laboratory*, Philadelphia, 1896.

kidneys in a man of seventy years; on the other hand, R. Atwood, in a boy three years of age.

The greater frequency of chronic tuberculosis or "cheesy nephritis" in middle age is largely due to the fact that the genito-urinary apparatus frequently represents the port of entry for tuberculosis in general, and particularly for tuberculosis of the kidneys. In many cases the tuberculous renal affection is secondary to tuberculosis in the region of the male sexual organs (the testicles and epididymis, seminal vesicles, tubules, and prostate gland), which is in itself a frequent affection of youth; and although it may occur in earliest childhood, it may not spread to the urinary apparatus, and especially the kidneys, until much later in the individual's life. K. Schuchardt[1] also believes that the disease may be transmitted during sexual intercourse, especially as a mixed infection with a coincident gonorrheal infection, and in that case leads to a tuberculous superficial catarrh without the formation of ulcers, which may later be followed by secondary tuberculosis of the genito-urinary apparatus. In children and very youthful individuals, on the other hand, the ascending form is rarer than so-called primary renal tuberculosis. In such individuals the general causes of tuberculosis (hereditary taint, debilitating influences) play an important part. But even during the earlier periods of life renal tuberculosis not infrequently develops secondarily to tuberculosis of the testicle or epididymis without being an ascending form—*i. e.*, it is probably caused by metastasis.

PATHOLOGIC ANATOMY.

Acute disseminated miliary tuberculosis, the result of a general infection, always affects both kidneys. As in the other organs, which are usually attacked at the same time, the tubercles appear as nodules the size of a millet seed or a pin-head, gray in color, surrounded by a reddened areola and with a somewhat opaque center, arranged singly or in groups underneath the capsule, in the cortex, and in the medulla, in the latter situation being often in the form of stripes or of a wreath. The nodules, as is their wont, develop chiefly in the perivascular connective tissue, but also in the glomeruli and in the interior of the uriniferous tubules (as so-called "excretion tuberculosis," referred to above), and go through their usual development with cell proliferation, the formation of giant cells, and the accumulation of round cells, going on to beginning caseation. Owing to the fact that death usually occurs early, the changes do not go any farther. For the rest, the kidneys present cloudiness of the parenchyma and swelling of the epithelium.

Chronic tuberculosis most frequently begins in the papillæ and in the pyramids of the kidney, even in cases in which a direct extension from the pelvis of the kidney and ureters cannot be demonstrated, and from there spreads through the entire cortex as far as the capsule. In other somewhat more exceptional cases one pole of the kidney is found to be diseased at first; the lower more frequently than the upper pole. This, according to Zondek,[2] depends on the fact that one pole is

[1] *Arch. f. klin. Chi.*, 1892, p. 449. [2] *Ibid.*, lix.

frequently supplied by a main branch of the renal artery or by a special renal artery.

From the part that has been attacked first the process spreads, miliary tubercles appearing first in the immediate surroundings of the already existing foci. By confluence of these tubercles, with necrosis of the tissue and round-cell infiltration, the so-called "caseous nodules" are formed, varying in size from that of a pea to that of a walnut. These disintegrate and break down, forming a cheesy mass, and finally a complete cavity containing a semi-fluid, mortar-like material, which either becomes still further inspissated through partial absorption or, if the cavity has an open connection with the pelvis of the kidney, discharges into the ureter. Not infrequently calcareous concretions are found in the interior of such cavities.

The number of these caseous nodules in the kidney is quite variable; sometimes the greater portion of the kidney may be destroyed and converted into a single yellow or grayish-yellow mass, consisting of larger or smaller spaces or true cavities. In the immediate neighborhood of the cheesy, infiltrated portions there is found a more or less advanced interstitial inflammation, from round-cell infiltration to new formation of connective tissue, and the epithelium of the uriniferous tubules presents various degrees of fatty or albuminous degeneration; the uriniferous tubules themselves may be collapsed or obliterated. The enlargement of the kidneys depends on the extent of the process; and if the caseation has advanced as far as the surface, local enlargements are present, over which the capsule is thickened and adherent to the parenchyma, and ultimately also becomes involved in the tuberculous process. When the interstitial inflammation is very widespread, parts of the kidney or the entire organ may undergo contraction.

In addition to the actual tubercles there may be simple *inflammatory* foci, also due to the presence of tubercle bacilli—small-cell infiltration surrounding the glomeruli—and leading to contraction without caseation (A. Heyn[1]).

Very frequently the *fibrous as well as the fatty capsule* becomes implicated in the disease, either in the form of a simple chronic inflammation with thickening and brawny induration, or in the form of tuberculous or non-tuberculous suppuration.

According to some of the older statements, which were based on postmortem findings, both kidneys are most frequently attacked by tuberculosis, although in a variable degree. Thus Bright, for example, found both kidneys attacked in 19 out of 32 cases; in 7 cases only the right and in 6 only the left was involved. More recent experience, gained in part at autopsies on the living subject during operations, teaches that one kidney is quite frequently attacked, and, as it appears, the left more so than the right. The process probably begins first in one kidney, and if it lasts long enough spreads to the other.

When, as is frequently the case, the pelvis of the kidney and the ureter share in the disease, the mucous membrane of these structures

[1] *Virchow's Archiv*, clxv.

first becomes thickened, then there are found in it and underneath it submiliary nodules which go through the same developmental process as the nodules in the kidney, coalesce, soften, and lead to ulcers which exude a purulent semi-fluid mass containing detritus, which mingles with the urinary excretion. The diseased ureter is converted into a rigid tube with thickened walls, and the lumen is greatly narrowed or entirely occluded by the swelling of the mucous membrane and the collection of semi-fluid material. This not infrequently leads to stagnation with dilatation of the pelvis of the kidney and hydronephrosis, which in a case observed by v. Ammon led to the formation of an enormous tumor, occupying the entire half of the abdomen from the false ribs to the crest of the ileum.

As is evident from the etiology, other portions of the genito-urinary apparatus, such as the bladder, prostate, ureters, testicle, epididymis, seminal vesicles and seminal tubules, are attacked primarily or secondarily in chronic renal tuberculosis or nephrophthisis. The process may also spread from the pelvis of the kidney to the neighboring tissue, especially the lymph glands of the abdomen, and from there still farther, giving rise to more or less widespread purulent and tuberculous destructive lesions. This is particularly apt to happen when a *secondary infection* by other bacteria, such as Bacterium coli or staphylococcus, has taken place. Finally, it is almost needless to say that other manifestations of tuberculosis, particularly in the lungs, the intestines, the bones, or the joints, may be associated with the renal condition, and that *amyloid disease* may develop as the result of tuberculosis.

In some cases of unilateral tuberculosis of the kidney *compensatory hypertrophy of the other kidney* has been observed (Camargo[1]); on the other hand, compensatory cardiac hypertrophy does not appear to occur.

SYMPTOMATOLOGY.

Involvement of the kidney in *acute general miliary tuberculosis* does not betray itself by any characteristic signs. It is possible, and indeed not improbable, that the diminution in the quantity of urine which is common in this disease, and the albuminuria which also occurs, although more rarely, are in part due to the tuberculosis; but as a number of other factors, such as fever, dyspnea, cyanosis, and failing heart power, are also concerned, and the kidneys may present the same urinary changes without tuberculosis, they are devoid of any diagnostic significance.

Chronic tuberculosis of the kidneys, when the process is not extensive, may also run its course without giving rise to symptoms, especially when the pelvis of the kidney escapes and is not in communication with the caseous foci. Even when the condition is widespread, all symptoms pointing to the kidneys may be absent unless the organs enlarge and the capsules become distended, or the foci degenerate and discharge their contents externally.

[1] *Revue méd. de la Suisse Romande*, 1892, 10.

In any case the symptoms are difficult to interpret, because all or most of them may be due to the coincident disease existing in other portions of the uropoietic system—*e. g.*, the ureters or the bladder. And, owing to the presence of tuberculosis in other organs than the kidney, the symptomatic picture may be extremely complicated.

In well-marked cases the chief alterations are found in the *urine*. Frequent micturition (*pollakiuria*), especially during the night, is often an early symptom; the desire to urinate may be associated with pain and, according to some authors (Guyon), there may also be an actual increase in the quantity of urine (*polyuria*). The frequent desire to urinate may be due to reflex irritation in the pelvis of the kidney or to a coexisting simple or tuberculous cystitis; the polyuria may be explained by deficient resorption of the urine in the medullary substance, which is usually the first to be attacked. In the subsequent course of the disease the initial diminution in the urine, unless it is due to occlusion of the ureter, may be corrected by compensatory processes in the kidneys, and the excretion of urine may become normal. An important symptom is the admixture of blood, pus, or mucopurulent or friable masses and shreds or minute fragments derived from the degenerated tissue and discharged with the urine.

Blood may appear at any time in the urine, but is most frequent at the beginning of the disease, and may be the first symptom. In quantity it varies from a scanty amount to a mere trace recognizable with the microscope, or it may be more abundant and constitute an actual hematuria. Slight admixtures recognizable only with the microscope are usually present during the entire course of the disease; more marked hematuria, on the other hand, occurs at variable intervals, during which the urine may be normal or may exhibit some other changes.

The admixture of *pus* or *mucopus* is also subject to variation, and unless a purulent cystitis or pyelitis exists is not usually marked enough to destroy the acid reaction of the urine. The *shreds* and *fragments of tissue*, finally, are, as a rule, embedded in purulent or caseous mucus, and vary in size from that of a grain of sand, barely recognizable with the naked eye, to particles the size of a pea. The microscope often reveals in these shreds of tissue, after they have been suitably treated, in addition to pus, mucus, and blood-cells, detritus and cells derived from various portions of the urinary apparatus, especially the pelvis of the kidney—*tubercle bacilli*, not infrequently arranged in large nests. Sometimes the sediment also contains distinctly recognizable tissue elements, particularly fibrous connective tissue.

The turbid urine after sedimentation and filtration, which are not always quite successful, contains a small percentage of *albumin*, corresponding to the quantity of blood or pus, and very rarely tube casts. Larger quantities of albumin indicate inflammatory irritation of the kidneys, and may be found in varying amounts and for a variable length of time, corresponding to the fluctuations in the inflammatory process, in which cases various kinds of tube casts and renal epithelium may also be found.

Aside from these last-mentioned alterations, the changes in the urine are not characteristic of *renal* tuberculosis, for practically the same changes are observed in tuberculosis of the *urinary passages*, the ureters, and the bladder, or of neighboring organs, such as the *prostate*, if rupture has taken place. Not infrequently the symptoms caused by the disease in the urinary passages are most prominent, be it that these organs are also the seat of tuberculosis or merely of an inflammatory irritation; these symptoms are disturbances of *micturition*—frequent desire to urinate, and the urinary changes characteristic of the respective diseases. Sometimes urinary disturbances, either frequent micturition or retention, are observed in the absence of any demonstrable disease of the urinary passages, and are therefore regarded as "consensual."

Pain localized in the region of the kidneys or emanating from these organs, and especially a *tumor* belonging to the kidneys, are more significant symptoms of renal involvement. Both, however, are inconstant. The pain is chiefly due to distention of the capsule. Like pain in the kidneys generally, it may radiate downward to the region of the bladder and into the thigh, and may be constant, or paroxysmal and increased by movement. True *colicky pain* in the kidneys may also occur if the pelvis or ureter becomes occluded with a thick, cheesy pus, either from disease of the structures themselves or by masses of disintegrated tissue that have been washed down from above.

Enlargement may be altogether absent or, on the other hand, there may be an unusually large tumor presenting a number of nodular prominences. The thickened fatty capsule, which may be infiltrated with pus and is often involved in the morbid process, may form part of the tumor even more than the kidney itself.

If, as has been explained, the pelvis or ureter becomes occluded, the occlusion may lead to a permanent or temporary *hydronephrosis*, the severity of which will depend on the completeness and duration of the occlusion. If hydronephrosis does not take place, the enlargement in tuberculosis of the kidneys rarely attains so high a development as in other renal tumors; but as the patients are frequently emaciated, the organ may nevertheless, by careful examination, be felt to be enlarged and may be painful on pressure.

The *general condition* depends altogether on the distribution of tuberculosis in the body, and may therefore be quite satisfactory in so-called "primary renal tuberculosis" or when the genito-urinary organs are only slightly involved, especially if the tissue has not broken down with the formation of pus. Suppuration, when it occurs, is attended by *fever*, which at first is slight and reveals itself only in an evening rise, but later, as the disintegration progresses, becomes more severe. By that time tuberculosis has usually made its appearance in other organs—the lungs, joints, etc.—or if it had already been present in these situations has become more pronounced, and hectic fever with a variety of symptoms produced by disease in the other organs develop, the patient becomes more and more feeble and finally dies. Sometimes

death results from *amyloid disease* or extensive suppuration in the neighborhood of the kidneys (*paranephritis*), or from general exhaustion or rupture into some important organ, as the pleura or the lung; still more rarely *uremia*, at least the well-marked acute eclamptic form, is the cause of death.

COURSE, DURATION, AND TERMINATION.

Acute disseminated tuberculosis of the kidneys is a concomitant of acute general miliary tuberculosis and runs a rapid course with fatal termination. Since, as has been said, the disease cannot be recognized, it has no practical interest.

Caseous nephritis or *nephrophthisis* is a chronic process lasting months or years. The duration cannot be stated accurately, because the first appearance of tubercles in the kidneys cannot be determined. Counting from the appearance of the earliest symptoms pointing to the disease—hematuria and pain—the duration, according to the old analysis by Roberts, may be from five months to three years at most. More recent observations, however, appear to show that the disease may possibly last much longer—at least five years and perhaps more—before terminating fatally. Death is brought on by extension of the tuberculous process to other organs or by exhaustion resulting from paranephric suppuration or septic processes; rarely by uremia.

Fluctuations in the symptoms, temporary improvement, are quite frequently observed during the early stages of the disease, and the improvement may continue until, after some sudden external insult—injury or exposure to cold—the condition becomes distinctly worse and then continues its downward course uninterruptedly. The fluctuations in the patient's condition may be explained by the intermittent mode of spread of the tuberculous process in the kidneys as well as in other organs. It is needless to say that the condition of the remaining organs materially affects the course and prognosis.

When renal tuberculosis is not amenable to operative treatment we know of no other termination than death; at least, recovery must be rare. In recent times, however, the fatal termination which was formerly regarded as unavoidable has sometimes been prevented by operation.

[The prognosis of tuberculosis of the kidney is, of course, bad enough; and, as Senator says, it is difficult or impossible in most cases to determine the duration of the process. It would seem not improbable that at times tuberculosis of the kidney may undergo temporary or permanent arrest, as it is known to do in nearly all other parts of the body. Senator's own case (p. 388, note) would indicate that even in non-operable cases recovery may at times be hoped for, so that the prognosis, while grave, is not of necessity hopeless. And I have seen a case lasting for over five years, although ultimately it was the cause of death. The prognosis as to duration is certainly very uncertain.—Ed.]

DIAGNOSIS.

In order to make a positive diagnosis of chronic renal tuberculosis—the acute form need not be considered, for reasons that have been given—it is necessary to demonstrate the presence of *tubercle bacilli in the urine* and to exclude any other organ but the kidney as their source. As a rule, the second point can be determined without any difficulty, because the organs from which the bacilli might get into the urine are almost all accessible to examination by inspection and palpation. Involvement of the bladder, *if the viscus is otherwise healthy*, can readily be excluded either by cystoscopic examination, which is the most reliable method, or by the absence of all the symptoms of a simple or ulcerative cystitis with or without tuberculosis.

On the other hand, the demonstration of vesical tuberculosis does not, of course, exclude the existence of tuberculous disease of the kidneys; on the contrary, it rather suggests the latter in the presence of symptoms pointing to the kidney, such as pain and a tumor in the loins. In such a case a decision might be arrived at by resort to *ureteroscopy* in addition to cystoscopy.[1] Every obstinate case of cystitis occurring in young persons should arouse a suspicion of tuberculosis, especially if no other cause can be found.

In order to find the bacilli a portion of the shreds or fragments described or, if necessary, of the sediment obtained by centrifugation, may be boiled with dilute caustic potash and stained according to one of the well-known staining methods. Unfortunately, these methods are somewhat unreliable, because the so-called "acid-fast" bacilli which simulate tubercle bacilli, especially the smegma bacillus and other pseudotubercle bacilli, also take the stain, and at best these methods are quite circumstantial. In doubtful cases, therefore, resort must be had to cultural methods, and to the inoculation of some of the suspected material into the anterior chamber or the peritoneum of guinea-pigs.

If, after the presence of bacilli has been demonstrated, it is impossible to exclude their origin from other organs, or if after repeated examination no bacilli are found in the urine, the diagnosis of renal tuberculosis must always be uncertain. The points on which the diagnosis may then be based with more or less certainty are: *renal hematuria*, *pain*, and *swelling of the kidney*, which may be determined by transillumination with Röntgen rays or by palpation, and finally the *demonstration of tuberculosis in other situations*, especially in the sexual organs (the testicles, seminal vessels, and prostate gland). An *evening rise of temperature* without other demonstrable cause, and the evacuation of *purulent urine with persistently acid reaction*, are valuable contributory symptoms and may even be the first to arouse a suspicion of renal tuberculosis.

The chief conditions which produce similar symptoms, particularly hematuria, pain, and swelling of the kidney, and are thereby most likely to give rise to confusion, are *renal calculus* and *cancer of the kidney*. In many cases it is impossible to guard against error. Generally speaking

[1] *Cf.* L. Casper, *Berlin. klin. Woch.*, 1896, No. 17.

the points against renal calculus are the absence of typical renal colic, and of sand or gravel in the urine, the occurrence of an evening rise of temperature, and the absence of other scrofulous or tuberculosis manifestations. A *combination* of tuberculosis and renal calculus also occurs, in which either may be the primary condition. The points against carcinoma are: the absence of marked cachexia and presence of pyuria, the latter being much more rare in carcinoma than in tuberculosis. In doubtful cases the injection of Koch's tuberculin may confirm other signs of tuberculosis, particularly if the injection of comparatively small doses ($\frac{1}{2}$–1 mgm.) produces a distinct febrile reaction, pain in the region of the kidneys when it had not been present before, or, if it had been present, a considerable increase of the pain, and bloody or purulent urine when the secretion had before been normal. The febrile reaction alone is not decisive, as there may be a tuberculous focus outside of the kidney.

The question that is so important—at least as regards treatment—as to whether both kidneys are diseased or only one, and in that case which is the affected organ, cannot be determined with certainty by the symptoms alone. On the other hand, valuable information can be obtained by collecting the urine separately from each kidney by *catheterization of the ureters* and examining the specimen for bacilli or, if necessary, resorting to inoculation. If only one kidney is diseased, this method enables one to determine at the same time whether the other kidney is healthy or, at least, retains sufficient functionating power, so that extirpation of the tuberculous organ can be performed without danger of uremia. For the methods to be employed the reader is referred to the section on Pyelitis (Diagnosis, p. 346).

In a number of cases, finally, a definite conclusion is only reached by an *exploratory incision*, which may, if necessary, be immediately followed by a radical operation.

[There is danger that the tuberculosis of the kidney as well as of other parts of the urinary tract may be overlooked because of the known presence of some other condition that might explain the symptoms. Gonorrhea with its sequelæ, such as prostatitis, cystitis, etc., may be or may have been present, and one might explain the findings as due wholly to this cause. The possible coincidence of these two conditions ought not to be forgotten (see Schuchardt, p. 428), and it should be remembered also that a prostate, seminal vesicle, or bladder previously damaged by a gonorrheal inflammation may be secondarily infected with tuberculosis, the tubercle bacilli finding a favorable soil in the diseased tissues. Tuberculosis of the kidney might have its origin, therefore, in such a case of gonorrhea with secondary tuberculous involvement of the lower urinary tract. Again, symptoms of pyelitis, with pain, pyuria, enlarged kidney, etc., may seem to be entirely explained when a calculus is shown by an *x*-ray examination. It should not be forgotten, as has just been mentioned, that calculus may be present along with tuberculosis, whether forming as a result of the tuberculosis or being present before the tuberculosis is not always clear.

The importance of determining the existence of tuberculosis of the

urinary tract and of the kidney is clear when we remember that the treatment, for example, of a calculous pyelitis might be very different from that of a tuberculous kidney and pelvis with a stone in the latter situation. Tubercle bacilli should be sought for in all cases in which there is the least doubt. That they are often easily overlooked is well known, hence the search must be long and thorough.

Tuberculosis of the kidney in its temperature behavior may, when associated with chills, be mistaken for malaria. This mistake could only occur where a hasty diagnosis is made; the examination of the urine and blood as well as a closer study of the region of the kidney will exclude malaria.—ED.]

PROGNOSIS.

So long as there is no absolutely certain remedy for tuberculosis, the prognosis of the disease in general, as well as of renal tuberculosis in particular, depends on the possibility of removing the tuberculous tissue by operation. Whenever this is possible the prognosis is accordingly not unfavorable. An early diagnosis is therefore of the highest importance and ought, if possible, to be made before the tuberculous process has had time to spread, when only one kidney has become attacked and the bladder is still healthy. When operation is out of the question the prognosis is determined on general principles. Although it is unfavorable as regards recovery, the disease is not necessarily an immediate menace to life, as under favorable circumstances life may be prolonged for a number of years.

TREATMENT.

In addition to the prophylactic measures which are indicated for the prevention of tuberculosis in general or, when the disease already exists, for its limitation, the occurrence of tuberculosis of the kidney may be guarded against by early removal of local foci of the disease, especially in the testicle, and by carefully treating the disease in those portions of the genito-urinary apparatus which may afford an entry to the tubercle bacilli, particularly diseases of the urethra and bladder.

Complete recovery or, at least, arrest of the disease and more or less permanent improvement, providing the disease is *unilateral*, can be accomplished, aside from very exceptional cases, only by operative means. The operations to be considered are *nephrectomy*, *partial resection*, and *nephrotomy*.

1. *Nephrectomy*—that is, removal of the entire kidney—is indicated when a large portion of the organ is diseased and the functional power of the remaining kidney is sufficiently good, a point that must be determined by the methods described above (Section X., p. 393). When the other kidney is functionally defective, also when only *one* kidney is present, the operation is, of course, contra-indicated. It is needless to say that in cases of advanced cachexia and debility and when other severe complications are present, a radical interference like nephrectomy must not be undertaken.

On the other hand, a coexisting *tuberculosis of the bladder* is not necessarily a contra-indication, for it is favorably influenced by extirpation of the kidney, as has been observed by numerous authors. J. Israel believes that this beneficial influence is due to (1) the removal of the tuberculous foci in the kidney and the consequent cessation of absorption of infectious material and products of decomposition; (2) the relief from colicky pains incident to the passage of the morbid products from the kidneys through the ureters, which themselves are sometimes diseased; and (3) the cessation of the continuous flow of tuberculous and purulent material into the bladder and consequent danger of renewed infection to its walls. If repeated infection of the bladder can be prevented, it is possible to cure tuberculosis of that viscus or, at least, to arrest the process if it is not too extensive, as the bladder then becomes more amenable to local treatment.

2. *Resection of the kidney—i. e.*, the removal of only a part of the kidney—has been variously recommended and performed with fairly good results for some time in cases in which only a limited portion of the kidney, usually one of its poles, was diseased. As a general rule, however, the operation is not to be recommended, because the remaining apparently healthy portion of the kidney may still be diseased or become diseased very soon after resection has been performed, and thus necessitate a second operation. Besides, such cases of partial renal tuberculosis are rarely observed or presented for operation, and P. Wagner,[1] König, Pousson, and others have accordingly rejected resection of the kidneys in tuberculosis.

3. *Nephrotomy—i. e.*, incision of the kidney and its pelvis, with or without curettement of the diseased portions—may be indicated when the kidney has been practically converted into a large pus sac and there is some doubt about the functional power of the remaining kidney. The procedure may also be considered as a preliminary operation for purposes of diagnosis or to improve the general condition by evacuating the pus.

In every case of renal tuberculosis, whether operative intervention is indicated or not, *general treatment* of the tuberculosis with every means at our disposal is never to be neglected. Hygienic and dietetic measures to improve the strength and powers of resistance of the organism form the chief part of the treatment. In addition the remedies devised against tuberculosis may properly be tried, among which the writer may mention *creosote* and *guaiacol*, *ichthyol* (internally and in enemata), *hetol*, after Landerer, and R. Koch's *new tuberculin*.[2]

There is also a wide field for *symptomatic treatment* in the non-operative cases: hemorrhages to be controlled, pain to be relieved, fever and urinary symptoms to be combated. The means to be employed are, generally speaking, the same as those which have been recommended in acute and chronic pyelitis (see p. 348).

[1] *Centralbl. f. die Erkrank. der Harn- u. Sexualorgane*, 1897, and *Schmidt's Jahrb.*, 1897, ccliv.

[2] In a case of tuberculosis of the testicles with signs of involvement of one kidney, the writer has seen the disease unquestionably arrested by the use of new tuberculin along with hygienic and dietetic measures.

CARCINOMA OF THE KIDNEYS.

LITERATURE.—Sennert, *Opera omnia*, lib. iii., part. 1. Miriel, "Réflexions sommaires," etc., cited by Rayer, *loc. cit.*, iii., p. 685. Velpeau, *Révue méd.*, 1825, i., iii., and 1826, iv. R. Bright, "Observations on Abdominal Tumors," *Guy's Hosp. Rep.*, April, 1839. Walshe, *The Nature and Treatment of Cancer*, London, 1846. Köhler, *Die Krebs- u. Scheinkrebskrankh.*, Stuttgart, 1853, p. 414. Hülmann, "Monographia de carcin. renum," *Diss., inaug.*, Halle, 1857. Döderlein, *Zur Diagnose der Krebsgeschwülste im rechten Hypochondrium*, Erlangen, 1860. Jerzikowsky, "Beitrag zur Kenntniss der Nierenkrebse," *Diss.*, Breslau, 1871. Rohrer, "Das primäre Nierencarcinom," *Diss.*, Zürich, 1874. Pereverseff, *Jour. de l'anat. et de la Physiol.*, 1874, 4, and *Virchow's Archiv*, lix., p. 227. Kühn, "Das primäre Nierencarcinom im Kindesalter," *Deutsch. Arch. f. klin. Med.*, 1875, xvi. Duzon, "Du cancer chez les enfants," *Thèse*, Paris, 1876. Cattani, "Sui tumori renali," *Arch. per le sci. med.*, vi., 1884, 8. Lachmann, "Das primäre Nierencarcinom," *Diss.*, Würzburg, 1883. E. Laur, "Ein Fall, etc., nebst Bemerkungen zur Differentialdiagnose zwischen Carcinom u. Sarkom der Niere, *Berlin. klin. Woch.*, 1885, No. 41. Fr. Lacher, "Zur Casuistik des primären Nierencarcinoms," *Münch. med. Woch.*, 1886, Nos. 45–47. E. Guillet, "Des tumeurs malignes du rein," *Thèse*, Paris, 1888. Fr. Rubinstein, "Ueber das Carcinom der Niere," *Diss.*, Berlin, 1889. Steinman, Diss., Würzburg, 1890. A. Lissard, "Die primäre Krebserkrankung der Nieren," *Diss.*, Würzburg, 1891. Th. Rössing, "Ueber die Diagnose u. Behandlung der bösartigen Nierengeschwülste," *Arch. f. Chi.*, xliv., 1894, p. 407. P. Manasse, "Zur Histologie, etc., der primären Nierengeschwülste," *Virchow's Archiv*, cxlii., 1895, p. 164. Th. Rovsing, "Ueber die Diagnose u. Behandlung der bösartigen Nierengeschwülste bei Erwachsenen," *Arch. f. klin. Chi.*, xlix. See also the text-books and hand-books on Pathologic Anatomy and Diseases of the Kidneys.

The descriptions of renal carcinoma found among the older writers leave us in doubt whether the conditions they had in mind were not some other form of tumor and swelling of the kidney, as they speak of severe suppurations or of scirrhus, a form of carcinoma that is extremely rare in the kidneys. The first trustworthy observations date from the beginning of the nineteenth century and were made by Miriel, Norris, Rostan, Cruveilhier, and others. The clinical varieties were first fully described by Rayer. Since then the literature has grown considerably and an attempt has been begun to distinguish between primary and secondary carcinoma, and in recent times much study has been devoted to the histologic nature and mode of origin of the tumors described as carcinoma and their distinction from related or similar forms, such as adenoma, sarcoma, and strumous tumors.

ETIOLOGY.

Carcinoma is comparatively rare in the kidney, much more rare than in other organs (uterus, stomach, mammary gland, skin, etc.). The kidney furnishes about 2 per cent. of all cancerous tumors, and if the secondary renal cancers are excluded, only 1 per cent. (Rubinstein). As elsewhere in the body, the carcinoma may be *primary* or *secondary*.

The true cause of primary renal cancer, as of cancer in general, is not known, and the many theories that have been advanced need not be discussed in this place. Certain *predisposing* factors, however, are familiar. In contradistinction to cancer in other organs, it is worthy of note that renal cancer is quite *frequent during childhood*, a fact which was pointed out by R. Bright, and later by Rosenstein. It must be

observed, however, that all the tumors described as "carcinoma," especially in earlier times, are not be accepted as such; for many of them must have been malignant sarcoma or mixed tumors.

The distribution as regards the different periods of life is as follows:

	Cases	Years.							
		0–10.	10–20.	20–30.	30–40.	40–50.	50–60.	60–70.	70–80.
Rohrer	96	37	4	5	10	10	17	10	3
Ebstein	102	39	4	8	11	10	20	8	2
Lachmann	251	81	7	21	24	22	49	39	8

It follows, therefore, that more than one-third of the cases of carcinoma occur in children under ten years of age. The distribution during the first decade of life appears from an analysis of 50 cases by Monti[1] to be as follows:

During the	1st,	2d,	3d,	4th,	5th,	6th,	7th,	8th,	9th	year of life.
	14	12	8	8	2	1	2	2	1	

The youngest child was two months old.

The occurrence of renal cancer in so young a child suggests an intra-uterine origin, a complete proof of which is found in a case reported by C. Weigert[2] of bilateral carcinoma in a newborn infant.

As regards *sex*, all the statistic studies agree in according the preponderance to males, thus:

Rohrer	found	among	99	cases	68	men	and	31 women.
Ebstein	"		108	"	73	"	"	35 "
Rosenstein	"		35	"	22	"	"	13 "
Rubenstein	"		63	"	36	"	"	27 "

During childhood also the greater incidence among males is quite marked. Thus, during the first decade, according to

Ebstein,	among	31	children	17	were	boys	and	14 girls.
Rohrer,	"	29	"	17	"	"	"	12 "
Monti,	"	36	"	24	"	"	"	12 "

Whether, as is generally believed true for cancer in other organs, *heredity* has any etiologic significance as a predisposing factor for renal cancer is difficult to decide, on account of the great rarity of the condition. In support of such a view, it is customary to adduce an observation reported by Ballard[3] of renal cancer in a man, seventy years of age, whose sister and son had died of cancer.

Cases in which cancer develops after *injury to the lumbar* region are somewhat more frequent and Cremer[4] was able to collect 15 such cases up to the year 1884. Although the trauma cannot be regarded as the true cause of the carcinoma, we may nevertheless, reasoning by analogy from its behavior in other organs, conclude that the injury tends to favor the growth of an already existing, although latent, carcinoma, or the development of a carcinoma in a predisposed individual. The occur-

[1] *Gerhardt's Handb. der Kinderkrankh.*, iv., 3, 1878, p. 457.
[2] *Virchow's Archiv*, lvii., p. 492.
[3] *Trans. Path. Soc.*, 1859, p. 189.
[4] "Nierencarcinom nach Trauma," *Diss.* Würzburg, 1884.

rence of cancer in cases of *renal calculus*, which is not an uncommon observation, may possibly be attributable to the traumatic irritation and ulcer formation with consequent atypical proliferation of epithelium, just as cancer of the gall-bladder and bile ducts is explained on the same grounds.

PATHOLOGIC ANATOMY.

Primary carcinoma usually attacks only one kidney, the right perhaps somewhat more frequently than the left. The proportion is shown in the following table constructed from a large collection of cases:

	Total number of cases.	Right side.	Left side.	Bilateral.
Rohrer	114	52	50	12
Ebstein	125	55	57	13
Rubinstein	62	28	27	7
Guillet	65	34	31	
Rosenstein	33	16	7	10
Lachmann	34	16	18	

With very rare exceptions, in which the organ retains its normal size or may even become diminished as a result of contraction of the parenchyma, primary carcinoma causes an increase in the size and weight of the kidney, not infrequently equivalent to twice or three times the normal, especially when, instead of merely a few carcinomatous nodules being present, they are found in every part of the organ. Guillet asserts that the increase in volume and weight is especially marked in children; in 16 cases the kidney showed an average weight of 8½ pounds. In adults the *absolute* increase in weight is, of course, larger, 10 to 15 pounds, and in exceptional cases a weight of 31 pounds (Van der Byl) and even 50 pounds (Elliotson) has been observed.

Owing to its increased weight, the kidney is usually displaced forward and downward, and may be found lying transversely in front of the vertebral column.

When the cancerous growth consists of individual nodules, the kidney exhibits corresponding prominences, varying in size from that of a nut to that of an apple, at the upper or lower pole, at the hilus, or on one of its lateral surfaces. When the disease is more extensive the entire organ becomes uniformly enlarged, but also presents some irregularities corresponding to the situations where the cancer has reached the surface. The carcinomatous portions are grayish-white or yellowish in color, with reddish linear and macular markings from dilated veins or hemorrhages. The interior of the nodules may undergo softening as a result of fatty or purulent disintegration or hemorrhages, break down, and become converted into a cavity containing a serous or very frequently sanguineous, semi-fluid, offensive material.

The commonest form of the disease in the kidney is the *medullary cancer*; more rarely a greater development of the connective-tissue stroma takes place, and the harder variety known as *scirrhus* results; but a great variety of transitional forms are observed between these extremes, just as the varying abundance of blood-vessels and hemorrhages and the colloid and fatty metamorphosis, which also vary in

intensity, may lead to the changes causing the growth to be known as *colloid cancer*, *fungus hæmatodes*, and the like.

It has been shown beyond a doubt by the investigations of Waldeyer, Lancereaux, and others that carcinoma begins in a proliferation of the epithelium of the uriniferous tubules, and differs from *adenoma* by its atypical mode of spread, breaking through and destroying the neighboring tissue. The line of demarcation between adenoma and carcinoma is often very difficult, as everyone knows, and transitional forms occur, which are described as "malignant" or "destructive adenomata" or as "adenocarcinomata," and these transitional or mixed forms are particularly common in the kidneys. Many of the cases described as carcinoma occupy the boundary line between cancer and adenoma. Besides, there is no doubt that "*sarcoma*" of the kidney and "*heterologous struma of the kidneys*," which can only be recognized by careful microscopic examination, were formerly often confounded with carcinoma.

The renal tissue in the neighborhood of the cancerous growth frequently exhibits pathologic changes. Sometimes there is a *compensatory hypertrophy of the epithelial cells of the uriniferous tubules*, at others *swelling and fatty degeneration* of these cells or *amyloid degeneration* of the glomeruli, or finally *proliferation of the interstitial connective tissue*, resulting in shrinking and diminution in the size of the entire organ notwithstanding the presence of cancer nodules (see p. 129). In cases of unilateral cancer the same changes may be found in the other kidney.

In the majority of cases the cancer begins in the cortical substance and extends outward to the capsule, and inward into the medullary substance, and finally into the pelvis or even into the ureter and the vascular trunks at the hilus.

When the cancer spreads to the pelvis of the kidney and to the ureter, which, as in tuberculosis, is converted into a rigid tube with thickened walls, the lumen may become occluded and cause a stoppage of the urine, which may be permanent or, if the occluding masses are capable of being softened or washed away, may lead to transient *hydronephrosis*. Sometimes the production of hydronephrosis is also favored by a coexisting *lithiasis*. Lithiasis, in all probability, is also responsible for cancer beginning in the pelvis of the kidney and extending from there to the parenchyma, but this is a much rarer form.

It is worth noting that extension of the cancerous process to the bladder is extremely rare.

The capsule appears to offer a comparatively obstinate resistance, which, however, is in the end overcome. At first it becomes adherent to the kidney, then gradually undergoes thickening, and finally softens and breaks down. The cancer then invades the neighboring organs—the pancreas, the suprarenal bodies, and the intestines—which have previously become adherent to the kidney, and may reach the other kidney by way of the surrounding tissue and lymph channels, a mechanism which probably explains many cases of *bilateral "primary" carcinoma* of the kidneys.

In many cases the lymph glands at the hilus and along the sides of

the kidney early undergo cancerous degeneration and become enlarged. *Metastasis* takes place partly from these enlarged glands and partly by extension of the cancer from the pelvis of the kidney into the renal vessels, especially the veins, including even the inferior vena cava; extension by metastasis is comparatively rapid and frequent in renal cancer. Roberts states that he found metastatic cancer in 31 out of 51 cases of cancer of the kidney that he collected; according to Guillet, metastasis took place in 168 out of 294 cases, particularly in the lungs, and after the lungs in the liver.

Secondary cancer of the kidney, when due to matastasis by way of the blood-vessels, is usually bilateral; but when it has spread by contiguity, from neighboring organs, it is very often unilateral. Metastatic cancer of the kidney almost always involves the cortical substance, very exceptionally the medullary layer. It leads to the formation of small nodules, varying in size from that of a pea to that of a walnut, scattered throughout the parenchyma and presenting the same structure as the primary cancer from which they are derived. The original growth in men is frequently found in the testicles or in the liver and in the stomach; in women, in the uterus or in the mammary gland.

SYMPTOMATOLOGY.

Primary cancer of the kidneys during its initial stage and subsequent course often produces only very insignificant and indefinite symptoms, which do not even make it possible to surmise the disease.

The characteristic symptoms are pain in the kidneys, hematuria, increase in size of the kidneys, and cachexia. No one of these is constant, nor is there any regularity about the time of their appearance.

Pain occurs comparatively early, although very rarely it may be absent during the entire course of the disease; but it is not characteristic, being, like all renal pain, sometimes localized or elicited only by pressure, again radiating downward or upward, or dull and oppressive, again simulating neuralgia, sciatica or renal colic—differences that probably depend on the distribution of the carcinoma in the kidney, the involvement of the capsule or of the nerve trunks at the hilus, and disturbance of neighboring organs by pressure or displacement.

Hematuria may occur at any time during the course of the disease, but, as a rule, belongs to the early symptoms; not infrequently it is the first to appear and precedes the pain, being for a long time the only symptom present. In many cases it appears first after the occurrence of an injury, a blow or a fall on the kidney region, or after the lifting of a heavy weight, and in such cases it is the accident that arouses the first suspicion of kidney disease; in other cases hematuria is produced by the injury when the tumor is already present. Altogether hematuria occurs in about one-half of all the cases (according to Guillet in 46 out of 128); it is, however, the *first* symptom in only one-quarter of the cases, and more rarely in children than in adults. The hemorrhage is also extremely variable; it may be so abundant as to threaten life from loss of blood, or it may be scanty, or represented

merely by a minute admixture of blood, barely enough to give the urine a bloody color, or recognizable only by the microscopic demonstration of red blood-cells, or the chemical or spectroscopic tests for hemoglobin. The hemorrhage may last some time or it may return at varying intervals. The blood itself may be recent or decomposed, and in the latter case lends to the urine the appearance of chocolate; it often forms clots which interfere with the evacuation of the bladder or urethra. Sometimes these coagula form casts of the ureter through which they have passed, being round or vermicular, of the thickness of a heavy knitting-needle or somewhat thicker, and varying in length from a few centimeters to 10 or sometimes, according to Guillet, to 20 or 22 cm.

The escape of the blood is not, as a rule, attended by pain unless the ureters become occluded by the coagula just referred to, and there thus results a sudden stoppage of the urine with colic and hydronephrosis. After a time the coagula are suddenly discharged with a large quantity of blood, and the colic subsides; such attacks of colic and swelling of the kidneys with normal urine, or urine containing a very small admixture of blood, may alternate repeatedly with periods of marked hematuria following the disappearance of the colic.

These differences in the character of the hematuria depend on whether the tissue of the tumor itself is very vascular or the destructive process has involved a blood-vessel; whether the blood is discharged directly into the ureter or first undergoes stagnation and disintegration; whether the blood-vessel becomes permanently or only temporarily occluded by clots of cancerous tissue; and finally whether the ureter is permeable or not. If the canal remains permanently occluded by the encroachment of the tumor or by compression from the outside, hemorrhage may never occur at all, or may be absent for a considerable period and even disappear altogether.

When the urine does not contain blood, its appearance and composition are in general normal. There may be a slight diminution in the chlorids and an increase of the nitrogen—conditions which are found in the cancerous cachexia generally. When, however, the other kidney is diseased or there exist other morbid processes, such as pyelitis and cystitis along with the cancer, the characteristic changes of these conditions may be found in the urine.

In contradistinction to tuberculosis of the kidney and cancer or other neoplasms of the bladder, tumor particles are rarely, if ever, found in the urine in cases of renal carcinoma. A few isolated cells or groups of cells somewhat resembling cancerous elements may be found, but they may be derived from the various portions of the urinary apparatus, especially from the various layers of the mucous membrane lining the pelvis of the kidney and the ureters, for these cells may simulate cancer cells.

The *enlargement* of the kidney is the most constant of all the symptoms. According to Guillet's statistics, the symptom was absent or not demonstrable in only 4 out of 133 cases, and in 1 of these cases the

condition was complicated by coincident ascites, which might have been responsible for the overlooking of the swelling. In the beginning, it is true, the enlargement is not often present, nor can it often be demonstrated before pain or hemorrhage occurs to indicate the disease. The size of the tumor, its shape, and consistence are variable; as a rule, the kidney as a whole retains its shape, but presents certain irregularities, is hard to the touch, or may be in places soft or even fluctuating.

Generally speaking, the tumors caused by cancer are among the largest that occur in the kidney; in children particularly the enlargement sometimes attains an astonishing degree in a comparatively short time. In a child of three years Fürbringer observed a right-sided renal cancer of such magnitude that the apex beat of the heart was displaced to a point below the left clavicle.

As the tumor grows the corresponding half of the body, of course, becomes distended, and visceral displacements and other disturbances such as accompany other large tumors of the kidney are produced, which require no special description. Among the more unusual phenomena are *pulsation* of the tumor, vascular murmurs of the same (Ballard, Holmes, and Bristow), and adhesions between the cancer and the skin, with *rupture on the surface of the body* (Guillet). [In 2 cases of carcinoma of the kidney I have seen pulsation and systolic murmur, reminding one of aneurism.—Ed.]

There are certain noteworthy consequences which are observed more frequently as the result of renal cancer than with other enlargements of the kidney, either on account of the greater pressure exerted by the tumor itself as it increases in size and weight, or on account of the involvement of neighboring lymph glands and resulting interference with the circulation.

One of these pressure phenomena is *varicocele*, which was first pointed out by Guyon (cited by Guillet, *q. v.*). He says it is a late, but very frequent, symptom, and occurs as well on the right, as on the left, side (in contradistinction to ordinary varicocele). The varicocele becomes distinct in the erect position and is caused by pressure of the neoplasm on the spermatic veins. [This I have seen in 2 cases. —Ed.]

In a similar manner the pressure of the enlarged kidney and lymph glands on veins and lymph vessels may produce varices and *edema*, first in the lower extremity on the *same side* as the diseased kidney and later also in the other extremity. *Ascites* also occurs from pressure on the portal vein or inferior vena cava, or from extensive swelling of the mesenteric glands and occlusion of the large lymphatic trunks. [Edema of the lower extremities or ascites may be due to the direct invasion of the cava or the portal vein by the new growth. This I have seen. Its possibility should be thought of before deciding on operative procedures. —Ed.]

During the subsequent course of the disease the external and superficial *lymph glands*, especially in the groin, become enlarged, first on the affected and later on the other side, and finally a great variety of dis-

turbances may be brought about as a result of metastasis, to which reference has already been made.

Cachexia develops sooner or later in the course of renal cancer, depending on the character of the growth, whether it is hard or soft, and its tendency to spread. In exceptional cases it is the first symptom to be noticed. Hand in hand with the cachexia and the progressive development of the cancer in the kidney and its neighborhood, *digestive disturbances*, especially diarrhea, and *nervous disturbances* of various kinds make their appearance. These are no doubt sometimes uremic in nature when they are associated with marked diminution in the quantity of urine, or they may depend on other forms of *auto-intoxication*, such as are observed in cancerous diseases. Well-marked acute uremia is very rare.

Fever, as a rule, is absent until toward the end of life unless it is caused by some other complication; the terminal elevation of temperature is probably due in part to embolic processes. In other cases death is ushered in by collapse with subnormal temperature.

Secondary cancer of the kidneys cannot usually be recognized because the *metastatic* nodules scattered through the kidneys probably have not time to grow large enough to form tumors that can be recognized during life or to produce hematuria, and the pain and other subjective phenomena which they may cause are too indefinite for purposes of diagnosis. Renal cancer due to *direct extension from neighboring tissues* might possibly cause the above-described urinary changes and the appearance of a tumor referable to the kidneys, but the phenomena would be overshadowed by the already existing objective and subjective symptoms.

COURSE, DURATION, AND TERMINATION.

The onset of renal cancer is always insidious, and by the time pain, hematuria, or even a tumor is noticeable, the growth no doubt has already existed for some time, so that its duration cannot be stated with any degree of accuracy. Counting the first appearance of symptoms or the occurrence of an injury that has immediately preceded the symptoms as a starting-point of the disease, the duration may be given in general as varying on an average from a few months to a few—that is, three or four—years; there is, however, a marked difference in this respect between childhood and adult life. In children the course is much more rapid and the duration shorter. In 14 cases of children, Roberts found a duration of ten weeks to fourteen months, or an average of seven to eight months; Rohrer also found the average duration in 28 cases occurring in children to be eight months, the longest being two to three years. In adults, on the other hand, the average duration was found by the same authors to be two or two and one-half years respectively, but a duration as long as four years is not rare, and a period of ten years and more is also given by various authorities. Thus, Guillet reports a duration of more than ten years in 6 out of 33 cases. In a case described by Jerzykowski, the disease is said to have

lasted more than seventeen years. Roberts' observation that cancer of the kidney is tolerated better and for a longer time than cancer of other viscera by adults appears to be correct. The phenomenon may be explained by the fact that the cancer in most cases attacks only one kidney, so that the function of the other can make up for the lost parenchyma, and that, as has already been stated, the capsule for some time offers an obstacle to the extension of the cancer to the neighboring tissue.

As regards the most important symptoms—pain, hematuria, and increase in size of the renal tumor—the course is not uniform or uninterrupted. Intervals during which the disease comes to a standstill are particularly frequent in adults. The termination, when the cancer is left to itself, is invariably fatal. Death usually occurs as a result of marasmus and advanced cachexia, the development of which may be hastened by frequent and copious hemorrhages. In rare cases death is the result of rupture and intraperitoneal hemorrhage (Bright, Rayer), and rarely is accompained by symptoms of uremia (Dittrich and others).

DIAGNOSIS.

It is to be observed in the first place that the diagnosis *renal carcinoma* can never be made in the strictly pathologic sense; all that can be done is to demonstrate the presence of *malignant neoplasm*, which may be a sarcoma just as well as a carcinoma, or a mixed form of either of these with other varieties—adenocarcinoma, adenosarcoma—which, as has been stated (p. 392), cannot be strictly divided pathologically.

With the exception of a few cases which, on account of the lack of distinct symptoms, cannot be recognized at all, the diagnosis of renal cancer is not difficult when the above-mentioned four characteristic symptoms—*pain* in the region of the kidney, *hematuria*, *tumor* of the kidney, and *cachexia*—are present. Of these the presence of a tumor is, of course, the most important, and *in childhood* in itself justifies the assumption that cancer or, at least, a malignant neoplasm is in all probability present even if the other symptoms are less pronounced or in part absent, because other renal tumors are extremely rare in childhood, especially during the years when cancer is most frequent. The condition with which renal cancer is most apt to be confounded is *cystic kidney*, probably because hematuria is also frequently present in that condition; but, as has been remarked (p. 367), cystic kidney is only observed in children immediately after birth, while cancer in childhood usually makes its appearance later. In addition, cystic kidney is almost without exception bilateral, while cancer is much oftener unilateral. The same is practically true of *hydronephrosis* in childhood; copious hematuria is a comparatively rare symptom, and it is usually possible to demonstrate some obstruction to the flow of urine from the kidneys (see p. 362). Finally, *echinococcus* of the kidney might be considered, but it is a rare disease and is only very exceptionally observed in children. (See page 433.) *Exploratory puncture*, which should be resorted to in all doubtful cases, will assist in estab-

lishing the diagnosis in difficult cases, and finally all other diagnostic aids that are available in adults must also be used in the case of children.

In *adults* the diagnosis presents greater difficulties, as the occurrence of other tumors besides carcinoma, not only in the kidneys themselves but in the other abdominal organs, is much more frequent, and the sources of diagnostic error are accordingly more numerous. The first thing to be determined, therefore, is the presence of a tumor belonging to the kidneys, for which purpose careful bimanual palpation, percussion, digital examination through the rectum and vagina, inflation of the stomach and intestine, cystoscopy, the technic of which has been repeatedly referred to (pp. 142, 310, and 362), and finally transillumination with the Röntgen rays may be brought into play.

When the presence of a renal tumor has been positively established, it is not usually difficult to determine its nature if the mode of development and presence of a possible cause as well as the other symptoms are given careful consideration. In addition to the tripod —pain, hematuria, and cachexia—which has been repeatedly mentioned, the early appearance of glandular enlargement or of cancer in other organs, and the character of the tumor, especially its irregular surface, are most important arguments in favor of the disease being malignant—that is to say, carcinomatous.

In the absence of a demonstrable tumor the diagnosis is always uncertain, although the presence of all the other signs referred to may make it very probable that cancer exists.

Hematuria, especially when it is the first or the most prominent and possibly also the only symptom, for some time may give a good deal of trouble. If the blood is recognized by the rules mentioned on page 52 as having come from the kidneys, the conditions to be considered besides cancer are renal calculus or renal sand, tuberculosis of the kidney, cystic kidney, hemorrhagic diathesis, either universal or confined to the kidneys (renal hemophilia), hemorrhagic infarct, and possible parasites (entozoa). Most of these conditions can be excluded by a careful weighing of the various factors in the diagnosis, by observing the time of the appearance of the hematuria and by repeated examination of the urine during the intervals of freedom from hematuria.

If the case still remains in doubt and cannot be cleared up even by means of an exploratory puncture, which is, of course, to be performed with the observance of all possible precautionary measures, an *incision for the purpose of exposing* the kidneys is justified, and is nowadays, with careful asepsis, attended with very little danger; the exploratory incision may, according to circumstances, be immediately followed by operative removal of the diseased kidney.

PROGNOSIS AND TREATMENT.

An inoperable cancer, according to the present state of our knowledge, must still be regarded as incurable, since even the most recent efforts to bring about recovery from cancer in some other way cannot be said to have progressed beyond the experimental stage. The *prognosis*

of renal cancer is therefore bad when operation is impossible or hopeless on account of the involvement of other organs. The operation, which is, of course, permissible only when the other kidney is healthy or, at least, retains an adequate degree of functional power, may be performed through the lumbar region—extraperitoneally or through the abdomen—the transperitoneal method. The choice of methods is a question which must be left to the surgeons.

In the inoperable cases the treatment, aside from the indication to keep up the patient's strength by placing him under the most favorable hygienic and dietetic conditions possible and the administration of tonics, is symptomatic and chiefly concerned with the relief of pain and control of the hemorrhage. The first indication may be met with compresses and narcotics, the second by the application of ice-bags or cold compresses to the loins, or the employment of ergot externally or hypodermically, and astringent remedies, such as tannin in combination with ergotin, lead acetate, hydrastis preparations, hamamelis, stypticin, injections of gelatin, and the like. [Calcium chlorid, in doses of 5 to 15 gr. every four hours, may help by increasing the coagulability of the blood. Adrenal extract (adrenalin) has also been employed.—Ed.]

SARCOMA OF THE KIDNEYS.

Literature.—Eberth, *Virchow's Archiv*, 1872, lv. Ferréol, *Union méd.*, 1875, No. 19. Cohnheim, *Virchow's Archiv*, 1875, lxv. Sturm, *Arch. der Heilk.*, 1876. Vogelsang, *Memorabilien f. prakt. Aerzte*, 1876, No. 2. A. Baginsky, *Deutsch. med. Woch.*, 1876, No. 10. Landsberger, *Berlin. klin. Woch.*, 1877, No. 34. Monti in *Gerhardt's Handb. der Kinderkrankh.*, iii., I., 1878, p. 449. Ebstein in *v. Ziemssen's Handb. der speciellen Path.*, 1st ed., ix. 2, p. 128. Fr. Neumann in *Deutsch. Arch. f. klin. Med.*, xxx., 1882, p. 377. Cornil and Ranvier, *Manuel d'histol. path.*, Paris, 1884, ii., p. 638. Rosenstein, *loc. cit.*, p. 587. C. Heitzmann, *Wien. med. Blätter*, 1890, Nos. 24 and 25. S. Pick, "Das primäre Nierensarkom," *Diss.*, Würzburg, 1893. Strübing in *Zülzer-Oberländer's klin. Handb. der Harn- u. Sexualorgane*, ii., 1894, p. 165. P. Manasse, *Virchow's Archiv*, cxliii., p. 281. O. Busse, *ibid.*, clvii. See also the Literature on Carcinoma.

Sarcoma of the kidneys, especially the primary form, is quite as rare as, if not rarer than, carcinoma, with which it was formerly confounded, a mistake that is not surprising, as the two conditions are practically indistinguishable clinically.

Like carcinoma, sarcoma of the kidney when *primary* occurs preferably in *childhood* and in the second half of life. A series of 30 cases collected by Rosenstein shows the following age distribution:

Years.							
0–1	1–2	2–6	6–10	10–20	20–40	40–60	60–80
6	3	8	1	4	1	6	1

In addition to Rosenstein's cases, the writer has found 27 in the literature (Ramdohr, Abercrombie 3 cases, Mackie, Brandt, Döderlein, Stedman, Taylor 2 cases, F. Krause, Kann, J. Israel, Borchard, Verholf, Görb, Albe 4 cases, Bloch, Manasse 5 cases, Wanitschek[1]), so that,

[1] *Prager med. Woch.*, 1898, No. 52.

counting 3 observations of his own, the writer has been able to collect 60 cases, which show the following distribution:

Years.							
0–1	1–2	2–6	6–10	10–20	20–40	40–60	60–80
7	9	20	4	6	3	8	3

It appears, therefore, that two-thirds of all the cases occur during the first decade of life. In a statistic collection of 135 cases by G. Walker,[1] the first and second years of life show the greatest incidence.

The female *sex* appears to be affected somewhat more than the male, and the left kidney more frequently than the right.

The fact that sarcomatous tumors are observed in newborn infants or in children during the first years of life suggests a *fetal* origin. The theory finds further support in the occurrence of striated muscle fibers *rhabdomyomata*), of *cartilage*, and *particles of bone* in many sarcomata. The explanation of the phenomenon, according to Cohnheim, is that during the development of the genito-urinary apparatus parts from the adjacent primitive vertebral plates, formed by defective constriction, enter the kidneys and furnish the starting-point for the later neoplasm.

A great variety of mixed forms of sarcoma also occur in the kidney, such as round-cell and spindle-cell sarcoma, fibro-, myo-, angiosarcoma, melanotic sarcoma, and adenosarcoma.

Sarcoma of the kidney, like cancer, also leads to *metastasis* in other organs, and conversely *secondary* metastatic renal sarcoma also occurs.

There is nothing in the *symptomatology*, *course*, and *termination* of sarcoma of the kidney to distinguish it from carcinoma. The course of sarcoma is not by any means always slow, especially in children, in whom, as a large number of observations show, it may run a very rapid course if the duration is counted from the first appearance of clinical symptoms—pain, hematuria, and tumor. According to Walker's statistics, the duration of cases not operated upon is on an average 8.08 months, and that of operated cases 16.77 months.

In many cases the symptoms, just as in carcinoma, make their appearance after an injury affecting the region of the kidneys.

For all these reasons the *diagnosis* between sarcoma and carcinoma of the kidney is extremely difficult and has no practical significance. As in childhood sarcomata and mixed tumors are more frequent than carcinomata, the probability in the case of children is always in favor of sarcoma or a mixed tumor. The presence of *isolated glandular enlargement* is not against sarcoma, although it seems to the writer that extensive infiltration of glands rather argues against the condition. The diagnosis is established if particles of tumor which exhibit the character of sarcomatous tissue are found in the urine, providing other signs of their being derived from the kidney are present. But such a finding has so far been exceedingly rare (Heitzmann). In a few cases the nature of the new growth has been determined by *exploratory puncture* and *aspiration*, and this procedure or, better, an *exploratory incision* may

[1] *Ann. of Surg.*, 1897, xxvi., 5.

be tried in every case with proper precautions (the incision being made extraperitoneally), because the diagnosis is often in doubt, not only between sarcoma and carcinoma, but also between one of these tumors and other enlargements of the kidneys. As in addition mixed tumors are not infrequent, a particle removed from one part of the tumor does not yield entirely trustworthy information in regard to the nature of the entire growth.

As regards *prognosis* and *treatment*, the reader is referred to what has been said about carcinoma.

HETEROLOGOUS STRUMA OF THE KIDNEYS (HYPERNEPHROMA AND OTHER NEOPLASMS OF THE KIDNEYS).

LITERATURE.—P. Grawitz, *Virchow's Archiv*, xciii., 1883, p. 39, and *Arch. f. klin. Chi.*, xxx., 1884, p. 824. P. Strübing, *Deutsch. Arch. f. klin. Med.*, xliii., 1888, p. 599, and in *Zülzer-Oberländer's Handb.*, p. 166. Horn, "Beitrag zur Histogenese der aus aberrierten Nebennierenkeimen entstandenen Nierengeschwülste," *Diss.*, Griefswald, 1891, and *Deutsch. med. Woch.*, 1891, No. 30. Ambrosius, "Beiträge zur Lehre von den Nierengeschwülsten," *Diss.*, Marburg, 1891. Villaret, "Beitrag zur Casuistik der Nierenstrumen," *Diss.*, Greifswald, 1891. R. Benecke in *Ziegler's Beiträge zur path. Anat.*, ix., 1891, p. 440. Jancke, "Zur Pathologie und Therapie der Nierenstrumen," *Diss.*, Greifswald, 1892. Sudeck, *Virchow's Archiv*, cxxxiii., 1893, and cxxxvi., 1894. Driesser, *Ziegler's Beiträge zur path. Anat.*, etc., xii. Askanasy, *ibid.*, xiv. Alfr. Ulrich, *ibid.*, xviii., 3. Birch-Hirschfeld, *ibid.*, xxiv. Lubarsch, *Virchow's Archiv*, cxxxv., 1894. P. Manasse, *ibid.*, cxlv. Gatti, *ibid.*, cxliv. and cl. Hellmuth Müller, *ibid.*, cxl. O. Busse, *ibid.*, clvii. D. v. Hansemann, *Zeits. f. klin. Med.*, xliv. Wilms, *Die Mischgeschwülste der Niere*, Leipzig, 1899. Burkhardt, *Deutsch. Zeits. f. Chi.*, lv.

Certain tumors described by Virchow as "heteroplastic lipoma" and by others as "adenocarcinoma," which are found quite frequently underneath the renal capsule in the form of small nodules about the size of a pea and yellowish-white in color, are derived, as P. Grawitz has demonstrated, from displaced particles of suprarenal tissue. They consist of a framework of connective tissue and blood-vessels, in which the cells of the tumor, which contain numerous fatty droplets, are arranged in the same characteristic way as in the suprarenal body. Sometimes these nodules develop into large tumors in which the arrangement of the cells is more irregular or the connective-tissue stroma is less abundant, or softening takes place with the formation of cavities and obscures the diagnosis, creating a similarity to adenoma or adenocarcinoma or even sarcoma and other kinds of cystic tumors.

The character of the tumor is also complicated by the fact that true renal tumors, or mixed tumors consisting of renal or suprarenal tissue, sometimes grow out into the kidneys themselves from the suprarenal body or from misplaced embryonic germs of suprarenal substance (Ritter).[1]

In the most characteristic neoplasms the cystic cavities usually contain, in addition to the débris of softened tissue, *blood* or *hemoglobin*, the presence of which is due to the great vascularity of these tumors and their tendency to grow through the veins. Another peculiar feature

[1] *Centralbl. f. allg. Path.*, viii., Nos. 8 and 9.

is the large quantity of *glycogen* which they contain, and which, according to Lubarsch, also argues in favor of their embryonal character. The significance of this phenomenon, however, is disputed by Hansemann, and it is not so important as the *fatty infiltration* of the cells (Ulrich); for glycogen is also found in other renal tumors, especially in such as have developed from preformed connective tissue (Manasse). According to Gatti, the *lecithin* contained in these tumors possesses diagnostic significance.

The larger tumors, if they manifest themselves clinically at all, behave in exactly the same way as malignant (carcinomatous and sarcomatous) tumors of the kidney, which they also resemble in their tendency to form metastases. They might under certain circumstances be distinguished from the latter by the condition of the urine if the secretion contains the characteristic tumor tissue, or by the findings in a specimen of the tumor obtained by puncture. To be characteristic, it should consist of a bloody or chocolate-colored, semi-fluid mass, according as it contains recent or decomposed hemoglobin, with an abundance of fat, as well as cells in process of fatty degeneration, and cholesterin crystals (and possibly also lecithin).

[Many of these hypernephromata seem, at least from a clinical standpoint, to be on the borderline between benignancy and malignancy. Some apparently last for three to five years before they cause death by extension to parts in the immediate vicinity, by metastases, hemorrhage, or so-called marasmus. The importance, therefore, of an early diagnosis before the tumor has spread beyond the kidney is clearly seen. Recognized early, it is not impossible by operation to bring about a cure or, at least, a lengthening of life.

The attempt has been made to utilize as an aid to diagnosis of hypernephroma the fact that an increase of suprarenal extract (internal secretion) would give rise to an increase in blood-pressure, and that by misplaced, exuberant even though atypical suprarenal tissue, such increase of the internal secretion might be caused and detected by the digital or instrumental study of blood-pressure at the pulse. Arteriosclerotic changes seem at times to be the result of long-continued high blood-pressure as seen in hypernephroma and may lead to rupture of cerebral vessels, a point brought out in the demonstrations in the dead-house at Vienna by Kolisko and others.—Ed.]

As regards *treatment*, the only hope is in extirpation of the diseased kidney, which has been performed in quite a number of cases. Any other operative treatment, such as *incision* with drainage or *evacuation* through *puncture*, is to be condemned, according to Strübing, on account of the great tendency to hemorrhage inherent in these tumors.

In addition to the neoplasms just described, the kidney may be the seat of a number of others which, owing to their great rarity or because they only exceptionally develop into large tumors, give rise to no disturbances and possess very little practical interest. These neoplasms are:

1. **Fibroma and Fibromyoma.**—The former are small whitish,

very hard nodules, ranging in size from that of a lentil to that of a pea, seated usually at the base of the pyramids, more rarely in the cortex around the blood-vessels, and containing in their interior the remains of uriniferous tubules. They occur in otherwise perfectly healthy kidneys, or as the concomitants or sequelæ of a chronic interstitial nephritis, and contain in addition to connective tissue a few smooth muscle fibers (from the muscle fibers which are normally present in the medullary substance?). Such muscle fibers are abundant in the *fibromyomata* which originate in the renal capsule; they develop much more vigorously and produce larger tumors (O. Busse[1]). There appears to be only 1 case (that of Wilks[2]) in which a neoplasm of the kidney, consisting in the main of fibrous tissue, made itself manifest as a tumor during life, ten years before the individual's death.

2. **Osteoma** and **chondroma** are said by Rayer[3] to occur occasionally in the kidney. They are exceedingly rare, and owing to their small size produce no symptoms whatever.

3. **Myxoma,** also exceedingly rare, has been described by Bezold[4] and H. Schlüter.[5]

4. **Lipoma** of the kidneys is not to be looked upon as extremely rare; and *lipomyoma*, which contains smooth muscle fibers, is even more frequent. These tumors usually have their seat immediately below the capsule, where they form yellowish nodules, varying in size from that of a pea to that of a cherry-stone, and may be quite numerous, but do not interfere with the renal function. They are not to be confounded with the proliferation of fat which sometimes surrounds the entire organ and has its origin in the fatty capsule of the kidney (p. 335).

5. **Rhabdomyoma** occurs in the kidney and in the pelvis of the kidney, and may attain a size greater than that of an infant's head; clinically, it behaves like sarcoma of the kidney (Manasse).

6. **Angioma,** described by Rayer[6] and by Virchow,[7] who state that it occurs coincidentally with similar tumors in the liver. It has no clinical significance.

[Yet possibly some of the idiopathic hemorrhages from the kidney may have their origin in angioma-like masses of vessels near the papillæ, as Fenwick[8] describes.—Ed.]

7. **Lymphoma** and (8) **gummatous nodules** (syphiloma) likewise have no clinical significance. The former occurs quite frequently in leukemia and the latter very rarely in syphilis in adults and in hereditary syphilis, along with similar changes in other organs. Gummatous nodules rarely attain a sufficient size during life to form a recognizable tumor or to produce symptoms that could be utilized for purposes of diagnosis. According to E. Welander,[9] on the other hand, "gummatous nephritis" manifests itself by the evacuation of a dirty-brown, tur-

[1] *Virchow's Archiv.* clvii.
[2] *Path. Soc. Trans.*, xx., p. 224.
[3] *Loc. cit.*, p. 666.
[4] *Virchow's Archiv.*, xxxiv., p. 229.
[5] Diss., Greifswald, 1890.
[6] *Loc. cit.*, p. 612.
[7] *Die krankhaften Geschwülste*, iii., p. 397.
[8] *Loc. cit.*
[9] *Arch. f. Dermatol. u. Syph.*, xxxvii.

bid urine containing a small quantity of albumin, blood- and epithelial casts and a great deal of detritus, and by the presence of gummatous affections in other organs; the condition is said to yield to specific treatment.

9. **Adenoma,** which in its purest form presents nodules ranging in size from that of a pea to that of a walnut, occurs in healthy kidneys or in kidneys the seat of chronic inflammation (see p. 269), but does not produce any disturbances. As has already been pointed out, however, numerous transitional forms between adenoma and cancer, as well as mixed forms representing both, also occur (see p. 392).

The **mixed forms,** which represent most of the other neoplasms, are difficult to classify in any one category. They are especially frequent in childhood and create the same clinical phenomena as carcinoma and sarcoma, from which they can only be distinguished with difficulty. According to Wilms, they owe their origin to the presence of a germ of embryonal tissue endowed with the faculty of developing into the various constituents (of tumors), just as the tissues of the body are developed from the ovum. According to this view, the origin of mixed tumors in the kidneys is to be referred to mesodermal cells in the region of the primitive kidney, from which the tumor elements belonging to the primitive segment, the mesenchyma, and the muscle plate, including, therefore, the glandular constituents, develop. The occurrence of epidermoid structures would seem to indicate the dislocation of embryonal germs at an even earlier period, when they still contain the anlage for the epithelium of the external germinal layer.[1]

RENAL CONCRETIONS.

(Concretions of the Kidneys.)

LITERATURE.—1. *Uric Acid Infarcts.*—Cless, *Würtemburg. Correspondenzbl.*, 1841, No. 15. Schlossberger, *Arch. f. prakt. Heilk.*, 1842, p. 576, and 1850, p. 545. R. Virchow, *Gesammelte Abhandl.*, p. 845. E. Martin. *Jena. Ann.*, 1850, ii., p. 126. Hodann, *Der Harnsäure-Infarct*, etc. *Verhandl. der schlesischen Gesellschaft f. vaterländ. Cultur*, Breslau, 1855. J. Parrot, *Arch. gén. de méd.*, 1872, ii., p. 169. W. Ebstein, *Die Natur u. Behandl. der Harnsteine*, Wiesbaden, 1884, p. 62. Kossel, *Zeits. f. physiol. Chem.*, vii., p. 7. Horbaczewski, *Wien. akadem. Sitzungsberichte*, 1889 and 1891. H. Spiegelberg, *Arch. f. exp. Path.*, xli., 1899. E. Schreiber, *Zeits. f. klin. Med.*, xxxviii., 1899. S. B. Wermel in *Casper and Lohnstein's Monatsber. f. Urologie*, 1901, vi.

2. *Calcium Infarcts.*—R. Virchow, his *Archiv*, viii., p. 103, and ix., 1856. Litten, *Zeits. f. klin. Med.*, ii., p. 483, and *Virchow's Archiv*, lxxxiii. Paltauf, *Wien. med. Woch.*, 1888, No 25. Neuberger, *Arch. f. exp. Path.*, etc., 1890, xxvii. Kobert and Küssner, *Virchow's Archiv*, lxxviii. A. Fränkel, *Zeits. f. klin. Med.*, ii., p. 664. Leutert, *Fortschr. der Med.*, 1895, No. 3.

3. *Pigmentary Infarcts.*—E. Neumann, *Arch. der Heilk.*, 1867, viii., p. 170, and xvii., 1876. Orth, *Virchow's Archiv*, 1815, lxiii.

4. *Renal Calculi.*—Robinson, *A Complete Treatise of the Gravel and Stone*, London, 1754. Marcet, *An Essay on the Chemical History and Medical Treatment*, etc., London, 1817. W. Prout, *Inquiry into the Nature and Treatment of Gravel, Calculus*, etc., London, 1821. Ph. v. Walter, "Ueber Harnsteine," in *Walter and Gräfe's Jour. f. Chi.*, 1820, i. Magendie, *Recherches physiologiques et méd. sur les causes de la gravelle*, Paris, 1827. Grosse, *On Urinary Calculus*, London, 1835.

[1] Wilms, *loc. cit.*, ii.; *Die Mischgeschwülste der Vagina*, etc., 1899.

Civiale, *Traité de l'affection calculeuse*, Paris, 1838; German ed., Berlin, 1840; and *Traitement méd. et préservatif de la pierre et de la gravelle*, Paris, 1840; German ed., Berlin, 1840. Bence Jones, "Remarks on the Calculi," in *St. George's Hosp. Med.-Chi. Trans.*, xxvi., 1843. H. Meckel v. Hemsbach, *Mikrogeologie*, Berlin, 1856. Heller, *Die Harnconcretionen*, etc., Wien, 1860. Oldfield, "Etudes sur les calculs du rein," *Thèse*, Paris, 1863. H. Thompson, *Clinical Lectures on the Urinary Organs*, London, 1868. S. Gee, "A Case of Renal Calculi," *Med.-Chi. Trans.*, lvii., 1874. M. Seligsohn, "Zur Casuistik und Theorie der oxalsäuren Concrementbildungen," *Virchow's Archiv*, lxiv., 1874. Krüche, "Ueber Structur und Entstehung der Uratsteine," *Diss.*, Jena, 1879. Ultzmann, *Die Harnconcretionen*, etc., Wien, 1882. C. Posner, *Centralbl. f. die med. Wissenschaften*, 1885, No. 15. L. Beale, *Urinary and Renal Derangements and Calculus Disorders*, London, 1885. E. Pfeiffer, *Verhandl. des* V. *Cong. f. inn. Med.*, Wiesbaden, 1886, p. 444, and *Berlin. klin. Woch.*, 1890, No. 24. C. Posner and H. Goldenberg, "Zur Auflösung harnsaurer Concretionen," *Zeits. f. klin. Med.*, xiii., 1888. W. Ebstein, *Die Natur u. Behandlung der Harnsteine*, Wiesbaden, 1884. The same, *Beiträge zur Lehre von der Harnsäure-Diathese*, Wiesbaden, 1891. W. Ebstein and Nicolaier, *Ueber experimentelle Erzeugung von Harnsäuresteinen*, Wiesbaden, 1891. Dieselben, "Ueber die Ausscheidung der Harnsäure durch die Nieren," *Virchow's Archiv*, cxliii., 1896. E. Golowin, "Ueber die Behandlung der Nierensteinkrankheit," *Petersburg. med. Woch.*, 1891, No. 48. A. Biesenthal, and Alf. Schmidt, "Piperazin bei Gicht- und Steinleiden, *Berlin. klin. Woch.*, 1891, No. 52 and 53. M. Mendelsohn, "Ueber Harnsäurelösung," etc., *Berlin. klin. Woch.*, 1893, Nos. 16 and 34. The same, "Therapie der harnsauren Diathese," *Verhandl. des XII. Cong. f. inn. Med.*, Wiesbaden, 1893. The same, *Deutsch. med. Woch.*, 1895, No. 18. Prochnow, "Beiträge zur Kenntniss der Harnsteinbildung," *Wien. med. Woch.*, 1892, Nos. 5 and 6. C. Greene, "Crystalline Deposits in the Urine," etc., *Boston Med. Jour.*, May and June, 1894. O. Kula, "Ueber den kohlensauren Kalk in Harnsteinen," *Wien. med. Woch.*, 1893, No. 52, and 1894, Nos. 1 and 5. P. Güterboek, *Die chirurg. Krankheiten der Nieren*, iv., 1898. L. Spiegel, "Ueber die Zusammensetzung der Nierensteine," *Berlin. klin. Woch.*, 1900, No. 27. C. Posner, "Ueber Harnsteine," *ibid.*, Nos. 44 and 45. J. Israel, *Chirurg. Klin. der Nierenkrankh.*, Berlin, 1901. Schmorl, "Zur Kenntniss der Harnconcremente," *Verhandl. der Deutsch. Path. Gesellschaft*, iv., 1902.

The normal or abnormal slightly soluble constituents of the urine may under certain conditions be excreted and deposited in the kidneys either in the form of a fine or coarse granular powder or of larger concretions. This process, which is called "*lithiasis*" (urolithiasis, nephrolithiasis), and the morbid phenomena to which it gives rise, were known to the physicians of antiquity (Hippocrates, Galan, Aretaeus, and their followers); in fact, constituted the greater portion of their knowledge of kidney diseases. Galen believed that there was a relation between lithiasis and gout, a view that was later especially defended by Sydenham.

Some light was thrown on the nature and origin of urinary calculi when Scheele, in 1776, discovered that they were composed chiefly of uric acid, which he also recognized as a normal urinary constituent. Following this discovery, Bergmann demonstrated the presence of calcium phosphate in renal calculi, Fourcroy and Vauquelin that of calcium oxalate, Wollaston discovered cystin, and finally, Marcet, xanthin. These discoveries gave a scientific basis and a new direction to the studies of the etiology of the disease and to the efforts of therapeutists which has been retained to the present day, and in quite recent times the treatment of nephrolithiasis received a new impetus by the introduction of operative procedures for the removal of the stone.

When the deposition takes place within the uropoietic parenchyma

of the kidney, in the uriniferous tubules, the concretion is known as an "*infarct*"; when it is found in the urinary passages at any point from the pyramids downward, it is known as a true *concretion*, and, according to the size, as *renal sand*, *gravel*, or *calculus*. Depending on their composition, the infarcts are known as *uric acid*, *calcareous*, and *pigmentary infarcts* of the kidney.

1. **Uric Acid Infarct.**—This form occurs in the *newborn* and in *gouty patients*.

(*a*) *Newborn infants* which have died during the first weeks of life present in about one-half the cases linear areas in the medullary substance, of a golden-yellow or yellowish-red color, becoming more abundant and brighter toward the pyramids and more scanty and delicate toward the cortex. These stripes, which were first described by Cless, are found on microscopic examination to consist of minute spheric bodies, situated chiefly in the collecting tubules and occasionally, according to Ebstein, also in the tubules of the cortex. Their chief constituent has been shown by Schlossberger to be uric acid.

This uric acid infarct is found more frequently in weakly, than in vigorous, children; but, on the other hand, is more common in children who were born alive than in the stillborn. It has also been found in the fetus during the last months of intra-uterine life, and cannot, therefore, as was formerly believed, be regarded as a sign that life had existed. Flensburg[1] believes that there is an albuminous exudate in the uriniferous tubules of newborn infants, around which, as a nucleus, the uric acid (which, according to Sjökvist, is combined with ammonia) is deposited. These deposits enter the urine and may be found, after centrifugation, in the form of infarct casts usually during the first half of the first day, rarely later than the sixth day. E. Schreiber's[2] explanation of the infarct is that the epithelium of the uriniferous tubules, which is particularly delicate in the newborn infant, is destroyed by the uric acid, which is secreted in great abundance and forms the framework for the deposit.

The large percentage of uric acid in the urine of newborn infants is possibly due to the changes that take place in the infantile organism immediately before and after birth and which are associated with great destruction of cells. According to the views of the present age, the alloxur bodies, and especially uric acid, are the derivatives of nuclein, and formed whenever nuclein-containing tissue—that is to say, cells—are destroyed in great numbers. The formation is even more abundant in the presence of destruction of leukocytes, which, according to Horbaczewski, are present in particularly large numbers in the blood of newborn infants. It is possible that certain other circumstances also contribute to the abundance of uric acid in the urine. It is at least noteworthy in this connection that, according to the experiments performed by H. Spiegelberg,[3] newborn dogs, after the injection into the

[1] *Nordiskt. Med. Arkiv.* See *Virchow's Jahresbericht*, 1895, ii., p. 207.
[2] *Zeits. f. klin. Med.*, xxxviii.
[3] *Arch. f. exp. Path.*, etc., xl.

blood of uric acid, secrete more of the substance in their urine than do adult animals.

The fact that uric acid infarcts are found chiefly in the medullary substance is no proof that they are formed in that portion of the kidney. It is more probable that the uric acid is washed down along with the organic ground-substance by the urine from the uriniferous tubules higher up, particularly the convoluted tubules, and deposited there as the fluid becomes inspissated probably by the absorption of water.

If the infant lives and develops into a vigorous child, the infarct disappears as the secretion of urine from the kidneys becomes more abundant. When, however, the secretion of urine is scanty, as in debilitated and ill-nourished children, especially such as suffer from vomiting or diarrhea, the urinary stream is not sufficiently abundant to dissolve or wash away the deposited masses, and they may remain for a variable time after birth and probably become the starting-point for calculi during childhood.

(*b*) *Adults* suffering from gout or so-called uric acid diathesis, even without any gouty changes in the joints, not infrequently develop uric acid infarcts, which appear in the pyramids as linear white deposits, consisting of lance-shaped or rhombic crystals of sodium urate, which on the addition of acetic acid allow the uric acid to separate in the characteristic whetstone crystals. The formation of these infarcts is related to the metabolic changes which occur in acute gout, and when they are found independently of any articular disease, the condition, according to Ebstein,[1] should be designated as "primary renal gout."

2. **Calcium Infarct.**—This is found most frequently in persons of advanced age and in any condition in which the blood, owing to resorption from the bones, is flooded with calcium salts, and metastatic deposits of calcium take place. It is quite frequent after poisoning with *bichlorid of mercury*, and occurs also after poisoning with *phosphorus*, *alum*, and *bismuth* (Paltauf and Neuberger), and in a few cases of *infectious diseases*.

The deposits occupy chiefly the pyramidal portion and, in the case of poisoning, the cortical layer as well; in the former situation they form white linear deposits, and in the latter an irregular collection of dots. Under the microscope the infarcts appear as amorphous, strongly refracting masses, occupying the interior of the straight uriniferous tubules or of the collecting tubules after the manner of casts. They may also be deposited in the form of granular collections in the membrana propria of the tubules and in their epithelial lining, as well as in that of the convoluted tubules and in Bowman's capsules, and are readily dissolved in acids, sometimes with the formation of gas. They consist of *calcium carbonate* or *calcium phosphate*. After poisoning with oxalic acid, deposits of *calcium oxalate* have also been found in the epithelial cells of the cortical and medullary tubules, as well as free in their interior (Kobert and Küssner and A. Fränkel).

[1] *Die Natur u. Behandl. der Gicht*, Wiesbaden, 1882, p. 155.

As Litten and Leutert have shown, calcium may be produced as the result of interference with the nutrition of the epithelium (after ligation of the renal arteries or poisoning). The cells become loaded with calcium derived from the blood, break down, and form calcium casts. Unless the calcification is extensive there is no functional disturbance; in severe cases the deposits may offer a mechanical obstacle to the excretion of urine, which is probably already diminished by the coexisting injury to the renal parenchyma.

3. **Pigmentary Infarcts.**—Pigmentary infarcts consist of hematoidin or bile pigment (*hematoidin or bilirubin infarcts*), and occur in icterus neonatorum, frequently in association with uric acid infarcts. The pigment is precipitated in the form of granular or rhombic plates from the bile pigment, with which the blood is overloaded, deposits itself in the interior of the collecting tubules as far as the apices of the papillæ, as well as in the epithelial cells, and even in the interstitial tissue. *Hemoglobin infarcts*, consisting of hemoglobin or methemoglobin, are also found in the medullary substance in hemoglobinuria, under which head they have already been referred to (p. 190).

The three forms of infarct here referred to do not produce any perceptible disturbances, and therefore have no special clinical significance.

4. **Renal Calculi.**—Under this name are included all those concretions which form outside of the true renal parenchyma, but not in the bladder—that is, in that portion of the urinary apparatus which, beginning with the papillæ, includes the calices, the pelvis of the kidney, and the ureters. As many renal calculi do not produce any morbid phenomena until they reach the bladder, it is impossible to make a hard-and-fast distinction between renal and vesical calculi.

Different terms are employed according to the size of the concretion. The most minute, which practically form a powder, are known as *renal sand;* stones as large as the head of a pin, or a millet seed at the most, are known as *renal gravel;* and all other stones as *renal calculi* in the narrow sense of the word.

The urinary constituents found in calculi (besides sand and gravel) are *uric acid*, *oxalic acid*, *calcium phosphate* and *carbonate*, and the corresponding salts of *magnesium* and *ammonium*, more rarely *cystin* and *xanthin*, and very exceptionally *indigo*. As a rule, the calculi contain a mixture of these substances, especially of the first-named; but as one or the other usually predominates, they are known as "uric acid, oxalate or phosphatic calculi," etc. A number of other accidental foreign bodies besides blood-clots and coagula of mucus may form the nucleus of the deposits.

ETIOLOGY AND PATHOGENESIS.

Calculi may appear at any *age*, but their frequency at different periods of life is quite variable. Considering renal *calculi* as defined above, the disease appears to be most common during the period of life between thirty and sixty, childhood and adolescence showing a much

smaller incidence. On the other hand, vesical calculi are comparatively more common in early childhood than in later life, until after the age of fifty, when they again become more frequent, a difference first correctly pointed out by Civiale. There may possibly be some causal connection between the remarkable frequency of vesical calculi in early childhood, up to the seventh year of life, and the occurrence of uric acid infarcts in the newborn.

The male *sex* is affected much more frequently than the female at every period of life, a difference which is no doubt due to the greater ease with which a concretion may pass through the shorter and wider female urethra. The same structural peculiarity, on the other hand, renders the conditions unfavorable for the occurrence of stagnation, which favors the development and growth of calculi in the bladder.

Heredity and *family predispositon* undoubtedly play an important rôle so far as the formation of *cystin calculi* is concerned, and also, although to a lesser degree, in the formation of *uric acid stones*. As regards the latter disease, the influence of heredity is shown both by the fact that calculous disease is directly transmitted and by the frequency of its occurrence in *gouty* families, although the association of the two conditions—gout and calculous disease—are not especially frequent in one and the same individual. The relations between gout and calculi were known as early as the time of Galen, and attention has since then been called to this relation by numerous experienced physicians (Morgagni, Sydenham, van Swieten, Scudamore, and others), and in quite recent times especially by H. Thompson.

Although gravel is not unknown in any region of the earth, certain countries—in fact, certain circumscribed districts—are remarkable for the frequency with which the disease occurs. According to A. Hirsch,[1] the continent of Asia heads the list in this respect. Africa, Mauritius, Réunion, and lower Egypt are the chief countries affected. In Europe, central Russia, especially the upper basin of the Volga, Holland, and Italy; in Germany, a limited portion of the Duchy of Altenburg and the region between Munich and Landshut in the Suabian Alps, the right bank of the Danube, and several districts in Hungary; the eastern and southern portions of England and Scotland, the western regions of France, Canada, etc. [In the United States renal calculus appears to be fairly evenly distributed over different parts of the country.—Ed.]

The greater frequency of calculous disease in certain regions has been attributed to *climatic influences*, especially dampness, and to *geologic conditions*, particularly the presence of *calcium* in the soil and in the *drinking-water* derived from the same. But it appears that this view, as A, Hirsch has shown by comparing all the facts that enter into the problem, is not well founded. J. Dsirne entertains a similar opinion, which he bases on observations made in various portions of the Russian empire.

The traditional view that the mode of life and diet, especially an abundant nitrogenous diet with wine and beer, coupled with insufficient

[1] *Handb. der histor-geogr. Path.*, 2d. Ed., 1886, iii., p. 319.

exercise, plays an important rôle in the production of calculous disease, does not appear to tally with the actual conditions, at least in a general sense. For, as has been remarked above, vesical calculus, on which most of the statistics are based, is most frequent in early childhood and in old age. In the case of children, it appears from the experience of physicians in every land, without exception, that it is the poorer portions of the population that furnish by far the greater number of patients with stone; while in old age most of the cases are from the well-to-do and wealthy classes. But there could hardly be a sharper contrast between the mode of life and diet of these two classes, the children of the poor, on the one hand, and the wealthy adults on the other. It is true that the calculi in the two classes of patients have a different composition; in the case of children they consist chiefly of uric acid and calcium oxalate, and in the older patients, of phosphates; and for that reason the origin of the former might be attributed to the insufficient food, poor in albumin, and the latter to the abundance of nitrogenous food with no lack of alcoholic beverages. But this again contradicts the current view that uric acid calculi are the fruit of too great an abundance of albuminous food and of a luxurious mode of life.

In short, the problem is not so simple, and the influence of *mode of life* and *diet* is not uniformly applicable in the etiology of every case. It is possible that in the case of adults the causes which are usually blamed for the condition—namely, an abundance of albuminous food, indulgence in alcoholic beverages, especially dry (sour) wines, and a sedentary mode of life—play a certain part; but *in children* these factors are of no moment whatever. The *uric acid calculi* which occur in children probably, as has already been intimated, bear some relation etiologically to the uric acid infarcts present at the time of birth; and in the case of uric acid calculi in adults or of *phosphatic calculi* with *a nucleus of uric acid*, excessive indulgence in albuminous food, especially food that is rich in cellular material, may be of some importance in view of the theory advanced by Horbaczewski (p. 406).

Local causes that favor calculus formation, for mechanical reasons, are *foreign bodies* in the kidneys, such as parasites (distoma), blood-clots, and shreds of tissue, because these substances furnish a nucleus around which the precipitate may deposit itself. In this way an injury may possibly be of some etiologic significance; but it probably happens more frequently that the effect of an injury first brings out the symptoms caused by an already existing stone.

In order that the calculus may be formed from the urine, two conditions are necessary. In the first place certain constituents must separate from the solution, just as in the case of *sedimentation* outside of the body, and there must be some *connecting medium* to thicken the precipitated particles and hold them together so as to form a *concretion out of the sediment.*

Sedimentation, of course, depends on the *reaction* of the urine, its *concentration*, and especially its *composition*. *Acid* urine never deposits the earthy salts of phosphoric and carbonic acids, the so-called *phos-*

phates; on the other hand, uric acid is readily precipitated from an *acid* urine. Ultzmann believes that the peculiar thorn-apple shape of the uric acid crystals is a favoring factor of calculous formation, because the sharp corners and points of the crystals readily adhere to the calices or pelvis of the kidney and irritate the mucous membrane. Acid urine also promotes the precipitation of *oxalates.*

Alkaline or *neutral* urine, on the other hand, precipitates the phosphates and, if the urine has undergone ammoniacal decomposition, the so-called triple phosphates (phosphates of ammonium and magnesium) as well. As conditions that favor the decomposition and alkalescence of the urine are much more frequently present in the bladder than in the kidneys, it is readily understood that phosphatic calculi are found preferably in the bladder and only exceptionally in the renal pelvis (for instance, in cases of pyelitis or phosphaturia), and that the *nucleus* of most vesical calculi, which is formed by a concretion that has been washed down from the kidneys, consists of *uric acid* or *oxalate,* while the phosphates subsequently deposit themselves around this nucleus on account of the alkalinity of the urine.

Cystin is found as a sediment in acid urine. *Xanthin* is soluble both in alkalies and in acids; hence there is nothing to be said about the influence of the reaction on the production of xanthin calculi, which in general are very rare. This substance is found in small quantities in almost all forms of calculi.

As regards the formation of the still rarer *indigo calculi,* it is probable that it is favored by ammoniacal decomposition of the urine.

It is needless to say that the *concentration* of the urine, or excess of the relatively insoluble constituents, especially uric acid, assists in the precipitation of such substances.

As regards the *composition* of the urine—that is, the character of its constituents—and its effect on the formation of a sediment, it is to be remarked that substances capable of holding other constituents in solution may be absent or diminished, while conversely certain other substances which favor the precipitation may be present in larger quantities, or finally the urine may contain some entirely new substance which acts as a precipitating agent.

The precipitation from the urine of uric acid particularly, which is the most important factor in the formation of renal calculi, is explained by the fact that the neutral sodium urate (disodium urate) which it contains under normal conditions combines with the *alkaline phosphates* of the urine and gives up all or part of its sodium, leading to the formation of insoluble monosodium urate (biurate), the triple acid salt (quadriurate), and finally free uric acid. The occurrence of this decomposition appears to depend on the proportions of the simple acid and double (acid) phosphates in the urine, for the preponderance of the latter seems to favor the precipitation of uric acid.

According to G. Klemperer,[1] the presence of *urochrome* is partly responsible for the urine containing uric acid in supersaturated solution.

[1] *Verhandl. des XX., Cong. f. inn. Med.,* 1902.

It is therefore quite conceivable that diminution of this pigment might contribute to the precipitation of uric acid.

Finally there are certain *acids*—for instance, lactic acid—that are present as foreign substances in the urine under abnormal conditions and may cause a precipitation of uric acid.

To the question as to what conditions govern the changes in the composition of the urine, the excess or diminution of certain substances, and the appearance of new substances, the present state of our knowledge does not permit more than a general answer, to the effect that these phenomena depend ultimately on certain nutritive disturbances or metabolic changes which may have their origin in the digestive organs or in abnormally lowered activity of other organs, including the kidney, and of the blood. These metabolic changes, in so far as they lead to the precipitation of uric acid or oxalic acid, are referred to the *uric acid* or *oxalic acid diathesis*, and were formerly supposed to be associated with an overloading of the blood and of the body juices with these substances, which in turn was attributed to retarded metabolism, and more particularly to diminution of the oxidative processes. But when oxidation is actually diminished by cutting down the ingestion of oxygen, the blood is not found to be at all overloaded with these substances, nor are they excreted in larger quantities in the urine, or if they are, it is due to some other cause. Nor has uric acid or oxalic acid been found in abnormally large quantities in the blood of individuals with calculi containing these acids. On the other hand, an excess of uric acid has been found, although not regularly, in cases of leukemia, chronic nephritis, chronic lead-poisoning, and gout. Although there is a certain etiologic relationship between gout and calculous disease, which has already been referred to (p. 409), yet the very fact that uric acid and oxalic acid calculi are so common in children in whom gout is very exceptional would seem to show that the two diseases are not simply due to the same change in the blood or body juices, not to mention the recent finding that the same quantities of uric acid may be present in the blood in other diseases as in gout.

All that is known in regard to uric acid metabolism appears to point, as has already been mentioned, to the *nuclein-containing* tissues, especially *leukocytes*, the decomposition of which leads to an increase of the uric acid. Whether excessive decomposition of leukocytes really takes place in the subjects of uric acid calculus, and if so in what situation, is a problem which remains for future investigation, and will require a special study of the *digestive organs* and of *the lymph glands*. *Digestion leukocytosis*, according to Horbaczewski, has an important bearing on the increase of uric acid, and it is quite conceivable that any *disturbance of the normal digestive processes* might lead to an excessive decomposition of the newly formed leukocytes and the increased formation of uric acid. On this theory a connection might also be established between other *diseases of the lymph glands* and the overloading of the blood with uric acid.

The generally accepted view that uric acid is a product of the decomposition of nuclein bodies is contradicted by Hopkins and Hope,[1] who assert that the excretion of uric acid is increased by administering thymus extract entirely freed from nuclein, and that no increase takes place when the animal is fed with large quantities of pure nuclein and nucleo-albumin. It appears, then, that other constituents of the thymus gland have some effect on the processes. According to these authors leukocytosis increases the formation of uric acid only when a great deal of nitrogenous food is ingested at the same time.

For the present we shall have to be content with this suggestive treatment of the pathogenesis of the uric acid dyscrasia and its probable connection with the formation of uric acid calculi. It may, however, be pointed out in justification of the theory that calculous disease is quite frequently accompanied or preceded by *digestive disturbances* and, on the other hand, that among the children of the poor, who furnish such a large contingent of the cases, *scrofulosis* is widespread and has been regarded by various observers (Meckel, v. Hemsbach, and others) as an etiologic factor.

In connection with the question of the influence of *digestive disturbances*, the writer may mention an instructive case reported by Eichhorst.[2] A boy, who up to that time had been perfectly healthy, had an atypical attack of renal colic, followed by the evacuation of uric acid calculi immediately succeeding an attack of vomiting and diarrhea. It is, of course, quite conceivable that the calculi may have been present before and became loosened and expelled as the result of the general shaking-up attendant on the act of vomiting.

As for *oxalate calculi*, and the increased formation or excretion of oxalic acid, the writer refers the reader to what he has said under the head of Oxaluria (p. 74). The frequent occurrence of oxaluria in children is explained by the fact that milk, which is comparatively rich in calcium and poor in magnesium, forms the chief constituent of children's food.

When we come to the second condition for the formation of calculi—the presence of a *connecting medium*—it is a matter of long experience that soft and sticky substances of any kind, such as *blood-clots, small masses of mucus* or *pus, particles of tumor*, frequently constitute the center and nucleus around which the urinary constituents deposit themselves. *Foreign bodies*, such as pieces of catheter, hairs, and the like, may appear in the same rôle, especially when catarrh of the mucous membrane or of the urinary apparatus is present or is produced by such foreign bodies. The occurrence of nephrolithiasis in *diseases of the spinal cord* is in all probability also attributable to the catarrh of the urinary passages. In most of these cases the calculi consist of phosphates.[3] Schmorl[4] found as a regular constituent of the concretion *bacteria* (Bacterium coli) embedded in a framework of albuminous material. Finally, it has been shown by H. Meckel and Reyer[5] that the *ova of distoma hæmatobium* may make their way into the kidneys and become the nuclei of renal stones.

[1] *Jour. of Physiol.*, 1899, xxiii., 4. [2] *Deutsch. med. Woch.*, 1895, No. 48.
[3] *Cf.* K. Müller, *Arch. f. klin. Chi.*, L., and H. Schlesinger, *Wien. klin. Rundschau*, 1901, No. 41. [4] *Verhandl. der Deutsch. Path. Gesellschaft*, iv., 1901.
[5] *Wien. med. Woch.*, 1856, No. 14.

It is evident that in all these cases the organic cellular detritus forms a kind of cement substance which holds the constituents of the sediment together. Fourcroy and Vauquelin pointed out this organic or "animal" foundation of renal calculi. Later Meckel v. Hemsbach made a study of these organic, non-crystalline, colloid foundations of calculi, especially of oxalate calculi, and believed that they possessed a considerable influence on the formation of stone. The primary and essential condition in the process he believed to be a specific catarrhal inflammation which he called "stone-forming catarrh," accompanied by the excretion of colloid pellets of mucus, to which the oxalate particles adhered as they became deposited. He thought the uric acid contained in the calculi was derived from the oxalic acid—*i. e.*, he regarded it as a secondary product, like the secondary deposition of phosphates around the original oxalate stone. Ebstein, however, was the first to show that while this observation of Meckel's is quite correct as regards the organic framework of all calculi, the process is not always caused by a well-marked specific catarrh, but may be due in a general way to inflammatory irritation of the urinary passages and of the renal parenchyma itself, which furnishes the necessary protoplasm for the framework.[1]

[The influence of bacteria in inducing a catarrh of the pelvis with "stone building" as a result, would seem not improbable when one remembers the part played by bacteria in the production of gall stones. It seems not unlikely that in a somewhat similar way bacteria may at times be responsible not alone for serving as a nucleus about which urinary concretions form, but that they may so alter the chemical composition of the urine that sedimentation occurs more readily in the pelvis of the kidney as well as in the bladder.—ED.]

Even in *cystin calculi* Ebstein found an organic foundation, although it is less abundant than in other forms. The first condition for the formation of cystin calculi is the existence of *cystinuria*, in the causation of which heredity or family predisposition plays an important part, while the second condition is an inflammatory irritation of the urinary passages. The cause of the cystinuria is unknown.

Whether *xanthin* and *indigo calculi* also possess an organic framework has never been made the subject of investigation, but its existence in these calculi also can hardly be doubted.

PATHOLOGIC ANATOMY AND CHEMISTRY.

Renal concretions are subject to very great variations as regards number, size, and composition. As a rule, the number is inversely proportional to the size; thus, while the smallest, which are designated *sand* and *gravel*, may be discharged with the urine or found in the kidney by the hundred, the number of the larger concretions, stones in the narrower sense of the term, is usually limited, and mostly varies

[1] Regarding this, *cf.* E. Schreiber, *Virchow's Archiv*, cliii., and Ebstein, *Naturwissenschaftl. Rundschau*, 1900, xv.

between 1 to 15 or 20, although in exceptional cases it may reach 50 or 100 or even more. Gee once found nearly 1000 concretions in the pelvis of the right kidney in a man thirty years of age. The calculi are more frequently found in one kidney only; according to Morgagni, more in the left than in the right, and are usually seated in the calices or in the pelvis, where they may attain a large size and become very numerous, or the stones may lodge in the ureters. They adapt themselves to the shape of these localities, and accordingly may be spheric, oval, or cylindric, or if they grow into and occupy several calices, may have an irregular, branched or stellate shape; the central mass in the pelvis of the kidney sends out branches into the calices, like the antlers of a stag. Calculi with circular central openings, allowing the urine to flow through, are also found. Genuine so-called renal calculi may attain the size of a nut or that of a hen's egg. One of the largest is probably the one found by Gee in the above-mentioned case, along with many other smaller ones; it weighed 36¼ oz. (1088 gm.).

The color, the character of the surface, and the consistence depend mainly on the composition of the stone; and when the kidney contains several these characteristics are, as a rule, identical in all of them, and only exceptionally present any differences.

The commonest renal calculi are those which consist chiefly or wholly of *uric acid*, usually with some sodium and ammonium urate and a small quantity of xanthin. The large quantity of coloring-matter which they contain gives them a yellowish, reddish-brown, or brick-red appearance, the surface is smooth or slightly irregular, and when there are several present in close proximity to one another they may be faceted. The stones are hard, crack readily when cut, and the cut surface presents a fairly regular concentric arrangement of alternating dark and light rings. Scrapings examined under the microscope appear needle-shaped or lance-shaped; they dissolve readily in caustic potash, and on the addition of acetic acid crystallize into the well-known barrel and whetstone forms. On heating with nitric acid and adding ammonia, the familiar murexid test is obtained, the purple color of which changes to violet on the addition of caustic soda. Small quantities of calcium oxalate are not infrequently mixed with the uric acid calculus, and if the urine undergoes stagnation and ammoniacal decomposition, the stone is apt to be covered with a crust of phosphates.

Oxalate stones consisting of calcium oxalate are next in frequency to the uric acid calculi, but are found more frequently at operations, because the symptoms to which they give rise are more marked and appear earlier. They are generally of a dark-gray, almost blackish color; the surface is mammillated like a mulberry, and they are harder and heavier than uric acid stones. They almost always contain also uric acid or xanthin and calcium carbonate, and when cut through with a saw the concentric rings are accordingly alternately dark and light. Oxalate calculi are readily recognized by their insolubility in acetic acid and their solubility in mineral acids, from which, on the addition of ammonia, the familiar octahedral crystals of calcium oxalate separate.

Phosphatic calculi, which consist in the main of calcium phosphate and ammonium-magnesium phosphate with frequently small quantities of calcium carbonate and xanthin, are rare in the kidneys, and when present are usually quite small. The phosphatic salts more frequently form the outer layer of other calculi, especially uric acid calculi. Both the formation of a phosphatic calculus and the incrustation with phosphate of a calculus of another kind presupposes an alkaline reaction of the urine within the kidneys, a condition that is usually due to the ammoniacal decomposition which takes place in pyelitis or pyelonephritis, or in rare cases, in the absence of these conditions, when an excessive quantity of alkaline carbonates or salts of the vegetable acids is taken with the food. Phosphatic calculi are whitish or grayish in color, and softer and lighter than either uric acid or oxalate calculi. The stones or crusts of phosphate surrounding other secretions are readily dissolved in organic acids. They contain a great number of *microparasites*, especially such as either cause or accompany the decomposition of urine. Sometimes they contain at their center a small quantity of decomposed urine.

Calculi consisting of *calcium carbonate* are rarely found in human kidneys, they resemble phosphatic calculi in their behavior, except that when they are dissolved by the addition of acids effervescence takes place. Calcium carbonate is found most frequently in calcium oxalate and in phosphatic calculi.

Cystin calculi are also very rare in the kidneys and attain at most the size of small peas. They are smooth, yellowish in color, waxy in appearance, and quite soft and light. They are soluble in alkali and in acids; but they can be dissolved out of an ammoniacal solution with acetic acid, and form hexagonal plates; they are also characterized by the presence of a large quantity of sulphur.

The literature contains so far but 10 cases of *xanthin calculi*, all of which were found in children (Marcet, A. Langenbeck, Laugier, Heyfelder, Taylor, Hoppe-Seyler, Lebon,[1] Garnier[2]). The surface is smooth, and the color yellow or yellowish-brown to cinnamon-brown. The stones are hard and give the characteristic xanthin reaction—*i. e.*, when a solution in nitric acid is evaporated a lemon-yellow residuum remains, which strikes a red color on the addition of caustic potash. Small quantities of phosphates or oxalates or uric acid were found in all these xanthin calculi.

So far as the writer knows only 3 cases of *indigo calculi* have been described (W. H. Ord,[3] Chiari,[4] and Forbes[5]). In addition to a nucleus consisting of organic material and phosphates, they contained bluish or blue-gray scaly deposits, which gave the reaction of indigo-blue and indigo-red, particularly sublimation in purple vapors.

A. Peipers[6] described so-called *albumin calculi* which he found in

[1] See Ebstein, *Die Natur u. Behandl. der Harnsteine*, p. 11.
[2] *Arch. de physiol. norm. et path.*, 1884, No. 6.
[3] *Berlin klin. Woch.*, 1878, No. 25.
[4] *Prager med. Woch.*, 1888, No. 56.
[5] *Med. News*, Aug. 18, 1894.
[6] *Münch. med. Woch.*, 1894, No. 27.

contracted kidneys with cyst formations, and which consisted of a nucleus of uric acid covered with a deposit of an albuminous substance. A kidney stone composed chiefly of *sulphur* was described by J. Israel.[1]

The name *urostealith* was used by Heller to designate concretions consisting of fatty substances, and found by him and others in the urine or in the bladder (Moore,[2] Boyer,[3] Krukenberg,[4] Horbaczewski[5]). These concretions are soft or like rubber, and burn with a smoky flame. According to Horbaczewski's analysis, they contain 85 per cent. of substances soluble in ether, consisting partly of free fatty acids and partly of neutral fat and traces of cholesterin, 12 per cent. of other organic bodies, 0.8 per cent. of mineral substances, and 2.5 per cent. of water. Krukenberg in his case recognized the fatty substance as paraffin, from a paraffin pencil which the patient had used as a bougie; he is probably correct in his surmise that most of the urostealiths described have a similar origin.

The *pathologic changes* found in nephrolithiasis are *primary*—that is, those which precede and favor the formation of stone—and *secondary*, or those which are produced by the presence of the calculus. The former include *inflammations of the pelvis of the kidney and of the calices* (pyelitis), which, if the process goes on to pus formation and ammoniacal decomposition of the urine, lead to the deposition of *phosphates* in the pelvis and, together with the mucus and the pus, furnish the organic framework for the concretion. It is possible that *inflammatory conditions of the renal parenchyma* may also be primary, and the resulting disintegrated epithelium may form the framework for the stone, especially for *uric acid calculi*. It has been shown by Ebstein and Nicolaier that the flooding of the kidneys with uric acid may be followed by the development of a chronic inflammatory condition, and it is therefore not impossible that renal calculi may be formed in this way.

The *secondary* inflammation of the pelvis of the kidney, and of the renal tissue as well, which is known as *calculous pyelitis* and *pyelonephritis*, and which is due to the irritation of the stones, is much more common and is followed by all the consequences of these affections, which have already been described (p. 340)—*i. e.*, an *ascending interstitial nephritis* or a *hydro-* or *pyonephrosis*—which in these inflammatory and congestive conditions due to calculous formation may attain a high degree of severity and may give rise to considerable swelling of the kidneys. Purulent pyelitis and pyelonephritis may, as has also been stated, either by direct extension or by rupture and discharge of the pus, lead to inflammation of the surrounding tissue (peri- and paranephritis —see page 439) and to pyemic infection.

Occasionally the ulcerations which develop after nephrolithiasis give rise to cancer.

In *unilateral nephrolithiasis*, when the destruction of parenchyma in the affected kidney has reached a certain point, the remaining kidney

[1] *Chir. Klin.*, etc., p. 276. [2] *Dublin Quarterly*, March, 1854.
[3] *Progrès méd.*, 1877, No. 1. [4] *Chem. Unters. zur Wissenschaftl. Med.*, 1888, ii., p. 239.
[5] *Zeit. f. physiol. Chem.*, xviii.

frequently undergoes hypertrophy, and the heart also may exhibit compensatory hypertrophy. Quite frequently, however, the other kidney is also diseased, either from the presence of concretions or from inflammatory changes, and especially from amyloid degeneration following long-continued suppuration.

SYMPTOMATOLOGY.

The symptoms produced by the concretions themselves, aside from the sequelæ of the condition, are purely mechanical, and are due partly to *obstruction* of some portion of the urinary apparatus and partly to *injury* or to *irritation* caused in the mucous membrane of the urinary apparatus by the concretions. The presence and severity of symptoms therefore depend on the seat and size of the stones, especially the size in proportion to the passages which they have to traverse, and on the nature of their surfaces. It is evident, therefore, that in the papillæ of the kidneys even the smallest concretions, no larger than renal sand or gravel, may cause grave symptoms, while the pelvis may harbor a larger stone for a long time without creating any symptoms, particularly when it has a smooth surface—in fact, not any until the stone gets into the ureter. Accordingly, it is not very uncommon to find at the autopsy renal calculi in the pelvis of the kidney, which had not betrayed their presence during life; or sand and gravel, or even a small stone may be voided in the urine when no sign of nephrolithiasis had been present beforehand. The larger the concretions and the rougher and more irregular the surface, the more likely they are to cause disturbances.

The symptoms of *obstruction* at some point in the urinary passages from the papillæ down to the bladder consist of *pain*, which varies in intensity, and when the obstruction takes place *suddenly* may assume the character of an intense renal colic, and in protracted cases the signs of urinary stagnation, *hydro-* or *pyonephrosis;* irritation or laceration of the renal mucous membrane may lead to *hemorrhages* or to *pyelitis.*

Fenwick[1] asserts that the presence of a stone in the *cortical substance* produces pain only *at a certain definite point,* and that the urine for years—twenty or more—remains normal. When the stone is seated in the *medullary substance,* the pain is either fixed or radiating as in colic; the patient is often unable to sleep unless he lies on the affected side, and the urine contains only microscopic traces of pus and blood.

True *renal colic* occurs, in the great majority of cases, when a stone is wedged fast in the ureter, and takes place either quite suddenly or after a considerable prodromal period, during which the patient suffers from sacral and lumbar pain and a sense of pressure in the region of the kidneys. Quite frequently the attack of colic is brought on by a definite cause, such as a severe shaking-up in horseback-riding or driving, or by an error in diet, especially indulgence in alcoholic and other beverages that stimulate the flow of urine.

[1] *Brit. Med. Jour.*, February, 1896.

A typical attack begins with a violent cutting and pressing pain in the lumbar region, radiating in various directions, most frequently toward the bladder and uretha, or into the perineum. The pain often radiates to the testicle on the same side, which is usually drawn upward by the contraction of the cremasteric muscle. The pain may also extend upward into the chest and shoulder. The patient bends over toward the painful side and tries to obtain relief by compressing the lumbar region and the abdomen with his hands. [The radiation of the pain of renal colic along the course of the ureter toward the testicle and penis is so classic and has become so firmly fixed in the minds of physicians as the typical manifestation of renal calculus that these other radiations to the thighs, chest, or shoulder, etc., are apt to be taken as indicating some condition other than renal stone. On the right side especially the radiation to the shoulder and scapular region is easily misinterpreted as indicative of gall-bladder disease. Attention to other points, however—the examination of the urine, the detection of local tenderness, etc.—will usually clear up the diagnosis. Particularly perplexing are the rare cases in which pain is referred to the side opposite the calculus. The *x*-ray will here be of material aid in locating the stone.—Ed.] The attack is attended by various reflex phenomena, such as chills, followed by sweating, frequent desire to urinate, vomiting, and, during the beginning of the attack almost involuntary defecation, which is replaced later by obstinate constipation. In very severe attacks the patient goes into collapse, the face becomes ashy pale and lifeless, the pulse is small, the extremities are cold, and in exceptional cases the attack may end in death.

The *urine* passed during the attack is scanty notwithstanding the frequent desire to urinate, and varies in composition, depending on the degree of obstruction in the ureter and the condition of the remaining kidney. When the ureter is completely occluded by the stone, the urine obtained is all derived from the other kidney, and may be perfectly clear and normal; on the other hand, when the occlusion is incomplete, the urine is turbid and contains an admixture of blood, mucus, and pus. In some cases of unilateral obstruction complete *anuria* has also been observed, probably as the result of reflex angiospastic ischemia of the other kidney, causing a temporary cessation of its function (*reflex anuria*, see p. 163). Complete anuria also occurs when both ureters are occluded by calculi, or in unilateral obstruction when the other kidney is functionally or actually absent. If the anuria last several days, the result usually is a fatal *uremia;* but in exceptional cases anuria has been known to last two or three or even four weeks without uremia developing (J. Russel,[1] Gangolphe,[2] and others.

When the ureter is completely occluded the corresponding *kidney swells*, but during violent attacks of colic, especially at the beginning of the attack, the severe reflex tension of the abdominal walls is so marked that it is rarely possible to recognize the renal enlargement distinctly except under anesthesia.

[1] *Med. Times and Gaz.*, November 27, 1880. [2] *Lyon méd.*, 1892, No. 4.

The attack of colic usually lasts several hours—rarely one to two days—and exhibits fluctuations in intensity which may possibly depend on the intermittent progress of the stone. As soon as the stone has been dislodged, usually by passing from the ureter into the bladder, the pain and all the other phenomena disappear at once and a large quantity of urine is voided which is still more or less turbid and contains gravel, and not infrequently the cause of the attack—namely, the stone which had been wedged fast; sometimes, however, the latter remains in the bladder. [The stone may, of course, drop back into the pelvis, and cause colic once more whenever it again becomes lodged in the ureter.—Ed.]

After an attack of colic, and in the intervals between the attacks, pain and other morbid symptoms may be altogether wanting and the patient may present the picture of perfect health, especially in the early period of the disease. But in other cases the patient, even though he has no attacks of true colic, may complain of all kinds of symptoms, such as dull pain in the lumbar region, increased by the agitation of the body incident to coughing or sneezing, and radiating in all directions. The pain is extremely variable, disappears at times, then again increases in intensity and practically resembles a mild attack of colic, and it is needless to say that every degree of severity between the latter and the most violent renal colic may be experienced. [Should the next attack of colic be on the opposite side, one must remember that calculi may be present in both kidneys, and not be too ready, on account of the bilateral pains, to exclude stone in the kidney as the cause of the attacks because of the rarity of this combination.—Ed.]

These pains or painful sensations which torture the patient more or less constantly are usually due to the presence of very large stones or of a large number of small stones in the pelvis of the kidney, or to stones with very irregular, jagged surfaces. The periodicity and changes in the intensity of the pain may be caused by movements of the stone, which is not necessarily wedged fast, and its pressure against the inflamed and irritated mucous membrane, alternating with periods when the stone is loosened by the flow of urine or by a change in the position of the body.

Other symptoms, caused by *pyelitis* and its results, which rarely fail to develop when the disease lasts any length of time, have been minutely described elsewhere (see p. 340). The most important of these sequelæ are *hydro-* and *pyonephrosis*. In a protracted case with repeated attacks of colic, the distention of the kidney and the loss of parenchymatous tissue, on the one hand, may be so great, and the emaciation of the patient from the pain and loss of albumin, on the other hand, attain such a degree, that the calculi can be felt by palpation through the thin, emaciated abdominal walls, as the writer himself observed in one case.

Before pyelitis has developed—that is, in the beginning of the disease, or when there are no large, rough, and jagged stones in the kidney, but only a little gravel or sand—the *urine* may at times be quite normal, and at other times, especially before, during, and after an attack of colic,

the above-mentioned changes may be present; or finally the urine may contain a large admixture of *blood*.

Hematuria may also occur in connection with an attack of colic, or independently of such an attack and unattended by symptoms, or only with very slight disturbances produced by the evacuation of blood-clots. Simple, profuse hematuria the result of erosion of small blood-vessels by a sharp stone is apt to occur in the beginning of the disease, rarely during its later course, when the urine, in addition to blood, which may be present periodically or constantly, usually contains signs of secondary pyelitis or cystitis. [Microscopic examination of the urine, even when there is no renal colic, will often show blood and give a valuable hint as to the presence of stone. The examination is especially likely to reveal blood after running, jumping, riding, or after rather violent manipulation of the kidney during the process of examination by the physician. —Ed.] During the later period the *general condition* of the patient is usually much impaired by the development of sequelæ and complications, especially chronic cystitis and vesicular calculi, and he is menaced by all the dangers that result from these disturbances. On the other hand, if these complications do not develop, the patient may retain his strength and nutrition as well as his efficiency for some time, except for the occasional occurrence of colic.

COURSE, DURATION, AND TERMINATION.

It follows from the above description of the symptoms that the course of nephrolithiasis is almost always chronic and presents a great many irregularities. It is very rare for a single attack of colic to take place and terminate with the evacuation of one or more stones without repeating itself sooner or later. In most cases the disease lasts a number of years and exhibits great fluctuations. Long intervals, during which the patient's health is fairly good or even excellent, are suddenly interrupted by attacks of colic and by exacerbations of the general condition, which at first are of short duration and, if the disease runs a favorable course, cease altogether, or in other cases become gradually longer and more obstinate, depending on the development and severity of the sequelæ that have so often been referred to—pyelitis, pyelonephritis, and cystitis.

Complete recovery is not a very unusual termination, but it can be expected only when the disease is recognized early, and especially when the sequelæ referred to do not develop at all or only in a very mild degree, and so long as only one kidney is the seat of the disease. Even after complete recovery, however, a tendency to relapse remains.

When the sequelæ have developed and have attained a certain degree of severity, the patient falls into a condition of illness which ends in death from loss of strength or from pyemia, uremia, or ammoniemia. In very rare cases death occurs in an earlier stage of the disease, as the result of and *during an attack of colic*, either in *collapse* from the intense reflex effect on the nervous centers of the heart and respiration, or in

uremic intoxication when *anuria* persists, or from *laceration* of the ureter with secondary peritonitis.

DIAGNOSIS.

The diagnosis of nephrolithiasis is positive and quite easy when the urine contains concretions the origin of which is clearly shown to be the kidney by the nature of the stones (uric acid) or the previous occurrence of a characteristic attack of renal colic. If there is any suspicion of lithiasis, therefore, the urine must always be systematically and repeatedly examined. If the urine is not sufficiently clear to allow the concretions or sediment to be easily recognized after a specimen has been allowed to stand, the urine should be strained through a fine sieve reinforced by a piece of gauze.

A suspicion of renal calculi is usually first aroused by the occurrence of *pain in the region of the kidneys*, especially a pronounced *renal colic* and *renal hemorrhage*, and later by the symptoms of *pyelitis* and *pyelocystitis*. When taken together these phenomena are strongly in favor of renal calculi, but the diagnosis can only be a probable one, because some, rarely all of them, may be the result of other diseases, such as neoplasms and abscesses, as has been remarked in connection with these subjects (see pp. 393 and 307), and with pyelitis (p. 344).

Of all the symptoms, *renal colic* has the greatest diagnostic value, especially when it occurs suddenly in the midst of otherwise perfect health. Typical renal colic is far more frequent in nephrolithiasis than in any other condition. But it may be produced, although more rarely, by other foreign bodies that have become wedged fast on the way from the kidney to the bladder, as, for example, particles of tumor, blood-clots, or entozoa; and there are cases of renal colic of purely nervous origin—in other words, true *neuralgia of the kidneys*—which has been described in another place (p. 145). These cases, as has recently been learned by exposure and examination of the kidneys, which is now done quite frequently, cannot be excluded with certainty when the remaining symptoms referred to are absent, or even when one or the other—for example, hematuria—is present in addition to the colic. *Hereditary predisposition* (see Etiology, p. 408) possibly is of some weight in favor of renal colic. In most cases an exploratory incision of the kidney will be found necessary.

Other difficulties in the way of the diagnosis are found in cases of *movable kidney* and attendant hydronephrosis, conditions which are also apt to give rise to attacks of renal colic (see pp. 138 and 359); the difficulty in these cases may sometimes, but not always, be removed by examining the urine.

Sometimes the diagnosis can be assured or, at least, materially assisted by *transillumination of the kidney region with Röntgen rays;* if the concretions are not too small they may be recognized by the shadow they form. The method proves most successful with oxalate calculi, and least so with phosphatic calculi. A great deal appears to depend

on the length of time transillumination is kept up and on other technical conditions. At all events a negative result does not prove the absence of stones.

[The value of the *x*-rays in locating stone in the kidney has passed beyond the experimental stage. Properly used the Röntgen rays will nearly always show a shadow when a stone is present. A failure with a stone present is likely to be an error in technic on the part of the operator. When a stone seems revealed by the skiagraph, confirmation should be sought by a second exposure, to avoid any possible error due to artefact. When with good negatives—and it is better to examine the negative than the print—no stone is found, one may be reasonably safe in excluding a calculus. Experience is, of course, necessary in interpreting what one sees in a negative. A good negative for the detection of a stone in the kidney should show, according to Albers-Schönberg[1]: (1) the transverse processes of the vertebræ; (2) the last two ribs clearly; (3) the outline of the psoas muscle. When, with these structures showing plainly, no stone is found, the evidence that none is present may be regarded as strong.

There are certain liabilities to error even with positive findings. Thus, in a man with several attacks of pain, regarded by his physician at one time as appendicitis, at another as renal colic, pyuria and hematuria led to the use of the Röntgen rays for probable stone. Two shadows, looking as though thrown by stones in the ureter—*i. e.*, rather low down for the kidney—were distinctly shown in each of two exposures. Operation was undertaken, old appendicitis with firm adhesions to the ureter and neighboring structures was found, and the concretions, the size of small beans, were in the mesenteric veins—*i. e.*, were phleboliths. One was removed for examination. This source of error is rare but worth remembering. The occurrence of hematuria and pyuria from appendicitis, either from a rupture of the appendicular abscess into the ureter or from an involvement of the ureter in the inflammatory process, with edema, exudation, etc., should be remembered as a confusing element in diagnosis that should, if possible, be ruled out before deciding upon a diagnosis of stone.—Ed.]

The *diagnosis of renal colic* as such—that is, its distinction from attacks of pain that have nothing to do with the kidney and emanate from other organs—is, of course, of the highest importance. Aside from diseases in the neighborhood of the kidney that are easily recognized, the conditions that must be considered in this connection are *intestinal colic*, especially in *appendicitis*, *ovarialgia*, *hepatic colic*, and *gall-stone colic*. The latter two varieties, especially in the absence of jaundice, cannot always be excluded with certainty, and the thickened vermiform process cannot always be distinguished from a thickened or contracted ureter. [The gastric crises of tabes must also be considered, for they occasionally resemble renal colic—and more closely—gall-

[1] Albers-Schönberg *Die Röntgentechnik;* see also Leonard, *Ann. of Surg.*, 1901 and 1903; J. F. Smith, *Chicago Med. Recorder*, April 15, 1904; Kümmel and Rumpel, *Beiträge zur klin. Chi.*, 1903, vol. xxxvii.

stone colic. And it is always to be remembered that a patient with renal stone may have more than this disease; he may have gall stones as well, or an ulcer of the stomach or a pleurisy producing the pain, etc.—Ed.] Painstaking examination, if necessary under anesthesia, careful weighing of the objective and subjective symptoms, of the etiologic factors, and of the origin and course of the disease, will lead the physician on the right track in many cases, but will not always guard him from errors which can be recognized only by operative interference.

If the operation is to consist in removal of the kidney, the presence and functional power of the remaining kidney must be ascertained with certainty, a precaution that has already been referred to on various occasions (pp. 311 and 351). As a rule, this can be ascertained by keeping the patient under observation for some time and by resorting to cystoscopy and ureteroscopy and collecting and examining separately the secretion coming from each ureter.

PROGNOSIS.

During the beginning of the disease, and so long as no sequelæ are present or present only in a very mild degree, the prognosis as to life is not unfavorable, as the stones themselves are not dangerous, and even the gravest symptoms that they produce—renal colic and renal hemorrhage—only in exceptional cases are so severe as to threaten the patient's life. But when pyelitis and cystitis have developed, and especially when the parenchyma of the kidney is involved, and pyelonephritis, hydro- and pyonephrosis are present, the patient's health, on the one hand, is undermined by the suppurative process, the hemorrhages and the attacks of pain which may be constant or repeated at short intervals, and, on the other hand, these diseases may give rise to conditions that are an immediate menace to life, such as uremia, ammoniemia, rupture and discharge of the pus, and the like.

As regards *recovery*, the prognosis from the beginning is, to say the least, doubtful, because even in the most favorable cases, when the disease is completely arrested by treatment, a tendency to relapse remains, especially in those cases in which there is an hereditary predisposition. The greater the duration of the disease, the more unfavorable the prognosis in this respect—*i. e.*, as regards the possibility of recovery or improvement. Finally, it is almost needless to point out that the prognosis depends not a little on our ability to influence the cause of the disease—for instance, the patient's mode of life.

TREATMENT.

The prevention of nephrolithiasis may become the duty of the physician when the development of a stone is to be feared on account of the existence of a pronounced *hereditary* or *family predisposition*, and in regions in which the disease is endemic. In the latter case the drinking of water, although its influence is very doubtful, would have to be

forbidden, and the question of early removal from the region would need to be considered; in the former case the physician has at his disposal only those means which are available for the treatment of the disease itself.

As regards treatment, the *causal indication* is fulfilled by keeping within bounds the formation within the body of substances that lead to stone and their accumulation in the kidneys, by measures intended to regulate metabolism; the *indicatio morbi* is to dissolve already formed concretions or to remove them from the kidneys just as they are. In accordance with the variable nature of stone formation a variety of methods must be adopted to influence metabolism and bring about the solution of the stone, while the remaining indications may be met in the same way in every case of nephrolithiasis by stimulating diuresis and flushing out the kidneys or by operative intervention.

In the case of those renal calculi which in frequency surpass all the others, the *uric acid calculi*, it has been the custom since antiquity to institute strict dietetic treatment, prohibiting above all an abundant meat diet, especially dark meats, and according to some authorities any kind of animal food (Magendie), as well as the drinking of spirituous liquors, and advising instead a diet consisting chiefly or even exclusively of vegetables or the drinking of copious draughts of water, and insisting on plenty of all kinds of exercise. This treatment was no doubt prompted by the experience that, in adults at least, uric acid calculi develop as the result of a luxurious mode of life, especially from indulgence in meat and spirituous liquors, coupled with indolence and sedentary habits. There is no doubt that in many cases this treatment has proved very successful, and later, when physicians became used to regarding uric acid as an unfinished product of albumin metabolism, a residual substance not yet oxidized to form urea, the treatment appeared to gain a sound theoretic basis. This theory, however, as has already been explained (pp. 406 and 412), has now collapsed, since it has been found that the formation of uric acid varies in different individuals between wide limits, and in amount is certainly not so much dependent on the food as was formerly believed.

Nothing but the ingestion of nuclein-containing substances has an unmistakable influence on its production, while it does not appear from the investigations that animal food (meat) produces more than a relative increase in the uric acid—that is, an increase corresponding to the quantity of nitrogen ingested; while in regard to the influence of other foodstuffs, such as fats and carbohydrates, opinions are divided (S. Herrmann,[1] Dapper,[2] Rosenfeld and Orgler).

Kionka[3] succeeded in producing in chickens, by a protracted course of feeding with meat, sodium urate deposits in the joints, on the serous membranes, and within the uriniferous tubules, as well as diffuse nephritis.

At all events the injurious effects of an albuminous diet, especially a meat diet, have been exaggerated in the past; and even if it were

[1] *Deutsch. Arch. f. klin. Med.*, xliii., p. 273. [2] *Berlin. klin. Woch.*, 1893, No. 26.
[3] *Berlin. klin. Woch.*, 1900, No. 1.

true that it caused an increase in the *formation* of uric acid, it may possibly stimulate the *excretion* of the acid in the urine, perhaps because *urea*, which is formed in abundance, as Friedrich [1] and G. Klemperer [2] have shown, is an efficient diuretic.

It is therefore with good reason that the *absolute* prohibition of albuminous foodstuffs and meat has been abandoned in recent times, although the foods containing a large quantity of nuclein, especially thymus, spleen, liver, brain, and kidney, fish roe, and possibly caviare, should be excluded from the diet. Meat extracts, strong tea and coffee, and asparagus, which tend to increase the quantity of uric acid in the urine, must also be avoided.

Unless, therefore, some special reason exists for a different course, a mixed diet including a moderate quantity of meat, but excluding highly seasoned, smoked, and pickled articles that might irritate the kidney, is to be recommended. In order to free the meat from extracts as much as possible, it should be boiled. *Milk*, which contains paranuclein and not nuclein, may also be recommended in large quantities, as there is no fear of its increasing the excretion of uric acid ; the same is true of *eggs*, especially the white of eggs. Other articles that may be permitted are ordinary mild cheese, jellies made with *gelatin*, and if a larger quantity of albumin is desirable in order to strengthen the patient, the artificial albuminous foods like tropon, eucasin, and especially those made from vegetable albumin—aleuronat and roborat.

Sugar and saccharin as well as strongly *farinaceous* foods, as well as *fat*, except in the form of butter, which may be allowed in moderate quantities, are regarded as injurious. *Fruit*, on the other hand, is to be recommended with confidence, and in the so-called fruit cures (grapes, strawberries, lemons) is sometimes ordered in large quantities.

Strong alcoholic beverages are to be forbidden unless they are indicated *medicinally* on account of debility.

It is impossible to give hard-and-fast rules to be followed in the making up of a diet list ; the general nutritive condition of the patient, and particularly the state of the digestive organs and the habits of life, must be allowed a certain influence.

Exercise in the open air, gymnastics of every kind suitable for the special conditions of the individual case, are to be recommended, if only for general reasons of hygiene, and are doubly indicated in those whose occupation forces them to a sedentary mode of life.

Dietetic treatment may be supplemented by the systematic employment of *warm baths*, especially mineral baths. The benefit of these baths probably depends, aside from the favorable influence which they exert on metabolism in general, on the increased diuresis and diminution in the acidity of the urine which follow their use, and on the fact that by their continued employment the excretion of uric acid is reduced, as appears to be shown by E. Pfeiffer's experiments with the Wiesbaden waters.

In order to increase the dissolving power of the urine for uric acid

[1] *Wien. med. Ztg.*, 1891, No. 35. [2] *Berlin. klin. Woch.*, 1896, No. 4.

alkalies in the form of carbonates or salts of the vegetable acid (citrates and acetates)—the latter of which are converted into carbonates in the organism—*alkaline earths*, and *lithium salts*, which are midway between the two, are employed. The latter have been especially recommended by Ure and Garrod,[1] because the combination of uric acid with lithium is much more soluble than its combination with any other alkaline earths or alkalies. But aside from the opposition raised by M. Mendelsohn against the equivalence of the chemical conditions and reactions inside and outside of the body, lithium salts are given in such relatively small quantities that their action in this respect must be exceedingly slight, so small as to be practically negligible. It is more probable that the action of all these alkaline remedies depends chiefly on their effect in reducing the acidity of the urine and changing it to a neutral or alkaline reaction; and, secondly, on their more important diuretic properties, by virtue of which a thorough flushing out of the body, and especially of the kidneys, is achieved. As, according to Mendelsohn,[2] the lithium salts, especially the citrate and acetate in doses of 0.1 to 0.2 gm. (2–4 gr.), given several times a day, possess a marked diuretic action, their use is justified on that account alone.

The alkaline earths, at least *calcium*, according to J. Strauss,[3] possess the faculty in a marked degree of diminishing the excretion of the monosodium phosphate; or, in other words, to influence the relations between monosodium phosphate and bisodium phosphate in such a way as to enable the urine to hold in solution a larger quantity of uric acid and at the same time to maintain its acid reaction (see p. 411). Kionka's observation, that the deposition of uric acid was diminished by the use of calcium in the chickens that he had rendered artificially "gouty," is also in favor of the efficiency of the substance (see p. 425). A knife-pointful of *calcium carbonate* given several times a day in Seltzer water is a simple and very efficacious remedy.

The use of alkalies and alkaline earths in nephrolithiasis is of very great antiquity. They form the chief constituents of most of the prescriptions of old, as well as recent, times, except that nowadays we use, instead of impure natural products and various mixed compositions, such as crude potash, egg-shells, and shells (bivalves), soap with all kinds of additions, the chemically pure bodies either singly or in composition with one another. The best of this series of composite bodies is Stroschein's *uricedin*, which consists of sodium and lithium citrate, sodium sulphate, and sodium chlorid, and which, prescribed in the dose of 1 gm. (15 gr.) several times a day in water, often proves very useful.

The salts of the *alkaline earths* are to be preferred to the salts of true alkalies, especially in cases in which, in addition to the presence of gravel or stone, there is catarrh of the urinary passages, pyelitis, and cystitis. In addition to *lime water*, which may be employed in the manner described in the section on the treatment of pyelitis (see p. 350), *magnesia borocitrica*, which appears to have been used by Paracelsus,

[1] *Med. Times and Gaz.*, March, 1873. [2] *Deutsch. med. Woch.*, 1895, No. 45.
[3] *Zeits. f. klin. Med.*, xxxi.

is an excellent remedy that has recently been again recommended by Köhler;[1] it should be taken as a powder, according to the following prescription: Magnesiæ borocitricæ, 50 (about 1½ oz.); sacchari albi, 100 (about 3 dr.); olei citrici, 1 (15 gr.).—M. S.: One teaspoonful three times a day in sweetened soda water.[2]

For continued use or as efficient adjuvants to the above-mentioned remedies, the *alkaline* and *alkaline earthy mineral waters* are most suitable. In many respects they fulfil the same indications even better than the salts themselves, since, when they are taken systematically during a "cure," large quantities of water are regularly introduced into the body and bring about a thorough dilution of the urine. They can be taken for a long time without upsetting the stomach, and an additional advantage, which is not to be underestimated, is that patients are more willing when they are at a watering-place to follow dietetic and hygienic directions than at home. Unless other indications are present in the digestive or in the respiratory apparatus, as, for example, constipation or bronchial catarrh, the *earthy saline carbonated waters*, especially Wildungen, Rudolfsquelle in Marienbad, Contrexéville, particularly when pyelitis or cystitis is also present; or the simple alkaline carbonated waters, such as Assmannshausen, Bilin, Fachingen, Neuenahr, Obersalzbrunn, Offenbacher Kaiser Friedrichquelle, Radein, Salvatorquelle, Vichy, Vals, and if pyelitis or cystitis is also present, the earthy saline carbonated waters of Wildungen (George Victor- and Helenenquelle) and Contrexéville. In addition to these quite a number of other springs may be used, and may even be preferable to those already named, in the presence of complications, such as catarrh of the respiratory or of the gastro-intestinal mucous membrane or, what is more common, disease of the urethra, gout, hemorrhages, etc. In such cases Carlsbad, Mergentheim, Kissingen, Ems, Wiesbaden, and many other springs may be useful, the choice depending on a number of other conditions, such as the use of baths and a variety of minor considerations.

Instead of natural mineral waters, *artificial substitutes* may be used with very good success, especially such preparations as are intended to combat the uric acid diathesis and gout; for example, Struve's "Lithionwasser," Ewich's "Natronlithionwasser," Mordhorst's "Gichtwasser." The main indication—to dilute the urine and diminish its acidity—is probably fulfilled equally well by all these different waters, and the secondary conditions prevailing at bathing-resorts, the complete relaxation and the constant living in pure air, with plenty of exercise, the observance of a proper diet, the systematic bathing and other physical methods of treatment, can be readily obtained in many good summer resorts.

The treatment with alkalies, alkaline earths, and the corresponding waters which has here been described should be kept up only so long

[1] *Berlin. klin. Woch.*, 1879, No. 44.

[2] The preparation known as *litholydium* (Dr. Zacharias), which is quite popular in Germany, is said to consist of magnesia, boric acid, citric acid, lithium, calcium, carbon, chlorin, and ammonia, and is taken by the teaspoonful in water.

as the reaction of the urine is acid, and must be discontinued as soon as the reaction becomes neutral or alkaline, on account of the danger of alkaline salts (phosphates) being precipitated from the urine and becoming deposited around an already existing stone, thereby increasing its size. But in those cases in which the urine is already alkaline as a result of decomposition, which is much rarer in cases of renal than of vesical calculi and occurs only in severe grades of chronic pyelitis, the *simple carbonated waters* as well as *carbonated chalybeates* (Apollinaris, Harzer Sauerbrunnen, Wernatzer, Elster, Franzensbad, Rippoldsau, etc.) should be ordered along with the remedies recommended above (see p. 350) for flushing out the kidneys, unless special indications demand some other course.

While the object in the employment of the above-named remedies—the alkalies and alkaline earths—is to increase the dissolving power of the urine for uric acid by diminishing its acidity and rendering it more watery, certain remedies have been recommended that are said to act as direct solvents of uric acid independently of the reaction and dilution of the urine. The most important of these, which was introduced by Biesenthal and Schmidt, is *piperazin*, which is given in doses of 1 gm. (15 gr.) daily in Seltzer water. The results obtained with this remedy, whose power of dissolving uric acid outside of the organism is unquestionable, are very variable. There is no doubt that it is surpassed as regards certainty of action by other more recent remedies. The same may be said of *glycerin*, recommended by A. Herrmann,[1] in doses of 50 to 100 c.c. (say 1.5–3 oz.). Personally the writer has seen the use of this remedy followed in one case by the discharge of gravel and also by a marked hematuria, and is therefore inclined to advise caution in its use, without, however, rejecting it altogether. Other remedies that have been recommended are *lysidin* (diethylenethenyldiamin), in the dose of 1 to 1.5 gm. (15–20 gr.) daily in Seltzer water, by E. Grawitz;[2] *lycetol* (dimethylpiperazin tartrate), in the dose of 1 to 2 gm. (15–30 gr.) daily in sugar water, by H. Wittzack;[3] *urea*, in the dose of 10 to 20 gm. in 200 c.c. of water (say 2.5–5 dr. in 6 oz. of water), 1 tablespoonful every two hours, by G. Klemperer;[4] and urotropin, 1 to 1.5 gm. (15–20 gr.), taken in one daily dose in water, by Nicolaier.[5] The last-mentioned remedy has the advantage that it does not affect the acid reaction of the urine and, in fact, inhibits ammoniacal decomposition; it probably deserves the foremost place among the remedies that are said to increase the dissolving power of the urine for uric acid. A drug that resembles it in this respect is *quinic acid*, which has been recommended by J. Weiss,[6] preferably in combination with lithium citrate as "*urosin*," given in tablets, 6 to 10 daily.

There are numerous combinations of the above-named remedies with one another, such as *sidonal* (piperazin quinate), 2 to 5 gm. (say .5–1 dr.)

[1] *Prager med. Woch.*, 1892, Nos. 47 and 48. [2] *Deutsch. med. Woch.*, 1894, No. 41.
[3] *Allg. med. Centralz.*, 1894, No. 7, and *Therap. Monatshefte*, 1894, No. 3.
[4] *Berlin. klin. Woch.*, 1896, No. 33.
[5] *Centralbl. f. d. med. Wissenschaft*, 1894, No. 51, and *Deutsch. med. Woch.*, 1899, No. 14. [6] *Berlin. klin. Woch.*, 1899, No. 14.

daily; *chinotropin* (urotropin quinate), 4 to 5 gm. (1–1.25 dr.) daily; *urol* (urea quinate), 1 to 3 gm. (15–45 gr.) twice daily; *citrurea* (a combination of urea, citric acid, and lithium bromate), 0.5 gm. (7 gr.) given several times a day; and *piperidinum tartaricum*, 0.6 to 1 gm. (10–15 gr.) three times a day. Each of these remedies has its defects, and they differ from one another, aside from the question of price, chiefly by the fact that some are better tolerated than others. They must therefore be used tentatively or changed from time to time, and even withdrawn altogether for a time, whenever the digestion begins to suffer. The best way to administer all of them is in Seltzer water or in one of the above-mentioned mineral waters.

The writer cannot forbear mentioning an old, purely empiric remedy which is frequently recommended from time to time, *tinctura urticæ urentis*, which should be given in the dose of 5 to 10 drops in water several times a day, and may possibly be of some use on account of its diuretic properties.

In the treatment of *oxalate calculi* the same dietetic and medicinal measures are to be recommended in the main as for oxaluria (see p. 76). As was stated in that place, the mineral waters containing calcium are to be avoided, and the so-called simple carbonated waters preferred. But as oxalic acid and uric acid are not infrequently found in association with one another, it is impossible to give definite directions for the choice of waters. As they all dilute the urine and flush out the kidneys —the two most important indications—they are all practically equal in value.

It was formerly and is even now sometimes recommended to dilute and dissolve *phosphatic calculi* and calculi consisting of *calcium carbonate*, which are rare in the kidneys, by the internal administration of mineral acids or of lactic acid (Cantani) or of carbonic acid—a hopeless undertaking, as the quantity that would be necessary either cannot be introduced into the body at all or, if it is introduced, does not reach the urine in its original form. If the kidneys are involved, the important indication in such cases also is to flush out the organs with as powerful a stream of urine as can be obtained, and to attain this end the *simple carbonated waters* are more to be recommended than the alkalies and strong alkaline waters, as they are only faintly alkaline and rich in carbonic acid; such waters are Apollinaris, Krondorf, the Wernatzer and Sinndorfer springs in Brückenau, the Richardsquelle in Königswart, Rohitsch, and Neudorf; or the *strongly carbonated iron waters* may also be recommended. If properly used the waters at Carlsbad, Wiesbaden, and other similar places, which are also diuretic, are also suitable, and finally the remedies recommended for phosphaturia (p. 79) and pyelitis (p. 350) may also be tried for the purpose of rendering the urine acid.

Xanthin stones may be treated in the same way as the uric acid stones, as there is very little difference between the two substances.

The presence of *cystin calculi*, which bear a certain relation to abnormal processes within the intestines, would require special attention to

any disturbances in the digestive system, and in addition, as in any case of lithiasis, direct flushing out of the kidneys. For both purposes the Carlsbad springs may be recommended.

Indigo calculi, supposing that the diagnosis were possible, would require chiefly the treatment of the complicating pyelitis and of any intestinal disturbances that might exist.

Among the symptoms and *sequelæ* of nephrolithiasis, *renal colic* most frequently calls for active interference at a very early stage of the disease. In cases of mild colic rest in bed with warm compresses and anodyne inunctions, or possibly continued hot baths, will prove sufficient. In more violent attacks the physician should not temporize with such uncertain remedies, but should proceed at once to the use of morphin, which is best given in a hypodermic injection, at least at first, although later, after the severity of the pain has been somewhat broken, the drug may be given by the mouth. If there is vomiting, it may also be given in the form of a suppository, 0.01 gm. (gr. $\frac{1}{6}$) with 1.5 gm. (say 20 gr.) of cocoa butter, or pure opium or extract of opium, 0.03 gm. (gr. $\frac{1}{2}$) to a dose, may be given. Tinctura opii simplex or, if there is any tendency to collapse, tinctura opii crocata may be given by the mouth or in an enema, 10 to 15 drops in 150 to 200 c.c. (5–6 oz.) of warm water or thin oatmeal, are also useful remedies; and for the purpose of inducing sleep, chloral hydrate by the mouth or through the rectum, and other hypnotics.

In rare cases, when twitching of the muscles or general convulsions complicate the clinical picture, it may be necessary to administer chloroform by inhalation, which also facilitates the expulsion of the stone that is wedged fast, by relaxing and contracting the ureter.

Aussilloux[1] recommends *olive oil* in tablespoonful doses for renal colic. It is said to act in the same way as in gall-stone colic.

Many patients find the *local application of cold*, in the form of cold compresses or an ice bag, more agreeable than heat, while the pain is violent. Cold is also to be preferred when there is profuse *hemorrhage* at the same time. In rare cases hematuria is so severe as to require other remedies. In such a case it would have to be treated like any other hemorrhage from the kidneys (as in renal carcinoma, p. 391). A slight degree of hematuria requires no special treatment, as it ceases with the dislodging of the stone and its entrance into the bladder. In order to facilitate this event it is well, if the state of the stomach permits, to administer the above-mentioned mineral waters during the attack of colic to stimulate diuresis; or one of the specific uric acid solvents which have been enumerated may be tried in order, at least, to diminish the size of the stone by melting off and breaking off some of the outside, even if the concretion cannot be completely dissolved.

It may also be mentioned that it has been proposed to remove the concretions *mechanically* by shaking the entire body, or, what would be preferable, the kidney alone by massage (tapotement) of the lumbar

[1] *Bull. de Thérap.*, 1893, No. 46.

region. The success of such a procedure, which may be extremely painful, is doubtful, and it might readily give rise to hemorrhage.

For the treatment of *pyelitis*, which often accompanies stone in the kidneys, the reader is referred to the corresponding section (p. 348).

If dietetic, hygienic, and medicinal remedies fail to remove the nephrolithiasis or even to diminish the disease to the point of toleration; if the patient has no interval of freedom from pain; or the pyelitis, owing to the severe suppurative process, attains an alarming degree or has even led to septicopyemic infection; if the patient has been brought to the edge of the grave by uncontrollable hemorrhages; and, finally, if his life is threatened by a persistent anuria, *operative interference* for the removal of the concretion or the relief of the obstruction is indicated. What this interference is to be, whether nephro- or pyelotomy or resection or extirpation of the kidney, will depend on the conditions of the individual case, and these frequently cannot be determined before operation. Diagnostic errors also must be reckoned with, as instead of the supposed nephrolithiasis some other renal affection, such as neoplasm or even an absolutely unrecognizable abnormality, has frequently been found (p. 146), and the other kidney may also be diseased and incapable of functionating, or only one kidney may have been present from the beginning.

In any case the first step is an exploratory incision for the purpose of exposing the kidney, the operator being prepared to shape his subsequent course by the result of the exploratory operation. When nephrectomy is to be performed, it has repeatedly been emphasized that the existence of a second kidney and its functional power must first be ascertained by methods that have been described elsewhere.

ENTOZOA AND VEGETABLE PARASITES OF THE KIDNEYS.

ANIMAL parasites rarely have their seat in the kidneys, and still more rarely possess any clinical significance. The only exceptions are the echinococcus in Germany (and other temperate countries) and the Distoma hæmatobium and Filaria sanguinis in certain tropic regions. All others, so far as known at present, are mere curiosities and accidental pathologic findings.

I. ECHINOCOCCUS.

LITERATURE.—Chopart, *Traité des maladies des voies urinaires*, i., p. 142. Rayer, *loc. cit.*, iii., p. 545. Lenepveu, "Considérations sur les fistules réno-pulmonaires," *Thèse*, Paris, 1840. Livois, "Recherches sur les échinocoques," etc., *Thèse*, Paris, 1843. Barker, *On Cystic Entozoa in the Human Kidney*, London, 1856. C. Bèraud, "Des hydatides des reins," *Thèse*, Paris, 1861. Spiegelberg, *Arch. f. Gynäk.*, 1871, i., p. 146. G. Simon, *Die Echinococcencysten der Nieren*, etc., Heidelberg, 1877. Frey, "Beitrag zur Lehre von der Tænia Echinococcus," *Diss.*, Berlin, 1882. Fr. Mosler, "Ueber endemisches Vorkommen der Echinococcenkrankheit," etc., *Deutsch. med. Woch.*, 1886, Nos. 7 and 8. P. Wagner, *Deutsch. Zeits. f. Chi.*, 1886, xxiv.; "Zur Operation des Nierenechinococcus," etc., *Centralbl. f. die Krankh. der Harn- u. Sexualorgane*, 1894, iv. Knie, "Nephrectomie bei

Echinococcus der Niere," *Petersburg. med. Woch.*, 1888, No. 37. F. R. Fairbank, "Retention of Urine from a Hydatic Cyst, *Brit. Med. Jour.*, May 31, 1890. Karewski, "Ueber Nierenechinococcsu," *Deutsch. med. Woch.*, 1893, No. 44. Manasse, *Centralbl. f. die Krankh. der Harn- u. Sexualorgane*, 1898, ix. See also F. Mosler and E. Peiper, "Thiesische Parariten," p. 99, furthermore, Neisser, *Die Echinococcenkrankh.*, Berlin, 1877, and the text-books on animal parasites, by Davaine, Küchenmeister, Leuckart.

ETIOLOGY AND PATHOLOGY.

Echinococci are the larvæ of Tænia echinococcus, and inhabit chiefly the intestine of the dog and of the fox. When the eggs of this parasite are eaten, the shells are dissolved by the gastric juice and the ova develop and enter the portal vain. They cannot reach the kidney, however, until after they have traversed the venous system and entered the right heart and have made their way from there through the pulmonary vessels into the arterial circulation. This explains why the kidneys are behind the liver and the lung as regards the frequency of echinococcus and occupy the third place among the organs affected. In Frey's collection the liver was the seat of echinococcus in 47 per cent., the lung in 12 per cent., and the kidney in 10 per cent. of the cases; Davaine found it in 30 out of 366 cases and Neisser in 80 out of 900. Vegas and Cranwell,[1] in the Argentine Republic, found among 970 cases of echinococcus the seat of the disease in the liver in 644, in the spleen in 30, and in the kidney in 20 cases.

In very exceptional cases the echinococcus enters the kidney through some channel other than the blood; thus, for example, by way of the suprarenal body, or, as in a case observed by C. Posner,[2] through a perforation from the liver to the right kidney.

The conditions that favor the introduction of the ova into the stomach are contact with dogs which harbor the parasite, and the ingestion of articles of food or the introduction of other objects polluted with the egg. Echinococcus is observed in the kidneys most frequently during the *third decade of life*, but it also occurs in children—29 of the 500 cases in Neisser's collection occurred in children under ten years. The oldest patient in whom the disease was observed was a woman seventy-five years of age. As regards *sex*, men show a slight preponderance; Béraud found the proportion to be 29 to 20 in favor of men.

In the last-mentioned collection only one kidney was the seat of the disease in 63 out of 64 cases, the left being attacked more frequently than the right in the proportion of 23 to 14. The tumor generally begins in the upper or lower pole of the kidney; according to G. Simon, usually in the cortex, rarely in the medulla, and, as a rule, grows toward the pelvis, following the line of least resistance; rarely, as in a case of Chopart's, the entire kidney is involved in the growth. Depending on the size of the tumor, the neighboring organs are more or less displaced and the corresponding side of the abdomen bulges. In all other respects, form and structure, it presents the same characters as

[1] Cited by *Berlin. klin. Woch.*, 1902, No. 14, p. 312.
[2] *Berlin. klin. Woch.*, 1898, No. 9.

in other organs, especially the liver, which is most frequently attacked by echinococcus. The number of echinococcus cysts also is as variable as in the case of other organs. Livois reports the case of a girl in whose kidney 133 cysts were found. The contents of the cysts, as a rule, do not differ from the contents of other echinococcus cysts, except that calcareous deposits are more common in the kidney cysts, which also contain occasionally as a special feature crystals of uric acid and other urinary salts.

The renal parenchyma immediately surrounding the echinococcus cysts is usually atrophic, while further away the tissue is in a state of chronic inflammation. When the cysts reach the capsule of the kidney they sometimes become adherent to adjoining organs and may discharge their contents into the latter. The most frequent mode of evacuation is into the pelvis of the kidney, according to Roberts in 52 out of 63 cases, although Henczynski[1] observed it in only one-half the cases. Pyelitis not infrequently develops at the same time.

Evacuation of the contents of the cysts is sometimes followed by atrophy and shrinking of the hydatid sac; but even when evacuation does not take place, the hydatids may die, and recovery may take place from shrinking of the cysts; or, finally, the sac may suppurate and rupture into the pelvis of the kidney or, exceptionally, into the intestine, or through the diaphragm into the pleura and the lungs (Lenepveu, Fiaux, Béraud), or the pus may form fistulæ in various directions (Turner)[2] or perforate the lumbar muscles and be discharged on the surface of the body (Rayer, Davaine).

In a few cases calculi have been found in the kidneys in association with echinococci (Parmentier);[3] when the parenchyma is greatly atrophied, the other kidney may undergo compensatory hypertrophy; and, finally, echinococci may be found at the same time in other organs.

SYMPTOMS, COURSE, AND TERMINATION.

The disturbances that may be produced by renal echinococcus are determined by the extent of the process and the nature of the sacs, whether they are closed or open, and in the latter case the direction in which they discharge their contents. It is obvious, therefore, that when the hydatid cysts are small and have no opening they produce no symptoms whatever, particularly as the functional loss due to the destruction of renal parenchyma is completely compensated for by hypertrophy of the remainder of the affected kidney or of its fellow.

Large cysts which distend the capsule cause *pain* in the region of the kidneys, and later a renal *enlargement*. The pain does not differ from that caused by other forms of renal enlargement, especially hydronephrosis, and if the cysts evacuate their contents into the pelvis and cause constriction of the ureter, the pain may assume the severity of renal colic. The distention of the abdomen and the bulging in the

[1] *Beiträge zur wissenschaftl. Med. Festschrif. f. Th. Thierfelder*, 1897.
[2] *Bull. de Thérap.*, 1848, p. 226.
[3] "Sur les abcès perinephrétiques," *Union med.*, 1862, No. 102.

lumbar region are also the same as in the case of other renal enlargements. When the abdominal walls are thin and the walls of the hydatids are not too thick, *fluctuation* may be felt, and even the so-called *hydatid fremitus* may be detected.

Unless some special complication coexists, the *urine* is entirely normal, or it may present the signs of catarrhal pyelitis, or, finally, if the cysts have discharged their contents into the pelvis of the kidney, the latter may contaminate the urine. As in the case of renal calculi, this is usually preceded by the occurrence of colicky attacks. The appearance of the urine may resemble that of soapy water or of amniotic fluid, or it may be milky, bloody or purulent and contain a variable quantity of albumin; while the sediment may contain the characteristic hooklets or shreds of membrane or even whole cysts, besides the signs of catarrh of the urinary passages and ammoniacal decomposition of the urine. A very great number of cysts may be evacuated both during a single attack and during repeated attacks in the course of the disease. Evans once counted several hundred in the case of a female patient.

As in the case of nephrolithiasis, such colicky attacks with the characteristic urinary changes may be repeated at varying intervals. The attacks are also followed by diminution of the tumor corresponding with the evacuation of the cystic contents, exactly as in hydronephrosis. In rare cases the first evacuation is followed by recovery, the tumor failing to grow again and becoming atrophic. On the other hand, evacuation of the tumor may be followed by *purulent pyelitis*, in the course of which the echinococcus also *decomposes with fetid suppuration*, and although the hydatids themselves are destroyed, the patient gradually wastes away and finally dies.

In a few cases *urticaria* has been observed to follow the rupture of a renal echinococcus, as happens after rupture of liver hydatids (Mosler).

Echinococcus of the kidney causes but little disturbance of the *general health*. *Fever* is altogether absent, unless it is caused by sequelæ or complications.

When rupture into some other organ takes place, the corresponding disturbances are usually very difficult to interpret. Even when the hydatids are discharged into the intestine or through the bronchi or through fistulæ into the lungs, as has been reported (see above), the diagnosis of renal echinococcus is so difficult that it is always doubtful whether the hydatids really are derived from the kidney; although the doubt might possibly be cleared up during the patient's life if the urine is found to contain cysts or parts of cysts, before or during the evacuation of the suspected fluid.

The *course* of renal echinococcus is always chronic and almost always irregular, being interrupted by the colicky attacks referred to. The duration, which cannot be determined with accuracy, is always counted by years, and the disease may drag along for more than twenty or thirty years.

If the contents of the cysts are evacuated with the urine, the disease

not infrequently ends in *recovery*—in 20 out of 63 cases, according to Béraud; but, as has been mentioned, purulent pyelitis may develop secondarily with a fatal result; or if the sacs rupture in some other direction, death occurs from protracted suppuration and putrefaction.

DIAGNOSIS.

The diagnosis of renal echinococcus is based on the demonstration of a *tumor* beginning in the kidneys and the *discharge of hydatids or their constituents in the urine* when it is certain that they are derived from the kidneys and not from other parts of the urinary apparatus, such as the bladder, or have entered the urinary organs after rupture from some neighboring structure.

In regard to the demonstration of a renal tumor, the student is referred to all that has been said about the diagnosis of Movable Kidney, Abscess of the Kidney, Hydronephrosis, Cystic Kidney, and other tumors with which the condition might be confounded (see pp. 141, 310, 362, 375, 385, 397). To determine the nature of the tumor and whether it belongs to the kidney, resort must be had to careful and repeated objective examination of the tumor if necessary under anesthesia, and with all the available diagnostic aids, including transillumination with the Röntgen rays, examination of the urine, of other organs, and of the general condition; and in addition every point in the history and every possible etiologic factor must receive due consideration. If necessary and in suitable cases positive information may be obtained by means of *exploratory puncture*, especially when the characteristic hooklets or shreds of membrane are secured or the evacuated fluid contains succinic acid, which is regarded as characteristic of echinococcus cysts. Even after an exploratory puncture has been performed, doubts may remain that are not cleared up until the tumor is exposed by operation for therapeutic purposes.

Rupture from the kidneys into the urinary passages is usually recognized by the *urinary changes* and possibly by a *simultaneous diminution in the size of the tumor*. It is not to be forgotten, however, that an echinococcus situated in the neighborhood of the kidney (peritoneum, Douglas' space) may also rupture into the urinary passages. If rupture takes place in some other direction, it is not possible to determine whether the fluid is derived from the kidneys unless other signs, such as a urinous odor of the cystic contents or the presence of unmistakable urinary constituents (urea, uric acid) point to the kidneys, or the diagnosis of renal echinococcus was reasonably assured before the occurrence of rupture, and the accident is followed by evident collapse of the tumor.

PROGNOSIS AND TREATMENT.

As a rule, echinococcus of the kidneys is not a direct menace to life, except in the rare cases when the disease is bilateral or when, as in a case of Roberts',[1] the tumor develops in a solitary kidney. Otherwise life is endangered by suppuration and rupture into some other organ,

[1] *Urinary and Renal Diseases*, London, 1865.

accidents that are, on the whole, uncommon. Without operative interference recovery takes place in only one-third of the cases by evacuation in the urine or shrinking of the cysts; with operation the number of recoveries is much greater.

The *treatment*, unless it be limited to guarding the tumor against injury and relieving the symptoms as they arise, must consist in surgical measures for the removal of the growth, as there is no internal medication that was ever known to have any effect. As, however, echinococcus is comparatively free from danger, the writer does not consider that such measures are indicated unless the tumor causes severe discomfort or has undergone suppuration.

The practice formerly in vogue of removing the fluid by aspiration and injecting various solutions for the purpose of obliterating the sac is uncertain in its results and not altogether without danger. It is probably altogether obsolete at the present time, and the equally uncertain method of treatment by electropuncture and gradual opening of the tumor with caustic paste, after Récamier, which is exceedingly painful as well as tedious, has met the same fate. The most satisfactory procedures are *incision* and *drainage*, as they have the advantage over *extirpation* of the kidney—which has also been proposed—of being less dangerous and leaving the sound parenchyma to carry on the function of the organ (P. Wagner). When the echinococcus is limited to a portion of the kidney, the affected part may be resected, as that procedure is followed by more rapid healing without the formation of a fistula.

Other operative measures may be necessitated by the occurrence of dangerous accidents, such as obstruction of the urinary passages, ulcerations, and the like.

2. CYSTICERCUS CELLULOSAE.

The larva of Tænia solium has been found in human kidneys in a few isolated cases. Trustworthy reports of the condition have been made by Stich,[4] who points out that the older statements in regard to its occurrence in the kidneys are probably based on confusion with echinococcus, and by Lombroso and Gellerstadt.[2] The parasite does not appear to have produced any symptoms in the reported cases.

3. EUSTRONGYLUS GIGAS (Palisade Worm).

This parasite, which is often found in the renal pelvis of the dog, the wolf, and many other animals, is exceedingly rare in man. Rayer[3] collected from the older literature a number of statements in regard to its occurrence, and called attention to the fact that most of them are based on a misapprehension, the suspected findings having been blood-clots or Ascaris lumbricoides that have strayed into the kidneys after death. Davaine estimates the number of cases observed and reported in man up to 1860 at a dozen. The more recent literature contains

[1] *Charité-Ann.*, 1854, v. [2] See Mosler and Peiper, *Thierische Parasiten*, p. 89.
[3] *Loc. cit.*, iii., p. 729.)

only one statement, by Cobbold, to the effect that there is preserved in the museum of the College of Surgeons in London a kidney which contains an eustrongylus in its pelvis. Quite recently Stürtz reported a case of *chyluria* in which the left kidney appeared to be the source of a discharge of milky urine which contained the ova of Eustrongylus gigas besides other ova of an unknown species. Nothing short of the demonstration of ova or even of the worm itself in the urine will serve to establish the diagnosis. If, as in this case of Stürtz's,[1] it can be demonstrated that only one kidney is the seat of the parasite, a cure might be effected by *nephrectomy* or resection of the kidneys.

4. DISTOMA HAEMATOBIUM.

LITERATURE.—Bilharz, *Zeits. f. wissenschaftl. Zoologie*, iv., 1851, and *Wien. med. Woch.*, 1856, Nos. 4 and 5. Griesinger, *Arch. f. physiol. Heilk.*, 1851, p. 561, and 1866, v., p. 96. Harley, "Endemic Hematuria of the Cape of Good Hope," *Med.-Chir. Trans.* 1864, xlvii. Kartulis, *Virchow's Archiv.*, xcix., 1. L. Rütimeyer, *Die Bilharziakrankheit*, Basel and Leipzig, 1894. See also the text-books on Animal Parasites, by Davaine, Küchenmeister, Leuckart and Mosler, and Peiper.

Distoma hæmatobium, which was discovered by Bilharz in Egypt in 1851, and which is the cause of the *endemic hematuria* in that country and on the neighboring islands as well as at the Cape of Good Hope, usually effects an entrance into the intestine along with impure drinking-water (Nile water) or impure food; from the intestine it makes its way into the portal vein, and from this with its innumerable ova into the vascular system of the urinary apparatus, and especially the mucous membrane of the urinary passages. Here the parasites produce hemorrhages to which may be superadded pyelitis, and later inflammation and atrophy of the kidney substance. The ova may also form the nuclei of renal calculi (see p. 410).

The *symptoms* produced by the condition are pain in the region of the kidneys and bladder, painful micturition, and especially blood in the urine, in which the eggs are found singly or in large numbers, appearing as oval bodies pointed at both ends, 0.12 mm. in length and 0.4 mm. broad. Coincidently there may be signs of catarrh of the urinary passages (pyelitis and cystitis) and of renal calculi, which in severe and protracted cases may lead to hydro- or pyonephrosis. On the whole, however, it is rare for such severe sequelæ with the attendant profound general disturbance to develop; in most cases the disease persists for a long time without producing any disturbances, and frequently terminates in recovery by evacuation of the ova.

The *diagnosis* can only be made by examining the urine and finding the ova.

Treatment.—In order to *prevent* the disease or hold it in check, in regions where it is endemic, the drinking of unfiltered, impure water and the eating of uncooked food must be avoided. For the purpose of flushing the ova out of the kidneys, mild diuretics in the form of alkaline carbonated waters, diuretic infusions, and the like are to be

[1] Session of the Gesellschaft der Charité-Aertze, held June 26, 1902, and *Berlin. med. Ges.*, July 17, 1902.

recommended. The administration of anthelmintics appears to be useless; on the other hand, salol has been found to have some effect.

5. FILARIA SANGUINIS.

These parasites are found in the lymphatic system of the uropoietic system and in the kidneys themselves. They are the cause of *tropic chyluria*, for a description of which the reader is referred to a former section (pp. 69–72).

The writer may also mention briefly: *Nephrophages sanguinarius* (see p. 54); different species of *rhabdites* (see p. 65), which have been observed in connection with and probably as the cause of hematuria; and *psorospermata*, which Lindemann claims to have found in Nijni-Novgorod (Nischney-Nowgorod), in the kidneys of a man who had died of Bright's disease.[1] *Amebæ* (Amœba urogenitalis) have been occasionally found by Bälz[2] and others in the urine, which may at the same time contain blood, pus, and shreds of tissue. The amebæ in these cases are probably derived from the urinary passages, the vagina, or the intestine, and not from the kidneys.

In a few cases *actinomycosis secondary* to foci elsewhere in the body, from which it had been carried by metastasis, has been observed. A case of *primary actinomycosis* of the kidney, which so far appears to be the only one of its kind, was observed by J. Israel.[3] A cure was effected by extirpation of the kidney. The diagnosis was made by the demonstration of actinomyces granules in granulations from the scar of an old exploratory incision, and by the presence in the urine of particles that suggested some actinomycotic structure.

PERINEPHRITIS AND PARANEPHRITIS.

LITERATURE.—Chopart, *Maladies des voies urinaires*, 1821, i. Ducasse Fils, "Abscès perinephrétique ouvert dans les bronches," *Arch. gén. de Med.*, 1827, xix, Rayer, *loc. cit.*, iii., p. 243. Féron, "De la perinephrite primitive," *Thèse*, Paris, 1860. Hallé, "Des phlegmons perinephrétiques," *Thèse*, Paris, 1863. Trousseau, "Abscès perinephrétiques," *Union méd.*, January, 1865, and *Clinique méd.*, iii., 1868, p. 696. Gordon, "Case of Renopulmonary Fistula," *Dublin Jour. Med. Sci.*, 1866. Tyson, "Cystic Abscess of Both Kidneys," *Am. Jour. Med. Sci.*, 1866. Naudet, "Du phlegmon perinephrétique," *Thèse*, Paris, 1870. Ravel, "Lésions traumatiques des reins," *Thèse*, Paris, 1870. Bowditch, "On Perinephretic Abscess," etc., *Med. and Surg. Rep. of Boston City Hospital*, 1870, i. Kraetschemar, "Des abscès perinephrétiques," *Thèse*, Paris, 1872. A. Bloch, "De la contusion du rein," etc., *Thèse*, Paris, 1873. H. Fischer, "Ueber paranephritische Abscesse," *Volkmann's Sammlung klin. Vorträge*, No. 253. A. Rosenberger, *Die abscedierende Paranephritis*, Würzburg, 1878. G. Nieden, "Ueber Perinephritis," *Deutsch. Arch. f. klin. Med.*, 1878, xxii. Tuffier, "De la perinephrite tuberculeuse," etc., *Gaz. hebdom.*, 1891, No. 19. Niebergall, *Deutsch. militärärztliche Zeigt.*, 1897.

INFLAMMATION of the *fibrous investment* of the kidneys, perinephritis in the narrower sense of the term, may accompany all the acute and chronic processes of the organ which it covers, and depending

[1] See R. Leuckart, *Die Parasiten des Menschen*, etc., 2d ed., i., p. 284.
[2] *Berlin. klin. Woch.*, 1883, No. 16.
[3] *Chi. Klin. der Nierenkrankh.*, Berlin, 1901, p. 266.

on the variety of the inflammation, leads to thickening, adhesions with the renal parenchyma, or to subcapsular suppuration. These perinephritic processes have been noticed in connection with the corresponding renal affections and do not require any special discussion, for although they produce *pain* or aggravate an already existing pain, they do not give rise to any special symptoms that would distinguish them clinically from the other conditions. It is to be noted, however, that the pain may occur *periodically like that of renal colic*, being probably due to traction on the adhesions in various positions of the body, movements of the intestines, or shaking of the body, and may thus give rise to errors in diagnosis. To this category belongs many a case of *nephralgia* cured by exposing the kidney and incidentally freeing it from adhesions (see p. 146).

On the other hand, inflammation of the *fatty capsule* of the kidney, although much less common than the former condition, possesses a great clinical interest because it represents an important disease with a pronounced clinical picture, and is therefore described in the oldest medical literature, usually, it is true, under the rubric "renal suppuration." Rayer, who distinguished suppurative processes of the kidney themselves from suppuration of the investment (see p. 301), includes the latter forms under the common term "perinephritis"; later, however, that name was used for the above-mentioned inflammation of the fibrous capsule of the kidneys, the inflammation of the fat-capsule being distinguished as "*paranephritis*." J. Israel,[1] on the other hand, wishes the latter designation to be restricted to inflammation of the retroperitoneal fat behind the kidneys, and proposes the term "*epinephritis*" for inflammation of the fatty capsule itself. (See also Pathologic Anatomy, p. 442.)

ETIOLOGY.

Paranephritis (epinephritis) is only exceptionally a primary disease, and the cause is then almost always *traumatic* in nature, be it a contusion in the lumbar regions from a blow or a fall, or a perforating wound. The class includes also those cases in which inflammation develops after concussion of the body in riding or driving over rough roads, or after lifting a heavy weight, the starting-point for the inflammation being probably formed by distortion or laceration of muscle fibers in the lumbar regions with hemorrhage into the perirenal connective tissue. When no such cause can be demonstrated, as happens in the majority of these rare cases, *exposure to cold* may be assumed as a last resort, and this may actually in some cases be the cause, although the direct influence of cold is difficult to prove.

Secondary paranephritis develops either from extension of the inflammation by contiguity from the neighboring tissues by way of the connective tissue and the lymph vessels, or by way of the blood—that is, by *metastasis*. When the inflammation is due to extension by contiguity it usually has its origin in a *purulent inflammation of the kidney itself*, which in turn may be due to a variety of causes, most frequently *puru-*

[1] *Chi. Klinik. der Nierenkrankh.*, Berlin, 1901, p. 580.

lent pyelitis and pyelonephritis, or in abscess formations, or neoplasms of the kidney that have broken down. Any suppuration in the cavity of the pelvis, whatever may be its origin, may burrow through the connective tissue and reach the fatty capsule of the kidney. Also to be mentioned as the starting-point of such suppuration are paratyphlitic and parametritic suppurations starting in the intramuscular connective tissue of the iliopsoas or from the vertebral column, burrowing abscesses originating in higher situations—abscesses of the liver, spleen, and other forms of subphrenic abscess—and finally suppurations within the thorax, as empyema and pulmonary abscess, the pus from these sources making its way between the pillars of the diaphragm until it reaches the capsule of the kidney.

Metastatic paratyphlitis may occur after any of the *infectious*, especially *septicopyemic, processes*, of which puerperal fever is the most important. In puerperal fever, however, there is in addition to the general infection a direct extension from the inflammatory foci in the abdominal cavity. Metastasis into the fatty capsule may also be derived from the *kidney* itself if the viscus is the seat of an inflammatory or infectious process, because often the capsular vessels do not leave the renal vessels until after the latter have entered the kidney (arteri perforantes of Haller).

It follows from these etiologic factors that *middle age* and the *male sex* furnish the larger proportion of the cases; for men during adolescence and in mature age are chiefly exposed to external injuries, to the influence of severe bodily labor and exposure to cold, which are the causes of *primary paranephritis;* and pyelitis and calculous pyelonephritis, which represent the commonest cause of *secondary paranephritis*, also affect men in greater numbers than women. According to Nieden's statistics, out of 138 cases, 97 occurred in men and 41 in women. Among the 166 cases which he collected, 26 occurred in *children* up to the age of thirteen, the youngest being a child five weeks old, in whose case the etiology is not mentioned; the five oldest patients ranged from sixty-one to sixty-nine years; the greatest number of cases occurred during the fourth decade of life.

PATHOLOGIC ANATOMY.

Paranephritis (epinephritis) has been observed somewhat more frequently on the right than on the left side; in Nieden's collection it occurred 76 times on the right, 60 times on the left side. The disease is said to have been bilateral in one case of Turner's (Rayer[1]), and in another of Rosenstein's.

It is rare that an opportunity is afforded to observe the beginning of the malady, the stage of inflammation which precedes that of suppuration. We may therefore assume, reasoning by analogy with other forms of inflammation, that the process begins with a hyperemia, which in the cases due to traumatism is probably preceded by hemorrhages. When the kidney is opened either in the living subject or at the autopsy

[1] *Loc. cit.*

table all that is seen is a more or less extensive suppuration involving the fatty capsule of the kidney and the loose retroperitoneal connective tissue surrounding it, usually in the form of a large abscess, or more rarely in small, circumscribed, discrete foci. The latter are observed chiefly when a pyelitic or pyelonephritic abscess slowly ruptures on the outside of the body. If the condition lasts for some time, the abscesses become lined with a special membrane. In other respects the condition is quite similar to that seen in phlegmons in other parts of the body, especially in the subcutaneous fatty tissue. In addition to discolored necrotic shreds of tissue, small masses of fat, recent or old hemorrhages, connective tissue in various stages of serous and purulent infiltration, and portions of indurated, brawny tissue are found.

The greater part of the pus in the case of large abscesses is usually found on the posterior wall of the kidney, and may extend from there upward to the liver or spleen, or downward into the true pelvis and into the cellular tissue between the lumbar muscles toward the surface of the body; or in rare cases it may spread in various directions, and after adhesions have been formed with various organs, rupture may take place into these organs and the process may continue to spread within them. Rupture has been observed into the kidneys, ureters, the bladder, the urethra, the intestine and peritoneum, the vagina; upward as far as or even through the diaphragm; and finally along the iliopsoas muscle as far as to the hip and the surface of the body.

The varying mode of propagation appears to depend on the presence of two separate layers of fat in the region of the kidney, an inner and an outer layer (Gerota [1]), which are separated from one another by the posterior layer of the renal fascia (fascia retrorenalis). The inner layer forms the true fatty capsule; the outer is known as the *massa adiposa parenalis*. Suppurations in the former are apt to spread along the ureter into the pelvis, while suppurations in the latter tend to spread into the lumbar triangle (*trigonum lumbale of Petit*) or to the iliac fossa.

Depending on the mode of origin of the paranephritis, the pus may be of the usual greenish-yellow color and odorless (“*pus bonum et laudabile*”), or if gangrene is superadded it may be discolored and putrid. Not infrequently it has a feculent odor as in other pelvic suppuration, even when no perforation of the intestine has taken place, undoubtedly because the knuckles of the intestine situated near the abscess have suffered impairment of their nutrition, and the walls therefore allow the gases to escape, or else the gas-producing bacteria in some way make their way into the pus.

If there is present from the beginning—*i. e.*, as the *cause* of the paranephritis, or secondarily as the *result* of the same—perforation of the pelvis of the kidney or of the bladder, followed by infiltration of the connective tissue with urine, the pus may be thin and give off a urinous odor. In such cases foreign bodies from the urinary apparatus (concretions, entozoa) have been found in the pus.

[1] *Arch. f. Anat. u. Physiol. Anat.*, section 1895, p. 265.

The kidney, in the neighborhood of which the suppuration has its seat, may, if it does not itself form the starting-point of the inflammation, be protected for a long time by its fibrous capsule against the invasion of the process, but ultimately it also becomes involved. The other kidney may likewise become implicated by extension of the inflammatory process, first to its fatty capsule and then to the viscus itself, or else by metastasis.

As regards other changes, the cadavers very frequently exhibit in addition to the causal processes, *pleurisy with effusion* of the corresponding side, such as not infrequently occurs as a concomitant or sequel of abdominal affections,[1] *metastatic processes* in various organs, and finally, as the result of the long-continued suppuration, a variable degree of *amyloid degeneration*.

SYMPTOMATOLOGY.

In the most frequent form of paranephritis—the *secondary*—the symptoms are usually obscured by the phenomena belonging to the causal disease, so that the infection may escape recognition not only in the beginning, but during its entire course as well. An exception is found in that form of secondary paranephritis which owes its origin to *metastasis* from an infectious focus, which until that time had remained hidden, or had not been recognized on account of its insidious course. In such a case the disease may make its appearance abruptly with a well-defined symptom-complex, just like *primary* paranephritis.

The latter, as a rule, declares itself by *pain* and *fever*. In cases due to external violence the pain begins somewhat earlier than the fever. In cases due to other causes, such as internal injury or exposure to cold, pain and fever may occur at the same time.

The *pain* is localized in the lumbar region of the affected side and is increased by superficial pressure, and especially by movements of the lumbar portion of the vertebral column, by turning, bending over, stretching, by deep-breathing movements, and by coughing. As soon as the suppuration has attained a certain degree, extension of the corresponding leg becomes painful on account of the pressure and irritation exerted by the exudate on the iliopsoas muscle which lies behind it, or on the nerves which have their course between the origins of the muscle causing contracture of the muscle. The patient lies on his back and keeps the thigh flexed at the hip joint in adduction, and his breathing is more shallow and more frequent than normal. More rarely, even if the kidneys themselves are free, the pain radiates toward the bladder and urethra, or follows the course of the lowest dorsal and highest lumbar nerves and passes to the hips or abdomen or to the thigh.

The *fever* usually begins with a chill, followed by a feeling of heat and sweating; it soon becomes continuous and attains a variable degree, or, depending on the extent of the suppuration, it may be remittent or even intermittent.

[1] See H. Senator, "Ueber Pleuritis im Gefolge von Unterleibsaffectionen," *Charité-Ann.*, ix., 1884, p. 311.

These symptoms may be accompanied by all kinds of disturbances, either due to local causes or reflex, such as vomiting or other digestive disturbances, particularly meteorism.

After a time—earlier in the form of paranephritis caused by external injury—a *swelling appears in the lumbar region;* at first the affected side appears somewhat flatter as compared with the sound side; later, however, it bulges more and more, the distance from side to side increases, and finally the enlargement becomes evident on the anterior surface of the body. The skin over the tumor in the lumbar region is *edematous*, and the edema may subsequently spread in all directions. Some times emphysematous crackling is demonstrable over the affected area and indicates that gas has developed in the pus (see p. 443).

The tumor can be felt on bimanual palpation and by sinking one hand deep into the abdomen, at first indistinctly, but as it increases in size, more and more unmistakably; in favorable conditions for examination it may exhibit fluctuation or may be felt to contain several thickened bands and irregularities. *It does not move with respiration.* When the pus forces its way to the surface, in doing which it does not always travel in the direction of the lumbar region, but may rupture in other places, such as the hip joint, the corresponding area begins to bulge, the skin becomes hot and reddened and thinner, and rupture finally takes place. If rupture takes place in the internal organs it is usually preceded by corresponding subjective symptoms; thus, rupture into the colon announces itself by frequent desire to defecate and by peritonitic phenomena; rupture into the bladder by strangury, and rupture through the diaphragm by dyspnea, desire to cough, and pleuritic phenomena, etc. The pus, however, may empty itself into the intestine, bladder, or vagina without the accident being observed, especially when paranephritis is merely a concomitant of some other pelvic inflammation, and the individual phenomena cannot be distinctly separated from the general symptom-complex.

In such cases also it is not always possible to demonstrate a diminution in the size of the swelling after rupture has taken place, a phenomenon which in less complicated cases is distinctly perceptible.

The evacuation of the pus is usually followed by relief from pain and subsidence of the fever, the improvement being more marked in proportion as the escape of the pus is more complete.

The *urine* in paranephritis suffers no alterations except such as are due to the fever; but it often shows the changes due to the primary disease of the urinary apparatus, which is the cause of the paranephritis, such as calculous pyelitis; and if, conversely, the paranephritic abscess ruptures into the urinary apparatus, pus and blood will appear in the urine.

COURSE, DURATION AND TERMINATION.

Primary paranephritis (epinephritis) usually begins suddenly and runs an acute course; much more rarely the onset is insidious with ill-defined symptoms until the suppuration has reached a certain height.

The behavior of the *secondary* form is the direct opposite of these: abrupt onset is the exception and an insidious development the rule.

The subsequent course in every case depends on the time and place of the evacuation of the pus. It is most favorable when the discharge is external in the lumbar region, particularly when the opening is large and affords free escape for the pus, which is rarer after spontaneous rupture than when the opening is made by an incision; for in the former case fistulæ are apt to form as in renal abscess and may become periodically occluded, and thus give rise to further disturbances.

Next in frequency, *burrowing* of the pus takes place along the iliopsoas muscle, along Poupart's ligament, or toward the region of the lesser trochanter or underneath the glutei muscles.

As regards *rupture into the internal organs*, the condition is most favorable when the pus bursts into the *cecum* or *colon*. Of 26 cases of perforation collected by Rosenberger, 6 had taken place into the large intestine, with 4 recoveries and 2 deaths. More frequent and also more dangerous is rupture into the *pleura* and into the *lungs*, which in the same series of 26 cases had occurred 13 times, among which were 5 recoveries after rupture into the lungs. Rupture into the peritoneum took place three times, in each case with fatal termination. Rupture into the *vagina*, *pelvis of the kidney*, and the *ureters* is extremely rare, and may run a favorable or an unfavorable course. One case of rupture into the *duodenum* is described by Rayer. The same authority mentions rupture into the *stomach* as possible, but knows of no authentic case either in the literature or among his own observations.

The *duration* of paranephritis in the most favorable cases—*i. e.*, when the pus finds an outlet in the lumbar region or is liberated by incision—amounts to several weeks. For the rest it varies according to the causes which are responsible for the suppuration and for its continuance, and according to the direction taken by the pus. If the cause persists—as, for instance, a purulent pyelitis or pyelonephritis due to calculous formation which has ruptured externally—the condition may last for years and ultimately, like all other forms of suppuration, bring on death by septicopyemic infection or by debility, with or without amyloid degeneration. The occurrence of *gangrene* hastens the course in every case and usually brings on death.

DIAGNOSIS.

Of the three main symptoms of peri- and paranephritis—*pain*, *fever*, and the presence of *swelling*—the last is the most important. But as it requires a certain time for its full development, the disease cannot be recognized with certainty at the very beginning, and cannot be distinguished from a variety of other affections which also present the two symptoms—pain in the region of the kidney and fever. The diagnosis is even more difficult in cases of paranephritis in which fever is absent and pain alone is the chief symptom. This is very rare, it is true, and only occurs during the very earliest stage, before the suppuration has developed.

At the very beginning, therefore, *lumbago* might have to be considered, and in some cases its exclusion would be possible only in the presence of a distinct etiologic factor in favor of paranephritis. The question might be decided by observing that in lumbago the pain is more apt to involve *both* sides of the lumbar vertebral column, and that pressure on the bones and symphyses is more painful than pressure on the soft parts. If fever were also present, one would have to think of certain infectious diseases that are apt to begin with sacral pain, especially *variola* or *influenza;* but the absence of all other phenomena belonging to these diseases would speedily clear up any possible error. From *malarial fever* paranephritis is distinguished by the irregular febrile curve and by the blood-examination. The condition may also be confounded with *renal colic*, and the error can only be avoided by repeated examination of the urine, unless the cause of renal colic itself, which in most cases is a concretion, has in its subsequent course led to paranephritis. In such a case the occurrence of that condition can only be recognized by the appearance of swelling and edema in the lumbar region.

If the swelling is present and the complete symptom-complex is thus fully developed, all other causes of swelling in that region must be excluded, especially swelling of the kidney itself. This is not always possible, because many of these conditions are etiologically related to paranephritis and may be combined with that disease. Next, enlargements of neighboring organs—the liver, spleen, intestine, and ovary—must be excluded according to the rules that have been laid down elsewhere (see pp. 141, 309, and 362).

In contradistinction to many other tumors of the abdomen, the swelling of paranephritis is characterized by the fact that it bulges more posteriorly toward the lumbar region than anteriorly and can be felt through the abdominal walls only on deep palpation, by the fact that the skin over the swelling is usually edematous, by the seat of the pain, and by the occurrence of fever, which is also absent, at least for a long time, in most of the other tumors that come under consideration in this connection. The condition of the urine is also important in the sense, at least, that a normal urine, in the presence of the three other symptoms, is in favor of the diagnosis "paranephritis."

Other suppurations in the lumbar region, especially a *burrowing abscess in the subcutaneous tissue*, may cause great diagnostic difficulties. These abscesses, however, are usually more superficially placed under the skin, are more diffuse in extent, and exhibit more distinct fluctuation. But these peculiarities are not always sufficiently distinct, and may also be present in paranephritis just before rupture is about to take place. In such cases it is important to look for a purulent focus higher up; for instance, somewhere in the course of the vertebral column. The *other forms of pelvic suppuration*, especially *peri-* and *parapsoitis*, *paratyphlitis*, and *parametritis*, if they are sufficiently extensive, may give rise to confusion, which can, however, in most cases be avoided by a careful consideration of the etiologic conditions, the development, and

by progress of the inflammatory phenomena; for the rest, the error is not very important from a therapeutic standpoint.

PROGNOSIS.

The prognosis depends on the cause and on the possibility of affording an escape for the pus. It is therefore most favorable in primary paranephritis which can be recognized and treated in time, and unfavorable in the secondary forms in proportion to the difficulties in the way of removing the cause. For the rest, it depends on the course of the suppurative process and the occurrence of complications, which have already been discussed.

TREATMENT.

At the very beginning, when, as has been said, the diagnosis is still in doubt, an attempt may be made by means of antiphlogistic measures —that is, *rest*, the *local application of cold* in the form of ice-bags or cold compresses, and *local blood-letting* with leeches or wet cups, or in debilitated individuals dry cups—to abort the inflammatory process and prevent the occurrence of suppuration. If these measures fail to relieve the pain, analgesic and antirheumatic remedies, such as the salicylic acid preparations, antipyrin, acetanilid, phenacetin, pyramidon, aspirin, and the like, may prove efficient *palliatives* and at the same time temporarily moderate the fever. If the pain is very violent and proves refractory to these remedies, it should be allayed, at least for a time, by an injection of morphin.

If the case is one of true paranephritis and not a simple affection like lumbago, the antiphlogistic and other methods of treatment will be ineffectual or have only a short-lived success, and as the suppuration cannot be prevented, it is then more advisable to hasten it, and replace the cold compresses by so-called Priessnitz bandages about the lumbar region and by hot applications. As soon as suppuration can be distinctly demonstrated—and if necessary any doubt can be removed by means of an exploratory puncture—evacuation of the pus is indicated. That this is best accomplished by means of an incision is probably conceded nowadays by everyone. Neither the method of opening with caustic paste, which was formerly in vogue, nor puncture and aspiration of the pus can rival the operative method in rapidity and in the certainty of its results. Not infrequently the incision must be followed by certain other surgical procedures which may be indicated by the causal condition, disease of the renal parenchyma or the like, or by sequelæ.

ANOMALIES OF THE RENAL VESSELS.

The changes that take place in the smaller vessels and capillaries in the various affections of the kidneys were included in the descriptions of these affections, and there remain to be discussed only the anomalies of the *larger vascular trunks*.

1. *Renal Arteries.*—Reduplication of one or both renal arteries is a rare condition that may be dismissed at once, as it is entirely without significance. Cases of *congenital hypoplasia* or *stenosis* with atrophy of the corresponding kidney from the diminished blood-supply have been reported by H. Hertz, E. Klebs,[1] Lancereaux, and others, and have already been referred to in this volume (see pp. 166, 270, and 299). *Acquired* narrowing due to disease of the arterial walls (atheromatosis and arteriosclerosis) is somewhat more frequent. The effect of all these forms of stenosis and the resultant deficiency in the blood-supply of the kidneys is congenital or acquired atrophy.

Three separate symmetric renal arteries originating from the aorta are described by Guillenimot.[2] The middle vessel entered the hilus and supplied the greater portion of the kidney; the upper and lower vessels each supplied 2 or 3 pyramids in the corresponding pole.

Embolism and *thrombosis* of the renal arteries have already been discussed (see p. 158).

Aneurisms of the renal arteries are exceedingly rare. As in other arteries, they owe their origin to arteriosclerosis of the vessel or to an injury. Gruber[3] and v. Hochenegg[4] have each recently described a case of traumatic aneurism; the cause in each was a fall on the back. Rokitansky[5] has described an interesting case in which the cause was arteriosclerosis, and in which numerous other moderately large arteries—the hepatic, coronary arteries, and internal spermatic—also exhibited aneurisms. Aneurism of the main trunk of the renal artery is situated outside of the fibrous capsule; aneurism of one of the branches, on the inside of that structure. The adjoining renal tissue becomes atrophic from pressure, or, in case of rupture, is destroyed and converted into a sanguineous, semi-fluid mass.

The *symptoms* that may be produced by aneurism when it attains a certain size are *sacral pain* and the appearance of a *tumor* in the corresponding half of the abdomen, where the patient sometimes complains of a beating sensation (Nebel), although it does not appear that pulsation or murmurs have ever been observed objectively. Rupture of the aneurism into the pelvis of the kidney or into the ureter is followed by *hematuria*.

The *diagnosis* has so far never been made, and it is not likely that with the means at present at our disposal it will ever be possible to do so.

A *cure* might be effected by operation, and was in fact achieved in a case of E. Hahn's,[6] in which a tumor of the kidney had been diagnosed—the nature of which was recognized later—by extirpating the kidney along with the aneurism.

2. The *renal veins*, according to Rayer,[7] are sometimes bifid or pre-

[1] *Handb. der path. Anat.*, i., Berlin, 1876, p. 670.
[2] *Jour. de l'anat. et de la physiol.*, 1895, No. 4.
[3] *Wien. med. Woch.*, 1891, No. 41.
[4] *Wien. klin. Woch.*, 1891, Nos. 4–28.
[5] *Lehrb. der path. Anat.*, ii., p. 318.
[6] *Deutsch. med. Woch.*, 1894, No. 32.
[7] *Loc. cit.*, iii., p. 590.

sent sacculations, conditions that sometimes occur in association with other malformations, when they have no clinical significance. *Varices* may give rise to hemorrhage, but probably cannot be diagnosticated.

The commonest disease of the renal veins is *thrombosis*. It occurs in a great variety of conditions whenever, owing to retardation of the blood-current or disease of the vessel walls, blood coagulates within the venous tube; hence, in cases of marked congestion, compression from without by tumors, or constricting masses of exudate, and the like. The most important form, *marantic thrombosis of the renal veins*, which occurs in children, has already found a place among the circulatory disturbances (see p. 157).

In the renal veins, as elsewhere, thrombosis of long standing may be followed by *obliterating phlebitis*, with thickening and proliferation of the intima and complete occlusion. It is rarely seen in marantic thrombosis, because death takes place early; somewhat more frequently in cases of compression of the vein by tumors or inflammatory adhesions in the neighborhood. *Purulent phlebitis* always forms part either of a local suppuration in the immediate vicinity of the veins or of a general septicopyemic infection, and is, therefore, obscured by the other symptoms.

Diseases of the Spleen

and

The Hemorrhagic Diseases.

By PROF. DR. M. LITTEN.

DISEASES OF THE SPLEEN.

PHYSICAL EXAMINATION.

In examinations of the spleen the patient should be placed on his back or on his right side. The abdominal muscles should be relaxed as much as possible, and the patient instructed to breathe quietly and regularly with the arms held close to the body. A careful examination can, of course, be made only if the body is sufficiently denuded. The same general methods of physical examination—viz., inspection, palpation, and percussion—that are employed in the examination of other organs are available in the case of the spleen. Chloroform narcosis is, as a rule, not indicated.

INSPECTION.

Pathologic enlargements of the spleen of considerable dimensions are generally plainly visible. The left hypochondriac region protrudes, the abdomen below the costal arch is prominent, and the lower thoracic aperture is enlarged. These changes in the outline of the abdomen are most conspicuous when the patient is lying down, less so when he is standing or sitting. A good light is necessary for a careful inspection, and care should be taken that it is not too brilliant and that it does not illuminate but *one-half* of the body, leaving the other half shaded.

In large splenic tumors the left side of the abdomen is vaulted and protrudes considerably more than the right; the right side may even seem to be retracted below its normal level. This is especially apparent in women, in whom the typical outlines may remain essentially intact on the right side, while they are markedly changed on the left. The swelling begins under the costal arch and may extend to a varying degree toward the pelvis; or, depending on the size of the tumor, may occasionally reach laterally beyond the middle line to the right. Finally, in enormous growths, the level of the whole abdomen may sometimes be raised above that of the thorax.

Very frequently the anterior margin of large splenic tumors is clearly outlined through the abdominal walls. With the patient lying on his back and breathing deeply, it is often possible to see the margin of the spleen moving up and down with each expiration and inspiration, the movements corresponding to those of the diaphragm. Occasionally this phenomenon can be observed not only for the margin of the spleen, but also for large portions or even for the whole of the organ whenever it

happens to be clearly discernible in outline on the abdominal surface. In the first instance, where we observe the excursions of the margin alone, we can readily mark the upper and the lower boundaries of these movements, and we shall find that the distance traversed corresponds exactly to the excursions of the diaphragm. The reader may remember that the writer has previously called attention to the fact that the movements of the diaphragm can often be recognized with the naked eye; it is an easy matter, therefore, to measure the distance on the thorax between the upper and the lower boundaries of the visible diaphragmatic excursions. It will be found that this distance corresponds exactly with that measured in the same manner for the excursions of the lower margin of the spleen. The writer shall refer to this "diaphragm phenomenon" in the section on Percussion, and demonstrate its fundamental importance in the examination of the spleen. These respiratory movements of the spleen can be observed, provided, first, that the splenic outline is clearly visible through the abdominal walls; and, secondly, that the organ is freely movable. When adhesions exist between the spleen and the abdominal parietes, this phenomenon will of necessity be absent however clearly the organ may be outlined on the abdomen. In the same sense, very large tumors cannot follow the to-and-fro movements of the diaphragm, because, owing to their bulk, they are often immovably wedged in.

We must call attention to one other phenomenon that is apparent to the eye in large splenic tumors. The spleen in such cases, owing to its weight and the relaxation of the ligaments that attach it to the stomach and the diaphragm, may sink so low that its upper margin becomes outlined in the shape of a furrow, extending transversely or obliquely across the epigastrium. This furrow seems to move up and down with each inspiration and expiration. In reality, however, the movement is not due to a respiratory change of position of the spleen, but is caused by a stretching and relaxing of the abdominal walls over the tumor. This peculiar lifting of the abdominal wall, which naturally causes a rhythmic play of light and shadow in the region of the furrow, is not characteristic of splenic enlargements, but is commonly observed in all smooth abdominal tumors.

PALPATION.

Palpation is the sovereign method of physical examination in the case of the spleen. The most positive information in regard to the state of the organ may be gleaned by this method provided the observer has a sufficient degree of skill and experience. As nearly all lesions of the spleen are accompanied by a change in the size and consistence of the organ, it can readily be understood that palpation in particular furnishes a diagnostic adjuvant of paramount importance. Palpation not only reveals that the organ is enlarged, but also teaches that its consistence is abnormal, and to what degree. Incidentally, changes in outline may be observed that point the way to important conclusions.

In order to palpate the spleen correctly, the patient should be

instructed to lie on his back and to breathe quietly; it is often practical to place the patient on a low bed. [The same result is reached if the patient is on a rather high bed and the physician stands. The point is that the physician should be so placed as to be able to use the *flat* of his hand easily and without undue cramping or bending of the wrist and fingers.—Ed.] The examining physician should sit on the right side of the bed, place the right hand, without exerting any pressure, flat upon the hypochondrium, so that the tips of the second, third, and fourth fingers are close to the left costal arch. [One of the commonest mistakes with beginners is to use too much pressure with the palpating hand and to move the hand too much. In general, more can be learned

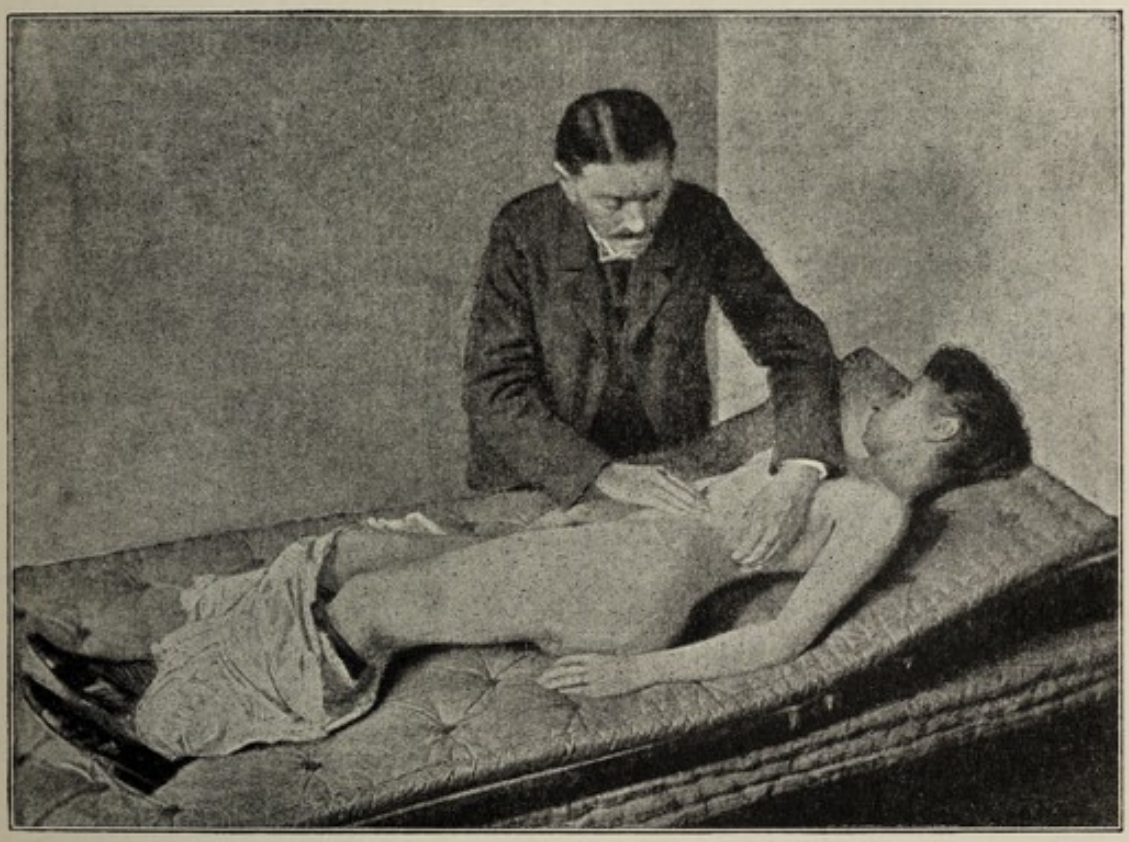


Fig. 1.

by keeping the hand still and letting the spleen come down to meet the tips of the fingers than by attempting forcibly to push the finger-tips against the organ. By the quiet, passive method there is less likelihood of interference from contracted abdominal muscles. These not only make the palpation of the spleen difficult, but, when tense, are apt to be mistaken for the edge of the spleen. By too deep palpation even the diaphragm may be reached and possibly be regarded as the spleen (Eichhorst).—Ed.] In this position the examiner notes whether it is possible to feel the spleen as it descends during normal inspiration. In case nothing is felt the patient is ordered to inspire more deeply, to see if in this way the spleen may be brought in contact with the finger-tips, when a peculiar gliding touch or impulse may be felt. If nothing is

felt on deep inspiration in the dorsal position, a change of position into the so-called diagonal or half right-sided position may lead to the goal. It is always best to examine *bimanually*. The left hand is placed posteriorly in the lumbar region, just below the margin of the ribs, the right anteriorly under the costal margin, as described above. In case the spleen can now be felt, it is important to decide whether it is palpable when breathing is suspended or only during inspiration. The former finding would indicate the presence of a larger tumor than the latter.

There is a popular notion to the effect that the normal spleen cannot be felt except when deformities of the spinal column coexist, and that its passage underneath the costal arch during inspiration escapes detection by palpation. This is not the case. In subjects of slender build, particularly in young women, the lower margin of the spleen can often be felt without difficulty, even when the organ is perfectly normal. The sensation on palpation is quite characteristic of these cases. It is as though a soft leaf-shaped organ of moderate diameter were gently pressing against the finger-tips. This is due to the softness of the normal spleen and the extreme gentleness of the impulse that is transmitted to it by the inspiratory act. The "feel" described is very delicate but altogether distinct.

A spleen that is normally palpable in this manner must not be confounded with an entirely different group. If the spleen be palpated as a routine measure in every case, it will be found that a great many persons suffer from chronic splenic tumors, the cause of which cannot be determined in the light of our present knowledge of the origin of such enlargement. Young subjects furnish a very large proportion of these cases, so that some clinicians have sought to establish a connection between splenic tumors of this kind and rickets. Such relations are, however, very obscure and improbable. It is not difficult, moreover, to differentiate such a tumor from a "normal" spleen that is occasionally palpable.

The lower margin of the spleen feels enlarged, rounded, and much harder than in normal cases, and occasionally the lower half of the spleen seems more or less conic. In very small splenic tumors nothing can be felt but the margin, which seems to "lick" [*i. e.*, touch very lightly] the finger-tips. In tumors that have reached more formidable dimensions certain areas of the anterior surface are capable of being palpated.

By palpating the anterior surface one has a good opportunity to study the *consistence* of the spleen. It is largely a matter of long practice to be enabled to form a correct conception of its consistence, and we earnestly advise beginners to palpate the spleen carefully as a routine measure in every case. In the living the spleen normally feels much harder than in the dead, especially in subjects which have died of acute infectious diseases. Spleens that felt fairly solid intra vitam may be found of almost mushy consistence post mortem. It is wrong, therefore, to draw conclusions from autopsy findings in regard to the state of the spleen during life. However, anyone who has had considerable expe-

rience knows what great differences in consistence palpation can reveal. It is simply a matter of learning by practice to recognize these differences. The normal consistence of the spleen is that of the "normally palpable" organ. Deviations from this standard are found, on the one hand, in acute infectious diseases, especially in the beginning (typhoid fever), when the spleen is abnormally soft; on the other hand, in certain chronic diseases (leukemia, pseudoleukemia, chronic malaria, amyloid degeneration, chronic congestion, etc., or very large tumors), when the spleen feels abnormally hard.

The larger the splenic tumor and the farther it extends downward into the abdomen, the more readily will it be palpable in all directions. Frequently even parts of the posterior surface may be felt and nodules recognized thereon that may give valuable diagnostic clues. Occasionally the margin can be grasped by the whole hand, with the thumb against the anterior, the fingers around the posterior, surface. In such cases the consistence and thickness of the organ can very easily be determined.

It is much more difficult to obtain information in regard to the thickness and consistence of the spleen in the case of small tumors that do not emerge below the thoracic wall. In these cases reliance must be had chiefly on *bimanual examination*, and the attempt must be made to bring the tumor between both hands either during or immediately after a deep inspiration, while the breath is still being held—that is, while the thoracic walls are still in the inspiratory position. Occasionally thickness and consistence can be determined in this way.

There is one other symptom revealed by palpation in the case of very large splenic tumors which is so characteristic that its presence alone determines positively that the abdominal tumor felt is the spleen. From one to four deep *indentations* can occasionally be felt on the median margin of the spleen (the so-called crenæ or incisuræ lienales) that cannot be confounded with anything else. They may be very shallow, or so deep as to give the impression that the spleen is lobulated. The larger the organ and the more rounded the margin, the more marked, as a rule, are these indentations. In very large leukemic or pseudoleukemic tumors these incisuræ are occasionally found both on the median and the lower margin of the spleen. [These splenic notches are of exceeding great value from a diagnostic standpoint, but occasionally indentations in other enlargements may so simulate them as to be very deceptive. Thus, in some tumors of the kidney, in a rolled-up tuberculous or carcinomatous omentum, or even in a carcinoma of the anterior wall and fundus of the stomach, the "notch" may so resemble the splenic notch as to lead to error if one depend entirely on this one point for diagnosis.—Ed.]

To return again to the palpation of the anterior surface of the spleen, this may yield much valuable information. In the first place the serous covering of the spleen may give rise to abnormal palpatory phenomena. The most important of these is a feeling of grating or rubbing, due to circumscribed areas of perisplenitis; and as such areas are found in

nearly all large tumors of the spleen, these sensations may be called quite characteristic of such lesions. *Perisplenic rubbing* is felt during or after perisplenitis under two conditions—namely, first, *synchronously with inspiration and expiration*, caused, in this instance, by the rubbing together of the two layers of the splenic peritoneum that are roughened by inflammatory exudates. We feel a soft rubbing or a rough grating, "new-leather rub." Second, *constantly or during pauses in respiration*, caused here by the pressure of the palpating hand on the exudation formed on the capsule of the spleen. The sensation here is one of crepitation and rubbing. If perisplenic rubbing suddenly cease after it had been previously felt, and if at the same time the spleen no longer follow the respiratory excursions of the diaphragm, then we are justified in concluding that adhesions have formed and that the spleen has become attached to the abdominal walls. We are not justified, however, in concluding that adhesions must necessarily form sooner or later because friction sounds or splenic rubbing have been observed, and surgeons especially should be careful not to make such an assumption the basis of operative procedure. As has been already emphasized, especially in the case of large tumors, these areas of inflammation on the wall of the spleen may be strictly circumscribed, and may shift their location, so that friction sounds may be heard first in one place and then in another.

Other points to be observed in palpation of the surface of the spleen are whether the substance of the spleen is uniformly homogeneous, elastic or inelastic, smooth or uneven, and, finally, irregular; whether nodosities can be felt, what their size and consistence may be, and whether at any point fluctuation can be made out. From all these findings important conclusions can be drawn. The degree of hardness and elasticity are especially important.

The presence or absence of *fluctuation* is of fundamental importance. The best way to elicit the signs of fluctuation is to place the second and third fingers of each hand on different parts of the tumor, an inch or two apart, and to press the swelling alternately, first with one hand and then with the other. By displacing the fluid in this way the feeling of fluctuation is given. If the tumor is not solid, but filled with fluid, a peculiar rocking movement will be felt, which is transmitted in waves from the fingers of the one hand to those of the other. It is this particular sensation that we designate fluctuation. The thinner the fluid contents of the cyst (serous cysts, hydatids), the smaller the waves will seem to be. In thick fluid (abscesses, dermoid cysts, etc.) the waves run more slowly and heavily. In cases where the cyst is very much distended, the fluid fluctuation can often not be elicited. It can be produced, however, if we remove a part of the fluid by tapping. Sometimes it is easier to feel fluctuation if an assistant presses the spleen forward from the lumbar region, thus bringing the sac of fluid nearer to the abdominal wall and to the fingers of the observer. Occasionally a typical *ballottement* can be felt by giving a series of short, quick taps; to produce it the left hand should be placed flat on the

tumor, while the fingers of the right tap the growth in the lumbar region. The impulse is transmitted through the organ and perceived by the left hand. The writer wishes, however, to call especial attention to the fact that this ballottement may be occasionally perceived in non-cystic tumors of the spleen.

Another important phenomenon felt only in cystic tumors of the spleen is the so-called *hydatid thrill*. We will recur to this at some length in the section on Echinococcus of the Spleen. Statistics in regard to the exact location, the frequency, and the mode of origin of this phenomenon are at variance. Frerichs claims to have found it in fully half of his cases; Mosler finds it in 2 only, and Finsen states that he did not find it once in 205 consecutive cases. The writer thinks that we can conclude from these varying statements, and the different descriptions that we have of this phenomenon, that different authors interpret it differently. According to his personal experience the hydatid thrill is in reality a very plain fluctuation, followed by a long-lasting tremor of the tumor and of the membranes surrounding it. The tremor may not be the same in all cases; in one instance the waves producing it may seem to be very weak and short, in another they may feel forcible and long. According to the character of the waves the sensation will be different, and it certainly requires a great deal of practice and experience to be able to recognize these fine differences and to interpret them correctly. The writer may compare the impression with the feeling one would experience on taking some echinococcus cysts or some coagulated meat jelly between the two hands and shaking it. Sometimes the waves are so coarse as to give to the touch a sensation which might be compared with that produced on the ear by humming.

The thrill is best perceived on percussion with the plessimeter and the percussion hammer. If the plessimeter be over the tumor and the ulnar side of the hand be placed lightly over the adjacent abdominal wall, then the vibration or tremble or thrill can be readily perceived as soon as the hammer strikes the plessimeter. The sensation can also be felt with the ball of the thumb if the plessimeter be held in the left hand, between the index finger and thumb, and be allowed to remain in contact with the abdomen for some little time after the tap of the hammer has been delivered. The writer considers the hydatid thrill as characteristic for echinococcus and peculiar to this form of cyst, and he does not think that it can originate in any sac containing fluid alone. It is certainly not independent of the presence of daughter cysts and membranes, and is not, in his opinion, perceived in any other pathologic condition; as, for instance, ascites, ovarian cysts, hydronephrosis, etc. The writer has been able to discover it in only one-half of the cases that have come under his observation, and always only in those that were characterized by the presence of numerous daughter cysts. The phenomenon may not be perceptible at all times, and may not always be felt with the same intensity. A great deal will depend upon certain physical conditions that may vary with each examination. Thus, for instance, the tension of the cystic sac, or even of the abdominal muscles,

may make a great difference. If the cyst be too much distended, the appearance of the phenomenon may be prevented. In several cases the writer failed to elicit the hydatid thrill over tightly distended echinococcus cysts, but could easily make it appear if 10 to 15 c.c. of the fluid contents were removed by tapping, thus reducing the pressure within the sac.

The spleen can be palpated exceptionally well in those cases that are designated as *enteroptosis* or *splanchnoptosis*, even though it be only slightly enlarged. An additional feature is observed in such cases that merits particular emphasis. As early as 1887 the writer originally called attention to the fact that in women, especially on the right side, occasionally on the left, the kidneys can be palpated, and that their movements with inspiration and expiration can be readily distinguished and recognized as a physiologic function. In women with enteroptosis the kidneys nearly always can be palpated, and in such cases we are further able to palpate *simultaneously* both the kidney and the spleen on the left side, and the kidney and the liver on the right. In palpating with the right hand alone applied as described above, on the left costal margin, the spleen taps against the extreme tips of the fingers on deep inspiration, while the kidney can be felt at the same time touching the under surface of the finger-tips. In bimanual palpation this phenomenon is still more characteristic. On deep inspiration the spleen is felt with the tips of the fingers of the right hand, while the lower portion of the kidney or even the whole organ can almost be grasped between the two hands and all its characteristic outlines felt.

The kidneys are differentiated from the spleen, aside from their characteristic outlines, by the following specific peculiarity. On inspiration the kidney that has descended can be pushed upward with a typical seesaw motion, a maneuver that cannot be executed on the spleen. This phenomenon is so characteristic that when once elicited it will never be forgotten. [The peculiar feel of the kidney as it slips back into place is, as said, quite characteristic and yet difficult to describe. It has to be felt a few times before its real diagnostic value is appreciated. When a "floating kidney" has descended during inspiration and is grasped by the bimanual method, it can, if freely movable enough to permit the hands to reach above the upper pole, be held down even during expiration. If, now, the pressure of the examining hands be very gradually relaxed, the kidney begins to feel slippery and acts almost as though it were trying to escape between the examining hands, till finally, with a little jerk, it suddenly slips back into its place. The patient often feels the little jolt and is startled by it.—Ed.]

In those cases where the spleen and liver are both considerably enlarged—as, for instance, in hypertrophic cirrhosis of the liver, and where the two organs meet in the median line, or more frequently to the left of it, in the left mammary line, and where consequently they cannot be differentiated by percussion—it is very important to be able to separate them by palpation. As a rule, in these cases an indentation can be felt that may correspond to the notch for the suspensory ligament of the

liver or to the boundary between the two organs. The writer has frequently been confronted with this question, and has been forced to leave it unsolved in the beginning. On autopsy, however, he has invariably found that this indentation corresponds to the line of junction between the liver and the spleen, the two organs frequently being in such close contact that they were closely wedged against each other. The indentation that was felt during life could always be clearly seen post mortem, and corresponded to a small space left between the two organs that were in contact everywhere else. It is self-evident that in such cases the notches in the spleen could not be felt.

PERCUSSION.

In the case of the spleen we distinguish the upper and the lower end, the posterior and the anterior margin, the outer and the inner surface. The spleen is situated to the left side of the spinal column, between the ninth and the eleventh ribs, in such a manner that its longitudinal axis is somewhat inclined, extending from above downward from the median to the lateral aspects of the body; it either follows the course of the tenth rib or forms an acute angle with it. The upper and more rounded end is usually removed from the spinal column by the width of two fingers; the lower end extends only very little anterior to the axillary line. The anterior margin of the spleen is usually indented and is more acute than the posterior margin. The convex outer surface presses against the concavity of the diaphragm. The inner one is divided by a longitudinal furrow into two divisions that are slightly convex. The anterior and larger one touches the infundibulum of the stomach; whereas the posterior and smaller one touches the upper end of the left kidney and is connected with the tail of the pancreas. The length and width of the spleen is about the same as that of the heart; its outline rhomboidal or oval.

For percussion of the spleen, its *relations to its surroundings* are more important than for any other organ. The difficulty in percussion of the spleen lies chiefly in the fact that we are capable of demonstrating and outlining only that part of the organ which is in direct contact with the thoracic walls. As a part of the spleen is covered by the margin of the lung, a second part is in contact with the left kidney, and a third one with the stomach and colon, we are enabled to determine positively only the boundaries between the lung and the spleen and of its anterior margin. The upper margin of splenic dulness—that is, the boundary between the covered and uncovered parts of the spleen—is formed by the lower boundary of the lung, which extends at about the same level as on the right side. This boundary line is found, close to the sternum, on the lower margin of the sixth rib, in the mammillary line at the upper margin of the seventh rib, in the axillary line at the lower margin of the seventh or eighth, in the scapular line at the ninth rib, and close to the spinal column at the eleventh rib. On deep expiration it moves upward; on inspiration and when the patient is lying on the right side

it moves downward, and on very deep inspiration it descends as far as the lower boundary of the pleural sac, in this way completely filling the so-called complementary space. If, therefore, we wish to percuss the spleen with the patient on his back, or, better, on the right side, it is preferable to percuss in the midaxillary line while the patient is breathing quietly and slowly. It is best to begin above and percuss downward toward the costal arch and to use light percussion.

As we gradually in this manner approach the region of the eighth rib at the boundary of the lung and spleen, the lung sound will gradually grow duller and duller, but we must not expect to find so absolute and intense a dulness as, for instance, over the liver. After determining the point where the sound on light percussion is most dull we designate it as the upper spleen boundary, mark it with a colored crayon, and continue percussing downward in the same vertical line. The nearer we approach the semilunar space, the more tympanitic the sound will become, until it ultimately merges into the loud sound of the stomach. This lower splenic boundary can only be determined if we percuss very gently, and we must never forget that if the fundus of the stomach be filled with food we get a dull sound, and that in such a case it is altogether impossible to differentiate the splenic dulness. It is still more difficult to find this lower splenic boundary if the fundus of the stomach be filled with air, and the loud tympanitic sound which it gives completely obliterates the dulness caused by so thin an organ as the spleen. In case we have succeeded in determining this lower boundary, we shall find it a finger's breadth or two above the costal arch. The lower boundary should also be marked with a colored crayon, and it will be found to be situated from 4 to 6 cm. below the upper boundary.

When we have succeeded in this manner in finding and marking these two parallel boundary lines, we must endeavor to find the anterior margin which connects them. To do this it is best to percuss from a point situated on the anterior aspect of the thorax in different directions toward the crayon outlines on the side of the chest, until we succeed in finding and connecting the line which represents the anterior margin. We usually find it to be part of a diagonal line extending from the left sternoclavicular articulation to the tip of the eleventh rib, and called the linea costo-articularis. This line is also several centimeters removed from the costal arch. If the spleen be of normal size, it is hardly ever possible to determine more than these outlines of the organ upon the thoracic wall, and it is almost never possible to outline by percussion that part of the spleen which is situated posteriorly near the spinal column. It is usually a very easy matter to demonstrate the movements of the diaphragm and the upward and downward excursions of the lung at the boundary line between the lung and the spleen. In order to do this we bring a good light to bear upon the left side of the body, and instruct the patient to breathe as deeply as possible. In this manner we can see the *movements of the diaphragm* and outline their amplitude on the thorax. [This is *Litten's diaphragm phenomenon*, or, as it is sometimes called, Litten's sign. It is often less distinctly made

out upon the left side than upon the right, but with a good light and a patient who can take deep inspirations it can be plainly seen. Adhesions of the pleura, pneumonia, pleural effusions, emphysema, etc., of course, interfere with this phenomenon.—ED.] The upper line will correspond to the highest point occupied by the diaphragm and by the upper margin of the spleen on deepest expiration. If we place the plessimeter on this line and percuss we get splenic dulness. If we instruct the patient to take a deep breath, and continue the percussing over the same point, we hear, instead of the dulness, a loud pulmonary resonance; and we are enabled to follow this downward as far as the lung expands on deepest inspiration, and in so doing covers the spleen. If we repeat the same experiment at the lower margin of the spleen we shall find that the spleen on deep inspiration descends just as much, diminishing the semilunar space of Traube.

As, according to these explanations, it is impossible to determine the upper third of the spleen, it is clear that the longitudinal diameter of the spleen found by percussion is smaller by just this distance than the anatomatic diameter. The width of the splenic dulness is usually from 5 to 6 cm.

However difficult it may be to percuss the normal spleen, it is an easy matter, comparatively speaking, to determine by percussion the outlines of the spleen when it is *pathologically enlarged*, especially in those cases where the anterior margin of the spleen reaches as far as the costal arch. The percussion of an enlarged spleen may, however, be exceptionally difficult in case there is tympanites, or when the distended intestines push the spleen upward or happen to lie in front of it. In typhoid fever the spleen is usually pushed back on account of this meteorism, so that in this respect typhoid spleens differ from other acute splenic tumors.

In order to study the increase or decrease in the size of splenic tumors, it is best to mark the boundaries of the dulness with a colored pencil. Especial care should always be taken to examine the patient in the same position, because otherwise errors may easily be made, especially if the spleen be freely movable. O. Schellung has given a very practical method, especially applicable in cases of malaria, of studying the amount of variation of the splenic dulness in the same person during the course of the disease. He marks the percussion boundaries of the spleen with colors on the skin of the patient, then places tissue paper over the region of the spleen, and determines the position of the sheet by special markings, noticing especially the outline of the costal arch. The outline of the splenic dulness is now traced through. On subsequent examinations the result of the new splenic percussion is drawn on the skin and then compared with the tracing of the preceding one, the tissue paper with the old outline being accurately laid in its original position.

Under certain conditions the exact determination of the size and position of the spleen may be exceptionally difficult or impossible—for instance, if fluid or gas has accumulated in the left pleural cavity; if

large pericardial exudates exist; if the stomach or intestines be distended; if air has entered the peritoneal cavity as a result of perforation of the stomach or intestine; or, finally, if a tumor be present in a neighboring organ, as, for instance, in the left lobe of the liver, the left kidney, the pancreas, the mesentery, the omentum, or the broad ligament. Also, if there are new formations in the mesentery as a result of chronic inflammatory processes, or if circumscribed exudates exist in this region. In all such cases the individual findings must be carefully interpreted.

Diminutions in the size of the spleen are very difficult to determine; in fact, we can say that they can only be determined in case previous examination has made us familiar with the size of the spleen before it was decreased in bulk. Distention of the stomach and of the intestine with air can make the splenic dulness appear smaller than it is in reality; atrophic conditions in old people can lead to a direct diminution in the size of the spleen.

The writer has already declared that palpation of the spleen is the sovereign method of examination, and wishes to emphasize again that he attaches very *little importance to splenic percussion;* his reasons for this statement have been given at length. Only in cases where the spleen can be definitely felt does he feel justified in rendering an opinion on its size and consistence. Percussion of the spleen is important chiefly in cases of floating spleen, where we must determine whether or not the spleen is in its normal position.

TRANSILLUMINATION BY THE RÖNTGEN RAY.

By transillumination of the thorax we may obtain a shadowgraph of the spleen under exceptionally favorable circumstances. In children we can regularly see a shadow on the screen, and the respiratory excursions are observable (Levy-Dorn).

C. Rosenfeld, in his book entitled *Diagnosis of Internal Diseases with the Röntgen Rays*, expresses himself as follows in regard to the examination of the spleen: "The upper inner and posterior margin of the spleen can often be seen; it is a band concave exteriorly, and extending from above downward; if this band extend very far outward, I have found that in such cases the spleen can be readily distinguished in the case of adults, and in the case of children even photographed. It appears in these cases as a shadow on the side of the stomach, corresponding more or less to the well-known outline of the spleen, about 5 cm. broad and 7 cm. high. It is possible to see spleens that are very much enlarged in very thin people, but we must not expect too much from transillumination of the spleen; on the screen the spleen can usually be seen fairly well."

EXPLORATORY PUNCTURE.

The writer has discussed the method and the value of exploratory puncture at such length in the sections on cysts and hydatid tumors of

the spleen that he will not refer to it at great length in this place. Exploratory laparotomy or puncture must be considered in those cases in which fluctuation has been elicited by palpation. Here examination of the fluid is necessary in order to determine positively the nature of the cystic tumor; we have to consider the contents of serous and blood-cysts, dermoid cysts, gall-bladder tumors, hydronephrosis, hydatid cysts, abscesses, circumscribed exudates, hematomata, pancreatic cysts, etc.; even after we have determined the nature of the cystic tumor we may still remain in doubt as to the organ to which it belongs. If, for instance, we have found hooks and scolices in the puncture fluid we know that we are dealing with an echinococcus; we do not, however, know where the cyst belongs, and the difficulties of a differential diagnosis in this sense are not removed by the puncture; we must attempt to determine the seat of the cyst by the aid of all other methods of examination. For instance, we can fill the colon with water or air and study the differences in sound which result from this inflation and the subsequent evacuation of the intestine; this method is especially useful in differential diagnosis between cysts of the spleen and of the kidney. We shall recur to this in our discussion on cysts.

The examination of the fluid obtained by puncture may give information that is absolutely conclusive in regard to the location and kind of cyst with which we are dealing, especially if we find constituents in the fluid that are specific for a certain organ, like, for instance, bile for the liver (in hydrops of the gall bladder), urea for the kidney (in hydronephrosis), pancreatic fluid for the pancreas (in cysts of the pancreas).

Since the dawn of bacteriology many clinicians have made it a practice to systematically *puncture the spleen in typhoid fever* in order to obtain material for bacteriologic examination; this procedure, rightly condemned on account of its danger, has been replaced by Widal's method. His reaction consists in mixing the blood-serum of typhoid fever patients with a pure culture of typhoid bacilli, in the proportion of 1:10; if agglutination of the bacilli occur we may conclude that the case is one of typhoid. Widal has given two methods, the macroscopic and the microscopic: in the first, 4 c.c. of typhoid bouillon culture are mixed with 8 drops of the serum; after from twelve to twenty-four hours the bouillon, which was uniformly clouded, becomes clear, and the individual germs have become agglutinated and settled to the bottom of the test tube. The microscopic method is as follows: A drop of the serum is mixed with 10 drops of the typhoid culture and examined in the hanging drop. Usually at once, at all events in the course of a quarter to half an hour, we can see that the bacilli have become immobile, paralyzed, clumped in groups, and agglutinated. These are the main features of the process; many modifications and precautions have been recently developed.

[Since Litten wrote this the technic of the serum test has materially changed. Dilutions of 1:40 or 1:50 are looked upon as necessary before an agglutination test can be declared positive. Tests with dead cultures are also made. The paratyphoid germ has been detected

and has to be reckoned with. And instead of puncturing the spleen—which procedure is, as just stated, not without danger—for typhoid or other germs a vein is punctured by a hypodermic needle (Luer syringe), and the blood thus obtained examined bacteriologically. The details of these methods do not belong in this volume, and must be sought in works on bacteriology or on the infectious diseases.—ED.]

PHYSIOLOGY OF THE SPLEEN.

OUR knowledge of the function of the spleen is still very meagre. The method frequently employed to gain information in regard to the significance of an organ in the human economy is extirpation; in the case of the spleen this method has yielded very little information. It was soon recognized that *the spleen can be removed without serious damage* to the organism; animal experiments and surgical procedures in human beings demonstrate this; in addition, cases of congenital absence of the spleen are on record in which no abnormal consequences were observed. The question arises whether extirpation of the spleen has any recognizable sequelæ; in several instances enlargement of the lymphatic glands has been observed after extirpation of the spleen, and this phenomenon has been interpreted as a process of compensation. However, enlargement of the lymphatic glands is not a constant occurrence. More frequently we observe a phenomenon explained by the close relationship existing between the spleen and the bone marrow in their common function as blood-forming organs. It seems that the hematopoietic activity of the bone marrow is increased after extirpation of the spleen. In this instance, too, we seem to have a compensatory process, the bone marrow performing an amount of additional work corresponding to the decreased activity of the spleen.

Another interesting observation has been made—*i. e.*, that occasionally after extirpation of the spleen *new formations* occur *in the lymphatic system* that have been interpreted as small organs whose function it is to replace the spleen. (Compare the section on Extirpation of the Spleen, p. 672.) In frogs extirpation of the spleen was followed by the formation of brownish-red nodules on the intestine. Tizzoni saw new formation of spleens on the mesentery of horses and dogs following obliteration of the parenchyma of the spleen and of the splenic vessels. Mosler also reports the presence of numerous tumors containing spleen tissue following the extirpation of the spleen in a dog; they were situated in the omentum and the mesentery, and proved to be telangiectatico-hemorrhagic lymphomata.

[The appearances described as occurring after splenectomy have been seen by many—Jizzoni, Winogradow, Eternod, Griffini, Mosler, and others. They are, however, differently interpreted by some later

observers. Warthin, by experimental work on the sheep and goat, finds that after total splenectomy there is hyperplasia of existing lymphoid tissue, transformation of hemolymph nodes into ordinary lymphatic glands, and a new formation of hemolymph nodes out of lobules of fat-tissue. Later there is proliferation of the red marrow. He believes a hemolytic function is assumed by the hemolymph nodes and lymphatic glands, and that this may exceed the blood-destroying function of the primitive spleen. Warthin's[1] papers should be consulted for a full exposition of the subject as well as for a complete bibliography.—Ed.]

The *volume of the spleen*, owing to the presence of unstriped muscle fibers, *is changeable;* irritation of these fibers or of the nerves that supply them by cold, electricity, quinin, ergot, or other drugs leads to a contraction of the spleen; the organ diminishes in size, looks paler and appears granular; on the other hand, the spleen enlarges if these nerves are severed. Landois found that on removal of the little nerve fibers situated near the hilus, enlargement of the spleen occurred in spots that have a bluish-red color. The enlargement of the spleen so frequently seen in infectious diseases has often been attributed to paralysis of these nerves, and the specific toxins designated as the poisons that produced it. However, the influence of fever temperatures must be considered in these cases, and also the possible invasion of the spleen proper by bacteria. The spleen may also become enlarged several hours after digestion at a time when the digestive organs, after a period of great activity, are no longer engorged with blood; it is possible, therefore, that the spleen is a *regulator of the blood-supply for the digestive organs.* The fact that the liver becomes enlarged as soon as we produce an artificial decrease in the volume of the spleen may be adduced as corroborative evidence in support of this hypothesis.

The quantity of blood that enters the spleen, and the rapidity of its flow through the organ, are not dependent alone on the blood-pressure in the splenic artery, but are to a great extent influenced by certain *rhythmic contractions* of the unstriated muscle fibers found in the capsule and the trabeculæ of the spleen. This important discovery has a particular bearing on the question under discussion, and for it we are indebted to Roy.

The spleen may be considered one of the *blood-forming organs.* It has two functions that seem to be diametrically opposed to each other. In the first place lymphoid cells are formed within the spleen, and it may be considered the chief producer of white blood-corpuscles. This is demonstrated by the constant presence of numerous lymphoid cells in the splenic veins; of these, many are destroyed in the blood-stream through fatty degeneration. In splenic leukemia excessive formation of white blood-corpuscles in the spleen occurs. [As a white blood-corpuscle producer the spleen must, according to recent views, take a rank inferior to the bone marrow and the lymphatic glands. Even in leukemia it is believed to be the marrow and the glands that play the

[1] *The Jour. of Med. Research*, vol. vii., No. 4, May, 1902; *Am. Jour. Med. Sci.*, cxxiv.

prominent part. In fact, Ehrlich and others discard the name splenic or spleno-myelogenic leukemia and speak of myeloid or myelogenic leukemia. In fetal life the spleen gives rise to new red corpuscles. This function is apparently continued for a short time only after birth. —Ed.]

On the other hand, the spleen must be considered an organ in which dissolution of red blood-corpuscles takes place. Kölliker and Ecker consider the spleen as a sort of scavenger for dead red blood-corpuscles; they base their view chiefly on the presence in the splenic blood of cells containing red blood-corpuscles. They describe them as large white protoplasmic cells possessing ameboid movement and that have taken red blood-corpuscles into their substance; the red blood-corpuscles undergo retrogressive metamorphosis within their hosts and disintegrate. The hemoglobin which is liberated in this way forms the mother substance of the splenic pigment which is similar to hematin. The whole mechanism of the spleen points very strongly to the fact that it is an organ in which red blood-corpuscles are destroyed; for aside from the ordinary constituents of the blood—the iron pigment—we find a variety of highly oxidized products of albumin, as leucin, tyrosin, xanthin, hypoxanthin, and taurin; and finally, by way of corroboration, the salts of the red blood-corpuscles are found in the pulp of the spleen.

We know the following in regard to the innervation of the spleen: the nerves of the spleen originate from a center in the spinal medulla; if this center be irritated, as, for instance, in asphyxia, contraction of the spleen occurs. From the medulla the fibers run through the spinal cord, passing through a series of ganglia situated between the first and fourth cervical vertebræ that are said also to be concerned in contraction of the spleen. Then the fibers enter the left splanchnic nerve, the semilunar ganglion, and end in the splenic plexus (Landois).

Under normal circumstances the spleen may change its volume, as already mentioned, corresponding to the stage of digestion. This reaction of the spleen makes it easier to understand how it may promptly swell after the invasion of the body by pathogenic bacteria. It is not yet clear to what degree the different possible causes of such swelling (fever, bacteria, toxins) participate. Experiments on the infection and intoxication of animals whose spleens have been removed promise to throw much light on this question. Pathologically, it is interesting to know that pressure on the splenic vein readily causes the organ to swell; this explains the distention of the spleen in portal stasis.

The action of quinin and other antipyretics in reducing the size of a spleen enlarged during infection, Binz explains as a result of inhibited or reduced production of leukocytes.

DISEASES OF THE SPLEEN.

CONGENITAL MALFORMATIONS AND ANOMALIES IN THE LOCATION OF THE SPLEEN.

ARRESTED development and malformations of the spleen are of very little practical interest, as they are rarely seen in healthy, normally developed individuals. In addition to this the spleen is not an organ absolutely essential for the maintenance of life, because we know that when it is absent, congenitally or by operative procedure (so-called splenectomy), its function can be assumed by other organs, notably the thyroid, the lymphatic glands, the bone marrow [and the hemolymph nodes (see p. 467).—ED.]. This important physiologic question is discussed at some length in the section on Splenectomy, to which we refer the reader, in this place giving only a brief synopsis of the most important forms of congenital malformations, according to C. F. Heusinger.

The most important groups of congenital malformations of the spleen are:

1. Absence of the spleen.
2. Abnormally small spleen.
3. Abnormally large spleen.
4. Abnormal shape of the spleen or division into several pieces; double spleen and accessory spleens.
5. Abnormal location.

1. **Absence of the Spleen.**—In the embryo chick the spleen appears at a very late period, and, according to Paletta, in the youngest human embryo the spleen is still absent. In the lowest forms of monsters the whole portal system—stomach, liver, pancreas, peritoneum, and spleen—is absent. Where in these acephalics organs resembling the liver are found, the liver and kidneys are usually united. The spleen is more frequently found in monsters with merely deficient development of the skull, but even in these cases it is frequently absent. Heusinger reports only 2 cases in which the spleen was absent where all the rest of the body was completely developed. One of these is communicated by Lemery. An infant girl, well proportioned and so handsome that Lebrun wished to paint her, died a week after birth; no liver was found, nor were the spleen and intestinal tract present. In the place of these organs a fleshy mass was found of about the size of a child's head, which was connected with the stomach but not with the anus, and contained arteries and veins.

The second observation the writer translates literally from the original French, as follows: "On the 11th day of September of the year 1564, Mathias Orrelius, a celebrated merchant of Antwerp, a German by birth, left this life. On the 12th an autopsy was performed by skilled surgeons, at which I (Schenck a Graffenberg) was present as physician, in order to see the digestive apparatus, notably the liver and

the spleen, for the patient had suffered from dropsy for several years. We looked underneath the diaphragm and the false ribs, but found no trace of these organs; certainly the most wonderful and unheard-of case; the whole substance of the intestinal tract was fleshy, and much more solid than muscle, so that it almost equalled in solidity the flesh of the heart; the vena cava originated from the intestinal tract itself in the same manner as the portal veins are distributed throughout the intestinal tract; this was unquestionably the reason why he suffered so frequently from inflammations and abscesses in the intestinal canal, for what is fleshy is more easily affected by inflammation and abscesses than what is more like the skin."

Haller says of this observation, "Ubi tamen credas connatorum viscerum confusam massam incisori imposuisse."

Obliteration of the spleen frequently reaches such a degree that it almost looks like absence of the organ; in animals atrophy of the organ can be produced experimentally by ligation of its arteries.

2. **Abnormally Small Spleen.**—In fetuses of mammals and of man, the spleen increases in size as the period of term is approached. In autopsies on the insane, and sometimes on perfectly normal people who had reached old age, the spleen was found round and thin, and so small that it weighed hardly 30 gm.

3. **Abnormally Large Spleen.**—This abnormality has frequently been observed in monsters, and also occasionally in normal individuals of great age.

Löwenwald, in the case of a girl of fourteen years, who had suffered from caries of the occipital bone and of the femur, found dropsy of the cerebral cavities, a very large heart, in the place of the stomach a dilated duodenum, a short and straight intestinal tract, a large liver, and a large spleen, the spleen situated, not in the left hypochondrium, but in the middle of the body, firmly attached to the spinal column.

In the case of a lady, who had been a very large eater, Pozzis was unable to discover any traces of the lung on the left side; he found a very large stomach, and an intestinal tract only a quarter as long as normal, a small liver, a very large spleen weighing 6½ pounds, and a colon whose diameter was much larger than normal. Baux found in the case of a child, who had been sickly and bloated since birth and had suffered from dyspnea (died eighteen months old), a liver that was enormously large, extending along the whole left side of the stomach, not divided into lobules. On the right side a very large but otherwise normal spleen was found.

4. **Abnormal Shape of the Spleen or Division into Several Pieces; Double Spleen and Accessory Spleens.**—In the human fetus and in very young embryos the spleen is often found indented or even divided into several pieces. These indentations, as we know, persist during life, and can frequently be felt on palpation on the anterior margin of the spleen; they are very characteristic, and frequently help us to decide by palpation whether we are dealing with the spleen or some other organ. This is especially the case in pathologic

enlargements. One, two, or even three such indentations (so-called crenæ lienales) may be found in the same organ; their depths are widely different; they may be so deep and extend so far that they divide the spleen horizontally by a well-marked furrow.

The changes of form assumed by the spleen under normal conditions and in malformations are very numerous; the spleen may be round or tongue-shaped, disk-like or roll-like, hemispheric, three-cornered, or cubic. In one case Meckel found the spleen of a fetus shaped like that of most quadrupeds—that is, twice as broad below as above.

Double spleen has been described a number of times. The two spleens may be either of equal and normal size, or of abnormal size and shape. In many cases other pathologic abnormalities were discovered at the same time; thus, in one case of double spleen the pancreas was absent, and one of the two spleens was drawn out to great length. In another similar case the stomach was found "very long and contracted, so as to form two parts."

Multiform division of the spleen, whereby five to seven single large lobes were formed, has also frequently been described; in the celebrated case of Abernethy the portal vein arose from the lower vena cava, and the spleen was divided into seven lobes.

So-called accessory spleens (lien succenturiatus or accessorius) also occur occasionally. They are usually small round tumors, resembling the spleen in color and consistence, but of very varying size. They are found partly in the omentum, partly in the ligaments of the spleen, partly in the head of the pancreas; they may vary in size from that of a lentil to that of a walnut; there may be from one to twenty; each accessory spleen occasionally has its own artery and vein.

Otto, in a monster, found the spleen of normal size, but divided by very deep indentations into a number of almost completely separated lobes; in addition to this 23 completely separated accessory spleens were found between the spleen and the fundus of the stomach; they were all spheric and identical with the spleen as regards bulk, consistence, and color; each had a small artery or vein, and they were all of different sizes, some as small as a lentil, others as large as a pea, the whole spleen resembling a bunch of grapes.

Heusinger, in the case of a soldier who had been a sufferer from respiratory difficulty and cyanosis, found the spleen divided by so many furrows and scars that it appeared to consist of from 8 to 12 different pieces that had apparently been separated at one time; besides, 4 accessory spleens were observed situated between the organ proper and the stomach; these were all spheric and very similar to the main spleen. The largest of these accessory organs weighed 47 gm.; the second, 34 gm.; the third, 3 gm.; and the fourth, 2 gm.; the main spleen weighed half a pound and was indented in several places on its margin.

Rosenmüller, quoting Mosler, makes the remarkable statement that among 400 autopsies made on cases from northern Germany he found an accessory spleen only once, whereas among 80 autopsies among inhabitants of southern Europe he saw only 5 cases that did *not* have accessory

spleens. This observation has been verified by Giesker. Henle, according to his experience in Heidelberg and Göttingen, contradicts the statements of Rosenmüller and Giesker. Dupuytren states that the occurrence of accessory spleens is very frequent in youth, and especially so in the fetus.

Occasionally these so-called accessory spleens are new formations. Some investigators claim to have discovered accessory spleens in animals after extirpation of the spleen; these would be newly formed spleens. The writer was unable to find in the literature any positive statements in regard to this. Mosler, however, has been able to verify this finding in a very interesting case. Among 50 extirpations of the spleen, he found in 1 case the whole omentum covered with small dark-red nodules, varying in size from that of a lentil to that of a bean, that from their outward appearance and even on section greatly resembled splenic tissue. M. Roth examined these nodules carefully, declaring them to be pathologic formations, to be classified as telangiectatico-hemorrhagic lymphomata. In the 2 cases, one of a young and the other of an old dog, Tizzoni saw the formation of numerous nodules after extirpation of the spleen; they were of the consistence and structure of the spleen, and were distributed all through the mesentery. Tizzoni considered these nodules to be new formations and not accessory spleens, for the reason that the latter never occur in such large number—*i. e.*, from 60 to 80—as in this case; because, further, the nodules observed were distributed all through the mesentery, and not only in the gastrosplenic ligament; and, finally, because he was able to study different phases of development in different nodules and, in some of them, even to discover red blood-corpuscles containing nuclei.

[These were probably enlarged and newly formed lymphatic glands and hemolymph nodes. Warthin,[1] in his experiments, was unable to make out new formations of spleen tissue.—Ed.]

An interesting fact merits chronicling—namely, that in typhoid fever and leukemia the accessory spleens may be enlarged as well as the main spleen.

5. **Abnormal Location.**—The *congenital anomalies* in the position of the spleen can be: first, extra-abdominal, as in ventral or in umbilical hernia; second, the spleen may be situated in the left half of the thorax, as in congenital defects or hernia of the diaphragm; third, it may be found on the right side in complete *situs viscerum inversus*. In fevers where the liver is enlarged the left lobe of this organ may frequently be mistaken for an enlarged spleen.

We will discuss the *acquired abnormalities* in the position of the spleen in the section on Floating Spleen.

Preuss reports an interesting case of absence of the spleen in a girl born with a defect of the abdominal wall. When the stomach, which was perfectly normal, was opened the spleen was found inside of it, connected with the mucous membrane through blood-vessels; the organ

[1] *Loc. cit.*

was small but otherwise normal. In the case of a female anencephalus, Klein found the spleen in the left half of the thorax, above the diaphragm. In another case of malformation Blanchot found the spleen high up in the thorax, above the incomplete diaphragm, but underneath the lung, which in this case consisted of a single lobe. Otto, in another case of anencephalus, found the spleen and part of the liver and the colon above the diaphragm in the thorax and not connected with the stomach by any vessels. The case of Löwenwald, which we have already mentioned (p. 470), also belongs to this category; the spleen was found, not in the left hypochondrium, but attached posteriorly to the spinal column.

FLOATING SPLEEN.

(Dislocation of the Spleen.)

Definition and Remarks.—Normally the spleen is situated deep down in the left hypochondriac region, in such a manner that its convex surface touches the diaphragm, its posterior margin filling the space left between the upper half of the convex margin of the kidney and the posterior abdominal wall. The longitudinal axis of the spleen is inclined so that its upper end is at the same time its posterior end, and it approximately follows the direction of the ribs. The position of the spleen usually corresponds to the space between the ninth and the eleventh ribs; its upper end is situated near the spinal column, at a distance of about two fingers, and the lower end near the margin of the thorax, at a distance of about three fingers. The serous covering of the spleen is a continuation of the peritoneal covering of neighboring organs, which after several duplications reaches the spleen. One of these duplications is called the gastrosplenic ligament; it extends from the infundibulum of the stomach to the hilus of the spleen, and includes the vessels and nerves of the spleen; another is called the phrenosplenic ligament, and connects the diaphragm with the upper end of the spleen; a third one, called the phrenocolic ligament, extends underneath the spleen to the left flexure of the colon. These bands hold the spleen in position; the most important is undoubtedly the *phrenosplenic ligament*, because it is the real suspensory ligament of the spleen.

The maintenance of the spleen in its normal position is dependent upon a great many conditions. In ordinary respiration, and especially on deep inspiration, the spleen is moved from its normal position through the descent of the diaphragm, usually in the direction of its longitudinal axis, so that in enlargements of the organ its lower margin can be distinctly felt. The spleen moves up and down with respiration, these excursions corresponding exactly with the excursions of the diaphragm.

Permanent changes in the position of the spleen as a result of pathologic processes may occur, and the spleen may be situated above or below the diaphragm. The spleen is displaced downward by all

effusions into the left thoracic cavity; these may be fluid or simply air (hydrothorax, serous pleurisy, empyema, hemothorax, pneumothorax, sero- or pyopneumothorax); or the dislocation may be the result of neoplasms in the left thorax or of malformations of the spinal column. Pneumonic infiltration of the lung and emphysematous enlargement never displace the spleen. [It is rare, too, for the normal spleen to be so pushed down by fluid in the left chest as to be palpable.—Ed.] A displacement upward occurs as a result of peritoneal effusions, whether free or encapsulated, of accumulations of air in the peritoneal cavity, meteorisms, ascites, and abdominal tumors of all kinds. Such dislocations are due to purely mechanical causes, and the ligaments of the spleen oppose no resistance to these movements. If the spleen is anchored by adhesions or parasplenitis, or is invaded by neoplasms from surrounding organs that tend to fix it, then the movements of the normal spleen may be diminished or prevented. All these dislocations, with the exception of that due to adhesions, are, of course, temporary, and as soon as they are relieved the spleen returns to its normal position.

In cases where the spleen is permanently dislocated and at the same time is freely movable we speak of a floating spleen. If we define floating spleen in this way we must except all those cases in which the spleen, normally situated, can be moved in different directions within certain narrow limits, or moves passively with a change in the position of the body. Floating spleen proper is characterized by the fact that the spleen is *not* found in its normal place, but is *permanently* located in another; properly speaking, this condition should be called *dislocation of the spleen*. The conception of a wandering spleen implies not alone dislocation, but mobility as well. As soon as a spleen of this kind, owing to inflammation of its capsule, becomes adherent in an abnormal location, it is no longer a floating spleen, because it thus loses its passive mobility; it now becomes a dislocated spleen. It all depends on the position of the organ after its dislocation whether it be movable with respiration; if it be completely surrounded with coils of intestine and situated in the middle of the abdomen, or if in the pelvis, or in the hollow of the sacrum, respiratory mobility can, of course, not be expected, be the organ adherent or not.

Etiology.—Dislocation of the spleen is practically caused through abnormal length, stretching, or tearing of the ligaments of the spleen; further, through an increase in bulk and weight of a chronically diseased spleen; or, finally, through relaxation and stretching of the abdominal walls.

The *relaxation and elongation of the ligaments* can be congenital or acquired. The ligaments connecting the spleen with the diaphragm and the stomach are the ones to be chiefly considered. Acquired relaxation of the ligaments is usually caused by stretching of these tissues through trauma or the weight of an enlarged spleen. The relaxation of the abdominal walls is in many cases caused by pregnancy, and this in part explains the fact that floating spleen is found only in the *female sex*. [It is occasionally found in men. The writer has seen one such case

in an adult male. Trauma was the apparent etiologic factor in this instance.—Ed.] The increase in bulk of the spleen is usually caused by malaria, leukemia, and pseudoleukemia; and in the cases that have been described the spleen frequently weighed 5 kg. or more. Hypertrophic floating spleen, according to surgical reports on spleen extirpation, is very frequent; however, it is infrequent in proportion to the number of cases of large splenic tumors in general. This comparison shows that the weight of the hypertrophied spleen cannot alone be the cause of its dislocation, but that in addition the suspensory ligaments must have become relaxed. This relaxation and yielding of the ligaments is not only a supposition, but is also demonstrated by certain anatomic findings; the gastrosplenic and phrenosplenic ligaments have been found enormously long (up to 6 in.), very narrow and thin in some cases, in others altogether atrophied, and in 1 case absent. It is not possible to decide in each individual case how far congenital or acquired anomalies of the corresponding folds of the peritoneum are responsible for this condition, or in how far the traction of an enormously heavy spleen has caused them. So much is certain, that occasionally a hypertrophy of the spleen may lead to a dislocation of the organ if the ligaments are damaged by trauma. Several observations scattered through the literature seem to give corroborative evidence in favor of this mechanical luxation of the spleen, and we can imagine that one or both ligaments may have been nicked or torn.

Such a case was described by Pirotaix, in the year 1874. A woman of thirty-five years fell from a wagon and was thrown against a stone wall; when she regained consciousness she felt a violent pain in the left hypochondriac region, followed by nausea and inability to rise. A physician was called, and discovered a tumor, which he tried to soften with leeches and mercury ointment; the tumor, however, did not grow smaller, and vomiting and pains in the region of the larger curvature of the stomach persisted with great obstinacy. The author was consulted six weeks after the accident. He found a tumor 15 cm. broad, 9 cm. long, situated vertically in the iliac region; it was freely movable and could easily be grasped. He recognized the organ as the spleen, replaced it, and kept it in place first with a napkin and later with a bandage. As soon as the replacement had been made the pain in the region of the large curvature disappeared, the vomiting stopped, and the patient swallowed a glass of Malaga wine with avidity; at the same time she was able to rise, whereas before she had remained in bed.

Another similar case is reported by Rezek. A woman was thought to be pregnant, and in the abdomen was discovered what seemed to be a hernia. On palpation a tumor was felt through the normal abdominal wall; it was hard and small, not elastic, freely movable, convex above, and furrowed on the lower margin toward the left side. The trouble was diagnosed at first as ectopic pregnancy, later as a tumor of the ovary. On careful examination Rezek found that the tumor was freely movable in all directions and could be forced into the right and left hypochondriums; moreover, it was not connected with any of the organs of the pelvis. The diagnosis of floating spleen seemed most probable to him, especially as he had learned that the patient had been suffering for five years from an intermittent fever, and had noticed a hard swelling in the region of the spleen fifteen months ago, immediately after a fall downstairs.

Ledderhose, to whom we are indebted for a very clear elucidation of the conditions causing floating spleen, calls attention to the fact that in some cases the ligaments are undoubtedly torn, and that we cannot assume that in all cases floating spleen develops only gradually, causing

the ligaments to become gradually distended. According to Kundrat and several of the older authors, dislocation of the spleen does not occur through a process of wandering, but from a *sudden displacement* of the organ; in other words, the change of position does not occur gradually, but suddenly. Further, displacement will cease as soon as the dislocated spleen finds a fixed point of support, either in the left iliac region or in the pelvis or against the symphysis. If the spleen continue to increase in size after this, then, of course, it may still change its location; for instance, if it fail to find sufficient room in the left iliac region it may wander into the right iliac region. We have already mentioned the fact that *relaxation of the abdominal walls* due to repeated pregnancies favors dislocation of the spleen. The position of all the other organs of the abdomen, of course, has a great bearing on the occurrence of floating spleen.

The condition of the abdominal organs which is designated as enteroptosis is an especially prolific cause of dislocation of the spleen. In this condition it is possible to outline all the abdominal organs with great precision; and as in these cases the abdominal walls are exceedingly thin and relaxed and all the ligaments are very much stretched and atrophied, a movement of the spleen from the peritoneal pocket in which it is normally situated into another can readily occur. In a case of this kind observed by the writer he was able to determine the much discussed question whether only enlarged and very heavy spleens are likely to wander, or whether the wandering may also occur in the case of the normal organ.

The case was that of a sewing-girl, who was afflicted with enteroptosis after having given birth to two children. She fell downstairs in the dark into a cellar; vomiting and pain in the left side resulted. After resting in bed for several days, with cold cloths placed over the region of the spleen, the patient attempted to rise and to resume her occupation (sewing cloaks). She suffered a good deal, and finally went to the hospital of the town in which she lived; finding no relief there, she came to Berlin seven weeks after the accident, in order to consult the writer. He felt a spleen of *normal size* underneath the umbilicus, with the hilus turned upward and to the right, and very painful on pressure. He had no difficulty in replacing the spleen to its original location, where prior to this replacement no percussion dulness had been elicited; a bandage was applied and her condition became much ameliorated.

Martin also found a spleen of normal size in the pelvis, which he could readily palpate by the combined method of vaginal examination; touching the spleen in its dislocated position was very painful, but as soon as it had been replaced it could be handled without pain. The pains were worse if the patient had been on her feet for a long time, and were also exacerbated during digestion. The patient could not sleep well and was incapable of attending to her work. Extirpation of the organ in this case relieved the symptoms.

In the 2 cases just quoted we are justified in assuming that the spleen was not enlarged at the time of the accident. In the writer's case the stretching of the ligaments was not congenital, but had developed in the course of those pathologic processes which had ultimately led to enteroptosis, and he feels justified in concluding that occasionally acquired

anomalies of the ligaments, combined with traumatic processes, can produce dislocation of a normal organ.

Anatomy.—The dislocated spleen has been found in almost *every part of the abdomen and pelvis.* Choisy found it in the middle of the abdomen; Maffei, in the left iliac and hypogastric regions; Fandacy, in the inguinal region; Van Swieten, in the hollow of the pelvis; Morgagni and Ruysch, in the contents of an inguinal hernia. It is most frequently found in the left iliac region, pressed against the crest of the ilium. In minor degrees of dislocation the spleen remains within the bony thorax, but can be moved from its normal position through pressure or through a change of position of the body. If the spleen be completely dislocated from its normal place, the left flexure of the colon will be found where the spleen should be. If perisplenitis exist, the spleen can be connected with almost any part of the abdominal walls or of neighboring organs, even with the bladder and the rectum. The hilus of the spleen may be directed differently according to the position of the organ; if the spleen be in the left cavity of the ilium, the hilus points upward and to the left; if in the right cavity, upward and to the right; and occasionally, if it be situated in the pelvis or stand transversely in front of the lumbar vertebræ, directly upward. As a rule, a dislocated spleen is found to be much hypertrophied, especially if the dislocation has occurred following enlargement through malaria, leukemia, or pseudoleukemia. Only *rarely is the spleen found to be of normal size* or even smaller. This occasional decrease in size after dislocation is demonstrated by the presence of atrophic parts in the parenchyma, and the wrinkling of the capsule. The spleen in these cases is usually described as being inelastic, dry, contracted, and of a dark-brown color; these contractions probably are the result of perversions of nutrition due to deficient arterial circulation. In other cases the spleen has been found to hypertrophy after the dislocation had occurred.

Quite frequently a floating *spleen becomes twisted.* It may be that the hilus of the spleen stands parallel or diagonally to the intestinal walls; or the floating spleen may turn around its horizontal axis. In this case a torsion of its pedicle occurs, which consists of the gastrosplenic ligaments and the vessels of the spleen. In the course of time this torsion may be repeated—that is, the spleen may be twisted several times around its axis. As a result of this torsion and traction, parts of the vessels of the spleen become obliterated; in many cases thrombosis of the splenic artery has been observed, and as a result disturbances in the circulation and nutrition of the organ follow; atrophy and contraction of the spleen result; pigmentary and fatty metamorphoses, and finally softening, occur. In these cases the artery and vein are partially obliterated, the spleen itself enormously contracted, the parenchyma transformed into a yellowish-red doughy mass, just as in an infarct of a degenerated spleen. In some places the tissue of the spleen is converted into a shiny mass, very rich in cholesterin and resembling the contents of a dermoid cyst. As a rule, the pedicle of the spleen is also affected. As a result of the traction exercised by the floating spleen,

the tissues of the pedicle are pulled and attenuated and its nutrition disturbed by the torsion, so that the spleen is found attached to a thin string consisting exclusively of connective tissue. Even this may ultimately be destroyed, so that it cannot be found at autopsy. Thus the spleen may become altogether separated from all its connections and float around free in the abdomen. Babesin described a case in which the gastrosplenic ligament was twisted three times around its longitudinal axis, and in which the artery and vein had become partially obliterated. Here the parenchyma of the spleen had become transformed into a reddish-gray ichorous mass, in which the degenerated connective-tissue parts of the spleen were suspended.

In many cases of floating spleen death has been produced by gangrene of the fundus of the stomach, due to traction on the stomach and narrowing of the lumina of its vessels. In another case the vessels of the spleen and of the pancreas produced compression of the duodenum, and as a result considerable dilatation of the stomach had occurred. The pancreas may occasionally be lengthened out into a long, twisted cord that contains not only the pancreas itself, but also the gastrosplenic ligament, the splenic artery, and the splenic vein. It seems that occasionally the pancreas can liberate itself again.

The writer wishes to record an interesting autopsy on the case of a peasant woman who had died of cholera, and in whom he found a floating spleen that was not hypertrophied. He reports it for the reason that autopsies of this kind are rare, and he wishes to remark that in this case we may possibly assume that a congenital anomaly of the ligaments of the spleen had existed. (The case came from Dittel.)

A peasant woman, forty years of age, was brought into the hospital, suffering from asphyctic cholera. In addition to the ordinary symptoms of cholera in this stage, the abdomen was found retracted and doughy, and percussion elicited an empty sound. At the level of the pelvis and situated transversely over the region of the last lumbar vertebra a tumor was felt, which was oval, hard, small, movable in all directions, and painful on pressure. The patient died twenty-four hours after admission to the hospital; an autopsy was performed a few hours after death; no air was found in the intestines—they were collapsed and filled with rice-water stools. The colon was situated deep down in the pelvis and seemed to fill it completely; the small intestine was covered by the spleen, which was situated over the last three lumbar vertebræ, and was 8 in. long, 4 in. wide, and 1 in. thick. The hilus pointed upward. The organ was small, hard, and movable in all directions; the stomach was much distended, with the pylorus situated tip down, but the splenic end occupied its normal position. From the stomach to the upper end of the spleen was stretched the gastrosplenic ligament; it was 6 in. long, narrow, and very delicate. No trace of the suspensory ligament could be discovered. The tissue of the spleen was dark brown with a tinge of red, almost inelastic, and the cut surface seemed dry; the capsule was moderately thickened and not creased. The position of the ascending and transverse colon was normal, but the left flexure of the colon occupied the place that normally belonged to the spleen and filled it completely, so that it reached to those parts of the diaphragm that the spleen would have touched had it been in its place.

Symptoms.—In studying the symptomatology of floating spleen we must separate the subjective from the objective symptoms.

The *subjective* symptoms produced by floating spleen will be different according to the location of the dislocated organ. Occasionally a float-

ing spleen will cause so few symptoms in the patient that she knows nothing of her trouble, and it is only discovered by chance when medical examination is undertaken for some other cause. More frequently, however, patients with floating spleen complain of *pain* of varying intensity. It may be of two kinds, either local, starting from the dislocated organ itself, or radiating into the surrounding tissues. According to the seat of the dislocated organ, these pains may radiate into the right thigh, the stomach, the region of the heart, or the region of the left shoulder. If the spleen be compressed these radiating pains are very frequent. In addition there are *general symptoms*. The feeling of a foreign body and of a weight in the abdomen are often described.

In judging of the significance of these last symptoms and of their value in the diagnosis of floating spleen we must not forget that all these complaints are occasionally made by females with genital lesions and by hysteric patients. The same applies for secondary symptoms of floating spleen, such as constipation, headache, nausea, vomiting, menstrual anomalies, dyspepsia, psychic disturbances, and insomnia; also, sometimes, paretic weakness in the lower extremities, formication, strangury, and occasionally pain in the dislocated spleen, which disappears when the organ is manipulated with the *supposed* intention of replacing it. We must always remember, in judging of the value of subjective symptoms of floating spleen, that in women the interrelationship of the abdominal organs is very varying. However, there can be no doubt that in certain cases the subjective symptoms may be exceptionally severe in comparison to the nature of the affection.

The objective symptoms are chiefly produced through the action of the dislocated spleen on surrounding organs; thus, paresis and formication of the lower extremities have been described as a result of pressure on the spinal nerves at the point of their exit from the spinal column; in other cases tenesmus of the bladder and rectum, where the spleen had become adherent to these organs. The literature on cases in which ileus has been observed as a result of compression of a coil of intestine through the dislocated spleen is abundant. [Symptoms resembling ileus may also be produced by a sudden twisting of the pedicle of the spleen, much as in the case of a fibroid with torsion of the pedicle and strangulation.—Ed.] Sometimes the weight of the spleen is combined with that of the pancreas, which follows in the direction of the traction exercised by the spleen, and thus the effect of this pulling is aggravated. Coumans and de Cnæp describe a case in which the spleen, which was situated in the right iliac fossa, had compressed the ileum so much that death occurred from complete closure of the intestinal tract. In a case reported by Babesin the coils of the jejunum had become incarcerated in an abnormal slit in the elongated gastrosplenic ligament. Klob and Rokitansky observed gangrene of the fundus ventriculi, and in another case dilatation of the stomach. The first occurred from excessive traction and obliteration of the arteries of the fundus; the latter, from pressure of the pancreas, which was in its turn pulled out of place on the duodenum.

Diagnosis.—The diagnosis of floating spleen is based on the finding that the spleen is absent from its normal place, and that a tumor found in an abnormal part of the abdomen or the pelvis can be recognized as the dislocated spleen. Percussion alone can determine whether the place normally occupied by the spleen is empty or not. As the tympanitic sound of the left flexure of the colon can always be heard in this spot if the spleen be absent, we usually cannot be in doubt. The matter may be elucidated still more if we fill the colon with water *via* the rectum, demonstrating a dulness in the region of the spleen, then allow the water to run off, and discover tympanitic sounds in the same place. In percussing the region of the spleen we must not forget that in old women, especially, contraction of the spleen may have occurred, which produces the impression of absence of the spleen. Palpation gives most important information in regard to the character of a tumor found in the abdominal cavity; if it be the spleen, its characteristic shape, the convex and concave margin, possibly the indentations that are always to be felt in large tumors, and finally the hilus with its pulsating arteries, must be demonstrated. If the abdominal walls are relaxed no difficulties will be encountered, especially if the spleen be freely movable, and if it can be, so to speak, rolled about. The diagnosis is made positive if it be possible to replace the floating tumor into the position of the normal spleen. In case the spleen is attached in some abnormal location, it will not be so easy to palpate the margin and the hilus; however, if repeated examinations are made, it will usually be an easy matter to recognize the tumor as the spleen. Occasionally it is possible to recognize the organ from its outline, as it is visible through the abdominal walls. If the floating spleen be situated in the pelvis, vaginal examination may give valuable clews.

Floating spleen can be confounded with floating kidney and a movable tumor of the ovary. The first mistake is made with less frequency nowadays, since the writer has demonstrated that in women, who alone are affected with floating spleen, the kidneys can regularly be palpated on both sides and their respiratory movements demonstrated; and, as we are usually dealing with individuals suffering with an enteroptoic abdomen, the determination of the location of the kidneys in their normal place is usually not attended with any considerable difficulty. Modern methods make it almost impossible to mistake a dislocated spleen for an ovarian tumor.

If friction sounds can be heard over the dislocated spleen we can assume that perisplenitis exists. If the spleen be very large and hypertrophic, especially as a result of leukemia, friction sounds are heard with great frequency.

[In doubtful cases an anesthetic may be necessary in order to determine the nature of the mass. Yet, even with the utmost care, the real condition is at times only discovered at the time of operation. Nearly every gynecologist of experience has been confused or deceived by a floating spleen that was lodged in the pelvis and simulated some other

condition. The writer once saw one removed from the cul-de-sac, the operation being undertaken for a supposed hematocele.—Ed.]

Treatment.—In all cases of floating spleen due to malaria we can attempt to decrease the volume of the organ by the usual remedies (quinin, arsenic, electricity, cold applications, and the ice-bag). In cases of leukemia all attempts to diminish the volume of the spleen through therapeutic measures must be designated as a loss of time. [Later, mention will be made of the temporary improvement, at least, that may follow the use of arsenic or the Röntgen ray.—Ed.] It is very important, even if no symptoms are directly traceable to dislocation, to anchor the spleen, if possible, in its normal place by the use of bandages, if for no other reason than to prevent it from becoming anchored in an abnormal place. Reposition and fixation are especially indicated, because pain is usually relieved. It is a matter of great difficulty to apply a suitable bandage, as difficult as in floating kidney, and great patience must be exercised on the part of the physician, the patient, and the nurse, so that by repeated trials and changes that degree of pressure can be discovered which does not bother the patient too much, and at the same time keeps the spleen in place. In the case of floating kidney the writer uses small bags filled with glycerin; they are well borne in most cases. Application of a bandage is also advisable, for the reason that it prevents synechiæ of the spleen with neighboring organs, especially the intestine; such an accident is most liable to occur if the enlarged spleen is exercising pressure in an abnormal location.

v. Engel recommends artificial twisting of the pedicle of the spleen, in order to produce partial contraction or atrophy of the organ. Such an operation is bloodless, it is true, and might seem indicated for this reason; but, on the other hand, it is dangerous and should be condemned, because we cannot control the degree to which we impede the flow of blood through the arteries; complete obliteration of the vessels would, of course, lead to gangrene of the spleen.

Rydygier in one case successfully sewed the spleen in its normal place. In this operation, which is called *splenopexy*, he proceeded as follows: An incision was made in the linea alba; in order to determine the size of the pocket that was to be formed through separation of the parietal peritoneum from the inner thoracic wall, the spleen was first replaced in its normal position; then it was pushed downward again, and a convex incision, corresponding in length and width to the spleen, made in the region of the eleventh, tenth, and ninth ribs, through the parietal peritoneum. Starting from this incision the peritoneum was separated from its attachments with a blunt instrument, so as to form a pocket large enough to receive the lower part of the spleen. In order to prevent an enlargement of this pocket downward, through the weight of the organ, the lower part was strengthened by a few sutures. The margin of the pocket was then sewed to the gastrosplenic ligament. As an additional precaution, the two lateral margins of the spleen may be attached by a few stitches to the peritoneum; these stitches must, of

course, be carried through the parenchyma of the spleen. In order still better to secure adhesions between the spleen and this pocket, the corresponding lower end of the spleen can be denuded; the edges of the peritoneum are then trimmed and, finally, the abdomen closed.

This operation, by which the dislocated organ was replaced in its normal position and sewed into an artificially constructed pocket, yielded comparatively good results. Three months after the operation the spleen was still in the place where it had been attached. In those cases, then, in which the floating spleen is not attached to its surroundings and where it cannot be retained by a suitable bandage, splenopexy may be attempted. As a rule, however, suitable bandaging will relieve most of the symptoms. The results of the operation recorded above are, of course, not conclusive, because the case was under observation for a short time only.

If patients complain very bitterly about the distress caused by a dislocated spleen that is not movable (or only slightly movable), and if no other remedy seems to lead to the goal, then extirpation of the spleen must be considered. This operation was recommended in 1856 by Kuechenmeister for those cases where it was impossible to bring about a diminution in the size of the organ, and where violent symptoms obtained. Simon, in 1857, limited the operation to those cases where very acute symptoms occurred, especially rupture and intestinal obstruction. Nowadays we operate only in those cases where violent distress exists or dangerous symptoms arise, and in case we have not succeeded in relieving the trouble in some other way. Rydygier's operation of splenopexy was only performed in the one case and the result was good, for an examination made three months after the operation demonstrated positively that the spleen had remained unchanged in the place where it had been attached. If the writer may be permitted to criticise, he would say that a period of three months signifies nothing at all when it comes to pass judgment on the final effects of an operation. His own experience, it is true, is limited to the field of kidney surgery; he has in many instances sewed floating kidneys into place, but with one exception the results were not satisfactory; the kidney always would detach itself from its stitches, and after some time begin to float around again, as before. In several cases the operation was repeated; in one instance the kidney was attached three distinct times; in every case it tore loose again. He attributes this chiefly to the constant respiratory movements to which the kidneys were subjected; this loosens the stitches and ultimately separates them, and he must assume that in the case of the spleen things are not very different. In addition, it is clear that this operation can be considered only in those cases where the spleen is not too much enlarged.

If, as is usually the case, we are dealing with a very much enlarged floating spleen, then extirpation of the organ is the only procedure which promises relief; and if the symptoms are very violent the results are usually quite satisfactory, at least so far as the amelioration of these symptoms is concerned. Vulpius, in a book published in 1894, col-

lected 40 cases of splenectomy that had been performed for floating and idiopathically enlarged spleen. Of this series 13 died, which represents a mortality of 32½ per cent. In all these cases, however, the tumors were very large, and Vulpius concludes that a weight of 3000 gm. should represent the limit at which it is wise to attempt extirpation. In very large floating spleen, therefore, in case the distress caused by the tumor is very great and the spleen does not weigh over 3000 gm., splenectomy is to be recommended. Too little material is at present available to allow us to draw any definite conclusion in regard to the value of splenopexy in cases of small floating spleen.

PERISPLENITIS.

Etiology.—Inflammation of the capsule of the spleen hardly ever occurs idiopathically. It is probable that it can occur only in cases of trauma, as, for instance, a contusion or a violent blow in the region of the spleen; the capsule in such cases can be inflamed over a large part of its surface. Much more frequently, however, we find localized inflammation which corresponds to diseased processes within the parenchyma of the spleen, or to a peritonitis which extends to the spleen by contiguity. The results of this perisplenitis are usually synechiæ with neighboring organs, the inner surface of the abdominal wall or the diaphragm.

Circumscribed perisplenitis is found most frequently in all localized diseases of the parenchyma of the spleen that extend to the periphery, chiefly in hemorrhagic infarcts and in abscess; further, it is seen in all acute and chronic tumors of the spleen, notably in echinococcus, leukemic and pseudoleukemic tumors, in malaria, and in amyloid degeneration. As in all these affections the inflammation of the capsule may involve first one place and then another, and as a new focus may start while another is in process of healing, we can often see post mortem all stages of inflammation side by side in a spleen that has been affected in this manner. It is interesting to observe in close proximity a fresh, scarcely recognizable, fibrinous deposit and a cartilaginous thickening or even calcification. [Some of the most marked perisplenitic changes are seen in connection with the so-called pericarditic pseudocirrhosis of the liver (Pick's disease, multiple serositis). Here the thick, whitish capsule may resemble that of the liver in "Zuckergussleber." —Ed.]

Pathologic Anatomy.—In acute cases the capsule of the spleen is covered with fibrinous deposits that glue the spleen to its surroundings, and in severe cases form pockets filled with pus. In chronic cases thickening of the capsule is seen on the convexity of the spleen, which is caused by new formation of connective tissue. The extent and thickness may be very variable. In severe cases the whole convex surface of the organ may be covered with a white smooth layer, of cartilaginous consistence, which may be several millimeters in thickness. In less severe cases this fibrous layer is less thick and limited to smaller areas.

The connective tissue very frequently has the white tendinous appearance of so-called inscriptio tendinal, and forms either round spots, like the "milk spots" on the pericardium, or irregular figures. The parenchyma of the spleen in these cases may be quite normal or slightly hyperemic; the spleen may be enlarged or reduced in size, changes that are not at all constant and are not necessarily related to the fibrinous thickening of the capsule. Only occasionally the thickened capsule contracts and compresses the spleen to such a degree that atrophy is induced or partial contractions occur, and in this way irregularities of the surface of the spleen are produced. In old age, in which the capsule of the spleen is usually thickened, less resistant and also less translucent, these fibrous thickenings occasionally become calcified and may even be changed into a bone-like mass. Andral states that in these instances calcification of the fibrinous trabeculæ of the parenchyma of the spleen can sometimes be seen.

Symptomatology.—Inflammation of the capsule of the spleen is undoubtedly frequently overlooked, as in many cases it produces no marked subjective symptoms. The writer has often observed this in leukemic tumors of the spleen, and in echinococcus; on examining these he would clearly hear friction sounds, while the patients had not complained at all, and even denied the existence of any pain after they had been told that they were suffering from a circumscribed perisplenitis. In other cases the disease manifests itself by pain in the region of the spleen, which may occur spontaneously or on deep inspiration, or when the patient changes his position. The pain in the region of the spleen may occasionally become so severe that the patient is deprived of his night's rest, and the administration of narcotics becomes necessary. On palpation a more or less distinct friction is felt, which increases with respiration and which can be also heard; sometimes it becomes so loud that it can be distinguished at some distance from the bed when the patient breathes very deeply. This rubbing resembles very much the so-called "Neulederknarren" of pericarditis. [It is not always easy to determine whether the pain in the left lower chest or in the left hypochondrium is due to a pleurisy or perisplenitis. Sometimes both are present, due to the same cause—*i. e.*, tuberculosis, localization of inflammation in septicemia, etc. With care and attention to the other symptoms and signs, and especially the probable causative factor, a diagnosis can usually be reached.—Ed.] A perisplenitis producing the loudest rubbing sounds and lasting for months need not necessarily lead to adhesions between the spleen and the abdominal walls. The writer could verify this statement in a case of echinococcus of the spleen, in which he observed the above phenomenon for a period of nearly four months, but where, on laparotomy, no adhesions were found; all that was seen was a cloudiness and opacity of the capsule, and deposits that were so slight that they could hardly be demonstrated. As partial contraction of the connective-tissue deposits on the capsule produces irregularities on the surface of the spleen, it may be possible to palpate them, under exceptionally favorable circumstances, during life. Adhesions of

the spleen are recognized clinically through the absence of respiratory motility of the spleen.

Treatment.—Treatment is purely symptomatic. When the pain is severe, cataplasms, dry-cupping, or sinapisms in the region of the spleen are indicated. If this be not sufficient to stop or reduce the pain, resort must be had to subcutaneous injections of morphin. [Tightly strapping the side, as in pleurisy or fractured ribs, may give some relief from the pain.—Ed.]

INFARCT OF THE SPLEEN.

We distinguish, in the case of the spleen, *hemorrhagic*, *white*, *mixed*, and *septic* infarcts. Most of these processes are caused by embolism.

Etiology and Pathogenesis.—By *embolism* we understand, in contrast to thrombosis (which, as we shall see, also plays an important rôle in the pathogenesis of splenic infarct), the occlusion of an artery by embolic material (so-called emboli). These emboli can be of different origin, and consist of the most different kinds of material. In most cases emboli come from the *left heart*, are forced into the arteries of the greater circulation, follow the blood-current, and continue to float in it until they become lodged in some vessel the diameter of which is smaller than that of the embolus. Those emboli, on the other hand, that get into the arterial vessels of the lesser circulation and remain in the lungs almost invariably come from the veins of the vena cava system, chiefly from the femoral vein in case of phlegmasia alba dolens, or from the veins of the broad ligaments in thrombotic processes during the puerperium. Only in rare cases do emboli that have their origin in an endocarditis of the right heart, either of the auricular or ventricular valves, enter the pulmonary circulation.

The emboli that are found in the greater circulation owe their origin in almost all instances to an endocarditis of the left heart, either to a fresh inflammatory deposit on the valves themselves, as is so often found in acute inflammatory rheumatism and many of the acute and chronic infectious diseases (especially pneumonia, typhoid, chorea, scarlet fever, etc.), or to a chronic valvular lesion of the mitral valves, with or without acute recurrent attacks. Again, *atheroma of the aorta* may exist with ulceration of the intima; here one or more of the small calcareous plates that are so often found in these ulcers gain an entrance into the branches of the aorta; owing to their hardness they cannot adapt themselves to the lumen of the smaller vessels, and consequently become lodged in them. Complete occlusion, however, does not occur until fibrin becomes deposited on the foreign body, entirely closing the vessel. Thrombotic material which becomes deposited on the atheromatous ulcerations within the aorta can also be the direct cause of embolism in branches of the aorta. As atheromatous changes within the aorta frequently lead to aneurism, and as thrombi are frequently developed here, such aneurisms may become a prolific source of embolic material.

Much more frequently, however, *thrombi in the left heart itself* cause

emboli in the greater circulation; this source ranks in order of frequency next to endocarditis. These thrombi may occur in any part of the left heart, and owe their origin to a retardation of the blood-current, as a result either of chronic disease of the muscular or valvular apparatus of the heart, or of a variety of chronic afflictions that are accompanied by cachexia or inanition. These thrombi of the heart, or polypi as they are also called, may occur in the left auricle or ventricle; here they become entangled with the papillary muscles or form the so-called ball-shaped thrombi that are frequently seen near the apex. Sometimes vegetations that become attached to the chordæ tendineæ of the mitral valve segments may become the cause of emboli. Finally, cestodes may enter the arteries in cases of cysticercus or of echinococcus and act as emboli.

We must, lastly, consider the occasional occurrence of *fat- and air emboli;* these are found chiefly in the finer vessels and in the capillaries. The latter form occurs if air bubbles pass through the lungs into the arteries when a vein is opened; the former, after fractures.

It will depend on the character of the artery and of its terminal branches in what part of the vessel the embolus will lodge. As a rule, arteries become considerably diminished in size immediately after they have given off a branch or have divided; the embolus, therefore, generally lodges at the point where the branch is given off or at the bifurcation; it often straddles the bifurcation in such a manner that it extends into both branches, not unlike a molar tooth with its two roots. If the embolus does not occlude the artery completely from the beginning, the coagulum that invariably forms will soon produce complete obstruction; it never occurs, however, that emboli from the sources enumerated above enter capillaries or wander through these into the veins.

Of the arteries of the greater circulation, the branches of the aorta are most frequently the seat of embolic occlusion, probably in the following order of frequency: First, the splenic and renal arteries, then the arteries of the brain (the Sylvian, the artery of the corpus callosum, the basilar), the coronary arteries, the superior and inferior mesenteric, and the celiac axis; the peripheral arteries are rarely the seat of embolism; the brachial artery is probably the one most frequently affected.

If an embolus constituted as above enter an artery circulation beyond the embolus will become impeded or interrupted. If the embolus become lodged in some part of the arterial tube, or be straddling the bifurcation of two arteries, the occlusion of the vessel, in case it be not complete from the beginning, will soon become so from the fibrin deposits that are formed. As soon as this has occurred the blood can no longer reach the tissues that are supplied by this artery. This does not necessarily mean that the blood-supply is completely cut off from this area; on the contrary, in the majority of cases arterial branches that are given off above and below the embolus form anastomoses with each other; in this way circulation is partially maintained. Other arteries occasionally enter into these anastomotic branches and into the

embolized artery itself below the occluded place, so that arterial blood in considerable quantities is carried to the affected area. Thus, a disturbance in the nutrition of a very small area only—viz., that immediately adjacent to that short piece of the main artery in which the embolus has lodged—is produced. Such an occurrence, as we know, has almost no significance in organs that are rich in blood, because they contain numerous anastomoses. This is especially the case in the muscles of the extremities, in the skin, in the fat-layers of the body, and in the subcutaneous connective tissue. The damage is very much greater if an artery be occluded that alone is the channel through which the blood flows to a certain organ or a certain part of an organ; when such an artery is occluded nutrition is completely cut off.

Arteries of this kind which are not connected with any neighboring arteries and have no collateral branches, or only capillary anastomoses, have been called by Cohnheim "*end-arteries.*" Their physiologic significance is such that when they are occluded that part of the body supplied by them immediately suffers from malnutrition and becomes necrotic. These end-arteries divide during their whole course in such a manner that each branch again forms an end-artery and is not connected by anastomoses with neighboring arteries. According to Cohnheim there are several such end-arteries—as the central retinal artery, the splenic artery, the pulmonary artery, the renal artery, and the arteries of the brain. Strictly speaking, neither the pulmonary artery nor the arteries of the spleen and kidney belong to this group, as they anastomose with other arteries in their vicinity, and in the case of the splenic artery the writer was enabled to demonstrate clearly that the spleen may even increase in size after ligation of the splenic artery and vein. Such a phenomenon can, of course, be attributed only to the influx of arterial blood which the spleen receives from the vessels of the capsule. The same applies, to judge from the writer's experiments, to the arteries of the kidney.

In case of occlusion of one of the main arteries of an organ or of one of its branches, the organ itself, or the part of it supplied by such a branch, no longer gets a sufficient supply of arterial blood for its nutrition, and *necrosis* of the tissue of the organ and loss of its function are the necessary results. The small quantities of blood that are still supplied through smaller arterial anastomoses after occlusion of the main stem never suffice to maintain the nutrition of the tissue supplied for any length of time, and necrosis occurs (so-called coagulation necrosis). We will refer to this later on.

The disturbance of function, or the complete inhibition of function, manifests itself differently according to the character of the organ. In the case of the glands their specific function ceases, and if no compensatory excretion occur in any other part of the body, this means finally an irreparable injury to the economy. In no location, however, is the disturbance of function more sudden and fraught with more immediately serious consequences than in embolism of a large artery of the brain or of the central retinal artery. The changes that result in the affected

tissues in embolism are, of course, dependent upon a variety of causes, chiefly on the nature of the embolic material.

The usual form under which the tissues die as a result of embolic occlusion of an artery is *coagulation necrosis;* in this necrosis the tissues are converted into a mass resembling coagulated fibrin in which the cell nuclei are destroyed. Weigert has demonstrated that this form of tissue death occurs wherever the tissues still receive a small supply of nourishment. In the case under discussion the tissue dies because it is no longer supplied with sufficient nourishment, and it dies in the form of coagulation necrosis because the minimal influx of nutrition that comes from the collaterals and the anastomoses is just sufficient to dissolve the nuclei and ultimately to cause their disappearance. As a rule, the dead areas of coagulation necrosis (embolic necrosis) assume the form of a wedge, the point of which is directed toward the occluded part of the afferent artery—that is, toward the embolus—while the base of the wedge is pointed toward the periphery of the organ. Such embolic necroses or "*white infarcts*" are met with most frequently in the spleen, the kidneys, the lungs, the heart, and, very rarely, in the liver. As the periphery of the infarct is in most cases surrounded by a more or less extended hemorrhagic margin, and as this margin is frequently wider than the necrotic area itself, the hemorrhagic extravasation is sometimes considered as the primary lesion—as a white or yellowish-white area of necrosis seems insignificant in comparison to a large hemorrhagic area. For this reason such infarcts have been called *hemorrhagic infarcts;* and as pathologists assumed; further, that the hemorrhage was gradually absorbed, so that white necrotic tissue took its place, a second stage of hemorrhagic infarction was distinguished, and such areas called decolorized hemorrhagic foci. This interpretation is altogether inaccurate, as the writer has demonstrated both anatomically and experimentally. The process is as follows: As soon as the end-artery becomes occluded embolic necrosis immediately follows; the peripheral hemorrhage is only secondary, and is caused by the compression of efferent veins as a result of the tumefaction of surrounding tissues. To speak of the discoloration of an infarct that has been hemorrhagic is incorrect, first, because the white area precedes the hemorrhagic area, as can be demonstrated in living persons in cases of embolism of the retina, and experimentally in animals where emboli of the spleen and kidney have been induced; second, because none of the constituents of the blood can be found in the so-called decolorized area. Such embolic necrosis can form in the kidney and the spleen twenty-four to thirty-six hours after the embolism, and the cell nuclei may degenerate in a very short time thereafter. All this the writer has demonstrated experimentally.

We have shown that the chief cause of infarct of the spleen and of other organs is embolism. The writer should like to call attention to one other rare cause of infarct of the spleen which is occasionally observed—*i. e.*, the formation of *arterial thrombi* in the splenic artery as a result of endarteritis or of erosions of this vessel. After such an accident small particles may occasionally be torn loose from the arterial

thrombus and be carried into the blood-current farther on into the finer branches of the splenic artery, there become lodged in a suitable place, and produce an infarct of the spleen. In this manner a thrombus of the splenic artery may cause embolic occlusion of its own branches. In view of the great interest which attaches to a process of this kind, the writer, in the Appendix, shall give a full history of such a case.

We shall now discuss *hemorrhagic infarcts proper;* these are found only in the spleen and in the lungs, and in the center of the organ as well as at its periphery. White infarcts, on the other hand, are usually found at the periphery and extend as far as the capsule. The hemorrhagic infarcts form round, sometimes wedge-shaped, areas of a uniform dark-red granular consistence, completely filled and impregnated with red blood-corpuscles. Disintegration and destruction of the tissue through extravasated blood, as it is found in apoplexy, is never seen. A circumscribed area of inflammation of the serous membranes (perisplenitis) is usually found where the base of the infarct reaches as far as the capsule. These foci become decolorized after a time as soon as the blood-constituents that have entered the diseased areas by diapedesis are again absorbed by the cells that immigrate from the neighborhood. In genuine hemorrhagic infarcts we are fully justified in speaking of a stage of decolorization. On examination of a bleached infarct all blood-constituents are found in process of retrogressive metamorphosis, just as in apoplectic areas. As to the origin of these true hemorrhagic infarcts of the spleen, the writer has never been able to find evidences that an embolus was the cause; so that he is willing to concede for only a small proportion that they can be of an embolic character. On the other hand, he has frequently succeeded in discovering thrombi of the venous sinuses in these cases. This would indicate that here we are dealing with a process analogous to venous stasis, a phenomenon that has been studied so very exhaustively by Cohnheim and Stricker in the tongue and web of frogs. In this demonstration the emigration of blood-cells from the congested blood-vessels is clearly visible.

According to the classic investigations of Cohnheim, those hemorrhagic infarcts that are caused by emboli are produced by a back-flow of venous blood that is said to occur as soon as circulation through the arteries has ceased. The hemorrhage is declared to be due to the disintegration of the wall of the artery as a result of anemia. According to my investigations, this venous back-flow does not occur in warm-blooded animals at all, because the pressure in the venous system is never positive, and certainly never great enough to permit of an influx of blood from the veins into the embolized district. The writer was also unable to demonstrate by his experiments that a disintegration of the vessel wall ever occurred.

The nature of the material constituting the plug is of fundamental significance for the sequelæ of an embolism. In our descriptions so far we have only considered the so-called bland emboli, understanding by this term such tissue as is found in the organism physiologically—for instance, fibrin and connective tissue. There is, however, another

group of processes that can be traced to infection by *emboli, consisting of pathologic inflammatory products and pathogenic micro-organisms.* The fundamental difference between bland and infectious emboli lies in the fact that the former occur exclusively in the arteries; whereas the latter, as they consist chiefly of micro-organisms, may wander into the capillaries. Under these circumstances, of course, the strict separation of left- and right-sided diseases of the heart, and of emboli of the greater and lesser circulation, cannot be made. If, for instance, we have in some part of the body an infectious focus containing pathogenic micro-organisms, infectious material can be carried to the other side of the body from here through the blood-vessels, and especially the veins; and as this material necessarily travels through the capillary network, it is impossible to predict in advance, even approximately, in which set of capillaries it will become lodged. Thus, for instance, in a septic pelvic peritonitis capillaries can become occluded by a septic infarct and thus lead to multiple septic abscesses in the lungs, or can produce a so-called metastatic panophthalmitis, or can lead to the formation of multiple abscesses in the spleen, in the kidneys, in the pancreas, etc. This is owing to the fact that the embolic material is so small that it can very easily pass through the capillaries of the lungs and become lodged in the choroid or the spleen just as well as it could be arrested in the lungs primarily and produce an infection there. The writer has called attention to these facts at great length in his dissertation on "Septic Processes," which appeared in the *Zeitschrift für klinische Medicin*, 1881, vol. ii.

It is a matter of small significance what the character of the embolic material in this last group may be; whether we are dealing with staphylococci, streptococci, gonococci, spirochetæ, Davaine's bacillus, aspergilli, tubercle bacilli, actinomycetes, or any other species that may be present; the main cause of the resulting lesions is the *infectious character* of the micro-organisms. Owing to this property they are capable of producing metastatic foci, in organs that are far removed from the original seat of the diseased, which are identical with those that could have been caused by direct transmission through the larger vessels of the blood- and lymph circulation. The foci caused by infectious emboli are differentiated from bland emboli particularly by their infectious character and their great tendency to cause rapid disintegration of tissue, thus producing multiple miliary abscesses of the size of a lentil, or even as large as a cherry-pit. In the case of so-called bland emboli, on the other hand, only one focus, usually wedge-shaped in outline, can be found. In the first instance the affected organs are completely permeated with miliary abscesses that are usually filled with a chocolate-colored, very thin, syrupy material. When, for instance, in the case of septic infection of a puerpera a septic ulcerative lesion of the endocardium is acquired, immaterial on which valve or in which division of the heart, and when *metastases* from these vegetations are carried into the spleen, then the same streptococci that are found on the deposits of the diseased heart valves and in the infected venous thrombi of the

broad ligaments will be found in the splenic abscesses. The same obtains in abscesses of the lungs which occur after septic infection of a wound. The same streptococci and staphylococci that are found on the deposit of a septic endometritis or on a diphtheric placental site can be cultivated from the deposits in the heart or from abscesses of the lungs. It is not necessary, as the writer has shown in the above-mentioned publication, that the disease of the valves of the heart should in each instance be the intermediary link between the focus of primary infection and the metastasis. The chief factor is direct transportation of the poison from the original seat of the lesion to the place where the metastasis has occurred, and we can mention no more analogous process than a so-called carcinomatous metastasis, which is also caused by direct transportation of the infectious cancerous material from one part of the body to another through the blood- and lymph vessels.

If, as a result of malignant or septic endocarditis, disintegration of the valves of the heart has taken place, or if through some other channel septic material has entered the splenic artery and its ramifications, then multiple abscesses with purulent areas of demarcation are formed in the neighborhood of the infected vessel. This same process, of course, can occur in the vessels of many other organs. In the case of the spleen, large or small portions of the parenchyma of the organ may in this manner be destroyed and dissected off, so that such pieces are frequently found in cavities filled with pus or fetid débris. The observations that the writer has made in this direction are particularly instructive; they are published in his studies on septic infections.[1]

In 35 cases of serious sepsis which ended in death, the writer found large tumors of the spleen without exception. The tumors were in a condition of so-called cloudy swelling, and many of them of a consistence that was gruelly and almost diffluent. Among these 35 cases, 14 —that is, 40 per cent.—had multiple abscesses of the character described above. The writer would like to quote a few of these as examples:

CASE IV.—Mrs. A. H., sextipara, became infected after a normal birth. *Contents of the skull:* pachymeningitis hæmorrhagica interna. In the beginning hemorrhages into the iris and the retina, then bilateral panophthalmitis and ulcers of the cornea. *Heart:* recent pulmonary endocarditis with a slight degree of ulceration of the valves. *Glands of the abdomen:* bacterial infarcts, abscesses in the spleen and the kidney, multiple hemorrhages in all internal organs. *Temperature:* high remitting fever with wide fluctuations and repeated chills. *Special remarks:* thrombophlebitis of the uterus with diphtheric inflammation of the placental site; from the latter, veins filled with purulent material can be followed as far as the spermatic vein. Bacterial abscesses of the lungs.

CASE V.—Mrs. E. R. Very large area of pachymeningitis hæmorrhagica interna, enormous hemorrhages on the retina and conjunctiva, usually with white centers. On the skin large areas of purpura, several with white centers; recent deposits on the mitral and aortic valves without ulceration. Tumor of the spleen with septic abscesses; the same in the kidneys. Very high temperature, up to 43.2° C., with repeated chills. Gangrene and diphtheria of the soft palate and of the labiæ.

CASE XII.—Mrs. L. K. Abortion in the third month; beginning of septicemia about the seventh day thereafter. Hemorrhages into the conjunctiva and retina; later bilateral panophthalmitis. Pachymeningitis hæmorrhagica interna.

[1] *Zeits. f. klin. Med.*, 1881, vol. ii.

In the beginning hemorrhages of the skin; later scarlatinal erythema with large and many small herpetic efflorescences with bloody contents; also pustules resembling pemphigus. Ulcerative endocarditis on the mitral valve; bacterial abscesses and multiple hemorrhages into the heart muscle. Very large, gruelly, very soft spleen, with multiple large splenic infarcts and abscesses. Metastatic abscesses of the kidneys. The large joints swollen and painful. Continuous fever, fluctuating between 39.5° and 40.5° C. Diphtheric areas in the site of the placenta. Hemorrhages in all internal organs.

The writer wishes to emphasize again that in many cases similar to those communicated the heart may be found intact.

Pathologic Anatomy.—*Hemorrhagic infarcts* are found most frequently in the peripheral substance of the spleen. Their form is, as a rule, round or wedge-shaped, corresponding to the distribution of the arterial branches; the broad end of the infarct is directed toward the capsule of the spleen, the point is directed inward, and the whole area is sharply outlined against the normal surrounding tissue, and when cut bulges over the level of the cut surface. The number of foci and their size may be very different. The substance of the spleen within the infarct usually appears dark red in the beginning, dense, and hard; later it becomes more and more decolorized, and finally presents a yellow, solid, homogeneous mass, strictly differentiated from the surrounding normal tissues of the spleen. The serous covering of the spleen over these areas is frequently congested or shows signs of perisplenitis; the whole organ, depending on the size and number of the foci, is more or less enlarged, and its substance congested. It is very easy to recognize hemorrhagic infarcts in a spleen that is removed from a dead body; in case they are situated near the periphery, the small areas of perisplenitis corresponding to them are clearly visible through the capsule, and can still more easily be felt, as they are hard and tense.

The subsequent metamorphoses of such an infarcted area are contraction, the formation of scar tissue, and partial calcification.

White embolic wedges of the spleen frequently have a bluish-red, livid, washed-out color, whereas analogous foci in the kidneys are pure white or yellowish white. This is a result of the natural color of the spleen and the large quantity of blood that it contains. Weigert[1] says: "It is not necessary in such cases to assume a real hemorrhage; the coloring-matter of the red blood-corpuscles that were originally contained in the meshes of the spleen pulp has become dissolved and is diffused; this is accompanied by a peculiar change of its color. If we examine these white or livid-red wedges we may often think, especially if we examine alcohol specimens, that no changes had occurred at all. Even in colored specimens single nucleated round cells are found in the focus that could induce a superficial observer to assume that the cells of the pulp were still undamaged. If we examine more closely, however, we will find that the original connective tissue, the bodies of Malpighi, the cells of the pulp, etc., are without nuclei, and that the red blood-corpuscles, which appear to be altogether normal, have lost their coloring-matter. In the spleen the other cellular elements are not

[1] *Virchow's Archiv*, vol. lxxix.

sufficiently numerous to allow us to assume that their coagulation could bring about the formation of so homogeneous a structure as the yellow wedge we see—exudation of fibrin does not occur; we must assume, therefore, that the red blood-corpuscles which constitute the great mass of the spleen tissue have coagulated themselves. Histologically, they are changed only in so far that they have lost their coloring-matter and have assumed a somewhat cloudy appearance; so that here we have an instance where parts which consisted almost exclusively of red blood-corpuscles became completely colorless. That this does not occur so rapidly in all blood-coagula is explained by the fact that only in the tissues of the spleen, owing to the plentiful supply and constant current of lymph on all sides of the coagulated area, is the coloring-matter more readily washed away. The same applies to the color of the spleen, which is independent of the color of the blood. This finding is another proof for the assumption that such areas, in reality dead but yet remaining in intimate contact with their living surroundings, are still permeated by a fluid containing fibrinogen; for their decolorization can be explained only by the constant influx and efflux of lymphatic fluid.

"All these areas of coagulation necrosis, however, show the outlines of the tissue elements—without nuclei—for a short time only; gradually these become more and more diffuse and indistinct, their outlines less clear, their substance cloudy and granular; finally, in the way we have described, the wedge of fibrin becomes absorbed and replaced in part or altogether by a connective-tissue cicatrix; finally the remaining scar may become calcified."

Very similar white infarcts of the same form as above, only of a pure white color, are frequently found in the spleen in large numbers in cases of acute infection, notably in recurrent fever, typhus exanthematicus, cholera, and typhoid. They have been most carefully studied in the case of *recurrent fever*, but no one has ever succeeded in finding arterial emboli or specific elements—*i. e.*, recurrent spirilla—in the capillaries. Ponfick thinks that probably the veins are primarily involved. He found in several of the veins of the spleen that started from the infected area thrombotic masses that were not of very recent origin. It is possible, as some authors assume, that these were secondary and had originated from thrombi in the capillaries; others assume that this was a primary thrombosis of the veins. Whichever theory is correct is immaterial, because, as Mosler has shown, in neither case could these findings be made responsible for the formation of such an infarct. In a venous thrombosis, as the writer has shown, hemorrhagic infarcts may occur, but never these pure white wedges, and a single glance at the microscopic picture of such a focus will show us that we are not dealing with a discolored hemorrhagic infarct, because no remnants of constituents of the blood can be found.

Symptomatology and Diagnosis.—The diagnosis of embolism of the splenic artery is identical with that of hemorrhagic infarct, because it is never possible clinically to demonstrate that the embolic

plug has entered an artery. The first thing we can determine is the formation of an embolic focus. Pain, possibly fever and chills, above all the suddenness of the attack and the demonstration of the presence of embolic material somewhere in the body (usually by demonstrating the presence of an endocarditis) are our chief diagnostic aids.

Pain in the region of the spleen is so uncertain a symptom, and is, moreover, so frequently absent, that its presence or absence cannot be employed with any degree of certainty in the diagnosis of this disease. The pain, if it be present, is as a rule dull, and is increased upon bodily movements; notably upon deep respiration. Violent pain in the region of the spleen is always attributable to accompanying inflammation of the peritoneal covering of the organ; radiation of the pain toward the left shoulder, axilla, or left side of the thorax is a rare occurrence and has no pathognomonic significance. [In rare instances one is able to locate the infarcted area with reasonable certainty. The spleen that has lodged several emboli may be permanently more or less enlarged, so as to be distinctly palpable. If, now, a fresh embolus lodge near the palpable edge of the spleen, the pain will call attention to this organ, and local tenderness may be limited over so small an area as to make one reasonably sure of the exact spot in which the embolus has lodged. —Ed.]

The *swelling* of the spleen is dependent upon the size and number of the infarcts, and rarely reaches a great degree. If hemorrhagic foci develop in an organ which is already chronically enlarged—as, for instance, in the spleen of intermittent fever or of amyloid degeneration —then the increase in volume is the result of the original disease.

Fever and chills are only rarely caused by involvement of the spleen, but are usually the results of ulcerative endocarditis, septicemia, or puerperal fever, in the course of which, as we have said, these septic infarcts and abscesses so frequently occur. Usually the original disease is accompanied by an acute splenic tumor. According to the writer's figures, septic abscesses occurred in the spleen in 40 per cent. of these cases, so that we must always look for the occurrence of such an accident; we are justified in suspecting the formation of such a focus if the spleen suddenly enlarge considerably, and a dull pain or a diffuse feeling of discomfort on pressure make its appearance in the region of that organ.

Treatment.—In the majority of cases there is essentially no treatment for infarct of the spleen. Aside from the difficulty of diagnosis we have no remedy which even can exercise any considerable influence, though the nature of the process has been correctly diagnosed. We must limit ourselves to the general rules of therapeusis. When pain is very severe we must resort to warm cataplasms or to narcotics, and possibly, in emergencies to the hypodermic injection of morphin. Attention must be given chiefly to the treatment of the original disease.

[In some cases the writer has seen relief from pain follow quite promptly the application of the ice-bag to the splenic region.

Where the source of the embolus is known to be some affected area,

such as the valves of the heart in ulcerative endocarditis, we may fear suppuration in the infarcted spleen. Close watch should be kept, therefore, for symptoms and signs of abscess of the spleen or for a spread of suppuration to the neighboring structures, such as the peritoneum. It must be remembered, however, that not every embolus from an infected source will necessarily produce suppuration. In the case of ulcerative endocarditis a staphylococcus embolus is more apt to be followed by demonstrable suppuration than is a streptococcus.—Ed.]

APPENDIX.

(History of a Case.)

Perforating gastric ulcer with fatal hemorrhage assuming the picture of a pernicious anemia; erosion of the splenic artery, with formation of thrombus, and secondary embolisms of this artery; infarct and abscess of the spleen.

J. A., coachman, aged thirty-two, treated by the writer in Frerich's Clinic, from the 29th of August to the 10th of October, 1880. Patient states that he was entirely well up to four weeks before entering the clinic, then gastric disturbance began, which consisted chiefly in frequent vomiting; blood was never observed. Patient came to the hospital on account of the increasing weakness and violent pains in his limbs.

Yellowish-white coloration of the skin and completely colorless mucous membranes; ears wax-colored; over the lower part of the sternum was heard a constant grating systolic sound, sometimes as intense as in a recent pericarditis; slight enlargement of the heart toward the right; the apex beat visible and to be felt over an abnormal area; a slight fremissement; pulsus celer; a venous hum which could be felt also on palpation; palpitation of the heart with dyspnea. The lungs intact. Urine normal in quantity and quality. Violent pain in the bones, especially in the lower extremities. Retina normal, except for traces of former hemorrhages.

This condition remained practically unchanged until late in September. The only important observation recorded was that, despite a very good appetite and regular digestion, the general condition of the patient steadily grew worse; his color became waxy and he complained of violent pains radiating from the epigastrium toward the left shoulder. Repeated retinal hemorrhages containing white centers occurred. The blood-examination showed that the leukocytes were not increased and that the red blood-corpuscles were very pale, varying in form and size; some were very small and shaped like pessaries.

On the 23d of September, without apparent cause, hematemesis suddenly developed; 700 c.c. of a deep dark-red fluid were vomited, mixed with remnants of food and containing large lumps consisting in part of coagulated blood. Almost immediately after the hemorrhage the patient complained of violent pain in the stomach, palpitation of the heart, and dizziness. The temperature dropped to 36.4° C., the pulse became small and thready. This condition lasted for several days, the radiating shoulder pains increasing in frequency and severity. The stools became diarrheic and for days contained lumps of coagulated blood.

The blood now contained nucleated red blood-corpuscles, but the number of leukocytes was not increased. In the retina punctiform and extensive hemorrhages occurred; pain in the bones increased. The urine was normal.

In the night from the 7th to the 8th of October another hemorrhage from the stomach occurred, and this time 800 c.c. of liquid cherry-red blood were vomited. When the writer saw the patient several hours later he found him comatose. Temperature 35.6° C.; pulse thready. The urine was passed involuntarily. The pupils on both sides were dilated and reacted very little to light.

The ophthalmoscopic examination made on the same day showed the following picture. Optic papilla very pale on both sides, not very prominent, and the boundaries indistinct. Extending from the papilla a white area of cloudiness was seen on the retina; the retina otherwise appeared normal and was of a very light-red color.

The cloudiness of the retina was found chiefly around the optic papillæ, whereas the region of the macula was intact. Multiple hemorrhages. The arteries appeared narrowed and could not be traced to the periphery; they, as well as the veins, appeared a very bright red. In the direct image a slight radiating cloudiness of the optic nerve and a hazy appearance of the papillary part of the retinal blood-vessels could be seen.

Despite all measures, the patient did not recover, but collapsed more and more, dying, on the 10th of October, in consequence of another severe hemorrhage. Death occurred during the hemorrhage. An examination of the fundus of the eye made on the day previous to death showed an exaggeration of the neuro-retinitic changes.

The *autopsy*, performed on the 12th of October, showed a pronounced anemia of all the organs. The heart was of normal size, its muscles very pale, grayish yellow, and fragile. On the cut surface gray foci and long streaks of gray appeared; in these areas the substance of the muscle seemed to have been destroyed and replaced by connective tissue; in places these gray spots were so numerous that the specimen appeared to consist almost wholly of connective tissue. The *spleen* was enlarged, its dimensions being 13.5 by 10 by 4 cm.; its surface appeared smooth, translucent, and covered with punctiform hemorrhages. In some places the capsule appeared uneven and rough, and covered with fresh exudate; in one place two large foci were seen, in which the parenchyma of the spleen was thickened and infiltrated. On incision into these areas, which were sharply defined, it was found that they were of an entirely different constitution from the rest of the spleen. The smaller one was incised; it was about as large as a hazelnut and situated on the inner margin of the spleen, extending to the middle of the organ; the larger one was situated more peripherally and occupied about a third of the whole organ; its dimensions being 5.4 by 4 by 2.5 cm. In the neighborhood of this latter wedge-shaped focus the parenchyma of the spleen was hemorrhagically infiltrated, colored brownish red, and solid. The artery leading to this hemorrhagic infarct was completely occluded by a plug. The other focus, which was more bowl-shaped, contained cheesy and granular débris, and was surrounded by spleen tissue infiltrated with pus. The contents of these abscesses of the spleen consisted microscopically of disintegrated spleen tissue, which in spots still showed the natural histologic structure of a normal spleen. The *stomach* contained fluid which was chocolate-colored and mixed with particles of food. In the center of the posterior wall, about 3 cm. distant from the small curvature and 7 cm. from the greater curvature, a hole was found with smooth margins, of an irregular outline, about 1½ cm. in diameter, and leading into a smooth-walled cavity about the size of a hazelnut. At the bottom of this cavity the pancreas was seén. A thrombus extended into the cavity, completely filling a perforation of the splenic artery. The thrombus was removed by a stream of water and a perforation in the artery discovered, so that a sound could be passed from the gastric ulcer into the lumen of the artery. The perforation was situated a short distance from the bifurcation of the splenic and the celiac arteries. Small thread-like masses of coagulum and others as large as lentils were found in different places along the course of the artery. In comparing the embolus found inside of the spleen with the thrombus which was found in the artery, it was ascertained that they consisted of the same material.

The bone marrow of the right femur, which alone was examined, was cinnabar-colored and contained very little fat. Microscopically, it was found to contain many so-called "blood-corpuscle-carrying cells," and red blood-corpuscles with nuclei.

Epicritic Remarks.—In the writer's opinion, the most remarkable feature in this case is that a process of repair, so complete and so useful as the formation of a thrombus at the place of perforation of an eroded artery, should at the same time be the direct cause of another serious complication. There can be no doubt but that the thrombus of the splenic artery caused embolism of peripheral branches of the same artery. It is interesting also to remember that hematemesis preceded the formation of each of the two infarcts of the spleen. If we carefully compare the clinical and anatomic findings we must arrive at the following conclusions:

The first hemorrhage of the stomach which was clinically demonstrated and observed by us occurred on the 23d of September; the next in the night

from the 7th to the 8th of October; and the last, immediately preceding death, on the 10th of October. On autopsy we found an old, completely softened, hemorrhagic infarct, and a recent, not faded, one. The occurrence of the gastric hemorrhages, however, gives us definite information in regard to the age of these infarcts. Above all it is clear that the first of the two which had led to the formation of abscess and the dissection of spleen tissue was necessarily much older than the one that was still in a condition of hemorrhagic infiltration. We certainly will not be far removed from the truth if we assume that the first one was at least fourteen days old, whereas the last one had existed only a few days. The hematemesis observed on the 23d of September—that is, seventeen days before death, and which was really the first positively demonstrated accident of this kind—was caused by the perforation of the ulcer into the splenic artery. The hemorrhage stopped as soon as the plug had formed at the point of perforation, which, as autopsy revealed, probably extended laterally into the lumen of the artery; a small portion torn from this thrombus then led to the formation of the first infarct, which later was changed into an abscess.

The origin of the second infarct and the cause of the second hemorrhage of the stomach was induced by a complete loosening of the thrombus within the artery and its transportation farther up into the splenic artery. Through this migration both the infarct and the gastric hemorrhage were probably induced. Finally, the thrombus became dislodged for a short time, and the third—fatal—hemorrhage occurred as a result. It is probable that in the last instance the thrombus merely became loosened and did not travel very far, because on autopsy it was found very near to the point of perforation; partly, in fact, still sticking through it. We see, therefore, in this case *that a thrombus of an artery can at the same time lead to embolism of the same vessel.*

Just why in one instance embolization of a branch of the splenic artery led to the formation of abscess is not clear, and we are not justified in assuming, necessarily, that septic or infected material caused it.

In certain cases we know that ordinary hemorrhagic infarcts that are caused by bland emboli in the lungs and in the spleen may become metamorphosed into purulent thrombi, and ultimately become absorbed by softening and sequestration. To judge from the writer's personal observations and experiments, the latter termination occurs when no collateral circulation is formed through the part of the organ which has become embolized. In these cases we do not get a hemorrhagic infarct, but from the very beginning necrosis without hemorrhage, and secondarily softening.

The writer refrains from further epicritic remarks, and will not speak of the absolute similarity of this case with one of pernicious anemia, because he is dealing chiefly with the changes that occurred in the spleen. He refers, for further remarks that he has made on this interesting case, to No. 49 of the *Berliner klinische Wochenschrift* of the year 1880.

ABSCESS OF THE SPLEEN.

Etiology and Pathologic Anatomy.—In the preceding section we have discussed chiefly those changes in the spleen which are the result of the mechanical action of emboli occurring in the splenic artery. If to this mechanical action are added causes capable of setting up inflammation or irritation, or if the character of the embolus be infectious, so that a *septic irritation* is produced from the beginning, then we observe inflammatory processes in the embolized part of the spleen and in its surroundings. We must, however, briefly state that in certain cases of abscess of the spleen an infectious cause cannot be discovered; they seem to be produced by bland emboli that act purely mechanically. The history of the case reported above may be considered almost a classic example of such an occurrence. In that case there was a bland thrombus of the splenic artery which had become perforated by a

gastric ulcer. From this thrombus a small piece was dislodged, entered the branches of the splenic artery, and here caused a simple infarct of the spleen, on the one hand, and abscess on the other. On autopsy no definite cause for this different result could be discovered, at least so far as the material constituting the embolus was concerned. A bacteriologic examination of the pus, and inoculations of animals with it, showed that the abscess was sterile. Th. Kölliker reports a similar case in an abscess of the spleen operated on by him. (See section on Treatment.) Bacteriologic examination of the pus of the abscess was completely negative; cultures were made and remained sterile; stains according to Gram and Löffler also remained negative. Lauenstein also reports similar results in a case of abscess of the spleen which he opened successfully. Occasionally such an abscess without perforating the diaphragm may produce a left-sided pleural exudation.

Abscess of the spleen is a rather rare disease; as a rule, it is secondary to some other primary lesion. In very isolated cases abscesses of the spleen occur, a *primary* cause for which cannot be found; in such cases indefinite causes have been made responsible, as cold, a blow or a fall, injuries of the abdomen, or even overexertion. Such attempts at explanation of primary abscess are, of course, rather fanciful.

[One must recognize, however, the part that may be played by exposure to cold and by trauma in the production of abscess of the spleen as of abscess in other parts of the body. Local damage to the tissue may so lower its vitality that micro-organisms that may at the time be in the blood or that soon after gain entrance, or micro-organisms from the neighboring stomach or bowel, whose wall may be injured by the same agency that has harmed the spleen and thus permit the passage of the germs, may lodge in the injured organ and cause suppuration.—Ed.]

Secondary abscesses of the spleen are divisible into two groups. The first group comprises those that are caused by *direct invasion* of the spleen from purulent lesions of neighboring organs. The exact pathology of this group is by no means clear, because in the few cases that have been reported the interpretation of the findings has been accompanied by difficulties, owing to the fact that the different observers were unable to state positively whether the spleen was really secondarily involved in the suppurative process. All other cases of abscess of the spleen can be regarded from a common point of view; they have their origin in *embolic infarcts* or metastatic inflammation. First, we see abscesses of the spleen develop from wedge-shaped embolic infarcts; infarcts that originate in an endocarditis of the left heart. The picture seen on autopsy is usually clear, because we find, primarily, an endocarditic process; secondly, in favorable instances the embolus; and lastly, near and around the abscess smaller infarcts of different age. This teaches us that at different times endocarditic masses have become lodged in the spleen. Diseases of the aorta have the same significance as endocarditis in the left heart. Abscesses that have such an origin are, however, comparatively rare. Infectious diseases are the chief

source of abscesses of the spleen, and among these recurrent fever occupies first place; in fact, the frequency with which abscess of the spleen occurs in *febris recurrens* is characteristic. Large infarcts of the spleen in this disease most frequently lead to the formation of abscess; however, we must not forget that this tendency to the formation of abscess of the spleen may differ in different epidemics. During the great epidemic of recurrent fever which occurred in Breslau in the years 1872 and 1873 the writer observed many hundreds of cases and did not find a single abscess of the spleen among them. At the same time, Ponfick and several Russian authors (Kernig and Petrowski) found a number of cases, some of which terminated in perforation and fatal peritonitis.

Other infectious diseases that are accompanied occasionally by abscess of the spleen are pyemia and ulcerative endocarditis. Occasionally instances are reported in some of the other acute infectious diseases, as in typhoid and typhus fevers.

W. Nolen[1] reports such a case of abscess of the spleen in typhoid fever; here infectious emboli were carried into the spleen from purulent foci. His report, however, does not seem to the writer above criticism. A woman, aged twenty-five years, was seized with typhoid fever and diarrhea six weeks after a normal childbirth. On account of a slight amount of pain that could be elicited in the ileocecal region on pressure, and on account of enlargement of the spleen, the diagnosis of typhoid fever was made. Ten days later, after the temperature had dropped to normal, the spleen could be felt very clearly; the organ was not very painful and no fluctuation could be elicited. The abdomen was opened and a liter of dirty-brownish pus, containing coagula, was removed from the spleen. The case recovered. It is most remarkable that in other instances of abscess of the spleen following typhoid fever typhoid bacilli have not been found in the pus. Small follicular abscesses are occasionally seen in the spleen, in addition to the larger purulent foci.

Abscesses of the spleen are, as a rule, rather small, corresponding to the size of the organ. Most of them are as large as a walnut or a hen's egg; however, occasionally larger abscesses have been noted. They probably originate through the amalgamation of two or more purulent infarcts, and when we consider that the parenchyma of the spleen easily disintegrates we cannot be surprised to find in exceptional cases the organ converted into a large abscess cavity, sometimes containing several liters of pus. In one case as many as fifteen liters are said to have been found. The etiology of the splenic abscess in a case reported by Monod[2] is very obscure. The cheesy character of the pus contained within the abscess cavity raised a suspicion of tuberculosis. Microscopic and bacteriologic examination, and inoculation of a guinea-pig with the pus, did not corroborate this suspicion. Micro-organisms were altogether absent and no symptoms of echinococcus could be found. The abscess was completely sterile.

[1] *Nederl. tigdschr. v. Geneeskunde*, 1894.
[2] *Bull. et. mêm. de la soc. de Chir. de Paris*, vol. xviii.

Diagnosis and Symptomatology.—The diagnosis of an abscess of the spleen is in the majority of cases very difficult. In the first place there are a great many cases in which no characteristic symptoms appear; this is especially the case in small abscesses that are situated within the body of the organ and develop insidiously. As a rule, they are rather old and have gone through several stages before they become perceptible. In contradistinction to this class of abscesses are those that develop with fulminating rapidity, soon convert almost the whole parenchyma of the spleen into pus, and lead to a complete destruction of the organ. Those cases in which the abscess is situated near the periphery of the spleen and where the inflammatory process leads to perisplenic and parasplenic inflammations, with resulting adhesions and an anchoring of the spleen to neighboring organs, are especially important. Depending on the exact location of the adhesions, on their size, and on the tissues that constitute them, the results will be different in case the abscess should perforate the capsule of the spleen. If this *perforation* occur in a place where a solid adhesion does not exist, then in the most favorable instances the pus may be poured out into a preformed and circumscribed intra-abdominal abscess. In other instances terminating less favorably the pus poured into the abdominal cavity is distributed over a wide area and usually causes a fatal peritonitis. And if, finally, the spleen be adherent to neighboring tissues, then it is possible under favorable circumstances for the pus to become evacuated through an opening leading to the surface of the body. The most favorable occurrence is the perforation of the pus through the abdominal walls. Several cases have been reported in which the abscess perforated the diaphragm and the pus entered the lung (Vidal, Mantell); others, in which the pus burrowed its way into a bronchus and was expectorated. In the first instance, where the pus enters the lung tissue, so much destruction is produced that death usually results. In Mantell's case a branch of the pulmonary artery was eroded. Even if pyothorax occur under similar conditions, the danger is great. The outlook is much more favorable in those cases in which the abscess perforates into one of the hollow organs, as the stomach or the colon (Herrmann, Cozé, and Fahner).

The *general symptoms* of abscess of the spleen are the following: Fever, which we would expect to find in every case, is occasionally not marked; in smaller abscesses it may be completely absent. Where the spleen is gradually destroyed by the pus we find a characteristic febrile disturbance, called "phthisis lienis"; the fever in these cases is hectic in character. A valuable clue in judging the temperature course with a view to deciding whether or not an abscess of the spleen is present is given in the fact that abscess of the spleen usually follows in the course of recurrent fever and of typhoid. If, therefore, we find, with failure of the spleen to reduce in size, a fresh outbreak of fever in which the remissions are large, then we are justified in suspecting an abscess of the spleen, especially if in addition we can observe some of the symptoms of infarction of the organ. Endocarditic processes are

of equal value in judging of the probability of abscess of the spleen. If, in patients who are suffering from valvular lesions of the left heart, chills with nausea, pain in the splenic region, and an increase in the splenic dulness occur, we are justified in using this complex of symptoms toward the diagnosis of infarct of the spleen. This we have discussed at length in the previous section. If, finally, an infarct of this kind become purulent, even though we may not be able to find the cause for such an accident, we will find increased pain on pressure in the region of the spleen, a remitting type of fever, possibly chills, and, above all, an increase in the dulness over the spleen.

We refer to the previous section for a consideration of the *local symptoms* of splenic abscess, especially the symptom of pain in the region of the spleen. Abscess of the spleen that is situated near the center of the organ and is chronic is usually painless. The other forms that develop rapidly and are situated nearer to the periphery cause pain when the capsule is involved, either by distending and stretching it or by causing inflammatory exudates upon it which may or may not lead to adhesions with neighboring organs. Deductions drawn from enlargement of the spleen must be very conservative, as its value in the diagnosis of abscess is small; we must always remember that the majority of the diseases that are complicated with abscess of the spleen usually lead to an enlargement of that organ even though no abscess is formed. Distinct fluctuation on palpation of the enlarged spleen is a valuable symptom, and exploratory puncture in these cases will often decide positively whether or not an abscess be present. [The value of a blood-count should be remembered. Especially in a disease like typhoid fever, that is not normally accompanied by leukocytosis, the detection of an increase in the polymorphonuclear neutrophiles may help materially in settling the question as to the presence of pus in the body.—Ed.]

If a spleen in which the signs of fluctuation had been clearly elicited suddenly become smaller, then we must suspect that the abscess cavity has suddenly become evacuated. We must be on the lookout for symptoms of peritonitis. Of course, if the pus perforate through the abdominal walls, the diagnosis is settled. The other possibilities of evacuation which we must consider are through coughing or vomiting, or passage through the intestine. Finally, we must determine the possible formation of a circumscribed intra-abdominal gathering of pus.

Prognosis and Treatment.—In making a prognosis of abscess of the spleen it must be remembered that this malady is almost exclusively a secondary lesion, and that the prognosis will depend essentially upon the character of the primary trouble. It is possible for an abscess of the spleen to *heal spontaneously*. We are justified in assuming from autopsy findings that the pus in certain instances can be absorbed in part and the area occupied by it become obliterated; this, however, probably occurs only in those cases in which small infarcts caused by bland emboli have become converted into abscesses. In one case reported by Lauenstein, in which abscess of the spleen was consecutive to typhoid fever, operative drainage of the abscess was followed by recovery.

The treatment of abscess of the spleen is necessarily surgical if treatment seems indicated at all. Of the procedures that can be employed, puncture, incision, and extirpation of the spleen must be mentioned. As soon as the presence of a tumor supposed to contain pus is probable, an *exploratory puncture* should be made with a trocar of large caliber. It is important that the instrument have a large lumen, because the pus found in abscesses of the spleen is usually very thick. One case is reported in which repeated aspiration of the pus led to a cure of the abscess. If on puncture pus be found, Ledderhose, following the suggestion of Lauenstein, advises leaving the cannula in the wound, so that it may act as a guide for subsequent incision. In the treatment of abscess of the spleen, Ledderhose states that nowadays the only treatment to be at all considered is an *opening of the cavity*, either in one or in two stages. If the spleen be situated behind the ribs, it is necessary to pass through the sinus of the pleura and the diaphragm in order to reach it; and if adhesions of the layers of the pleura exist within the sinus, then an incision can be made at once without hesitation even if the spleen be not adherent to the costal wall. If it be found, however, that the sinus pleuræ is not adherent, then it is safer to extend the wound only to the surface of the spleen, pack, and then to wait the formation of adhesions between the leaves of the pleura, opening the abscess cavity in a subsequent operation. If the spleen be so much enlarged that it protrudes in part below the costal arch, it will be possible in most instances to reach the abscess through the abdominal walls, letting the degree of the existing adhesions decide whether a single or a double operation should be made.

If the pus has burrowed through the capsule and entered the parasplenic tissue, or if it be enclosed between peritonitic adhesions, then we need not hesitate to incise the spleen in one operation.

Under certain conditions we must seriously consider the advisability of *extirpating the spleen* for abscess; in those cases, notably, where the spleen is in part destroyed through one or several abscess cavities, where parts of it have become gangrenous, or where the spleen is found floating in an abscess. In cases of the latter class extirpation of the spleen has repeatedly been performed with good results. Ledderhose, however, believes that in these cases perisplenic or parasplenic gatherings of pus existed, and not true abscesses of the spleen.

A careful perusal of the literature up to date shows that 6 cases of abscess of the spleen cured by operation have so far been reported; one of these is the case mentioned above, reported by W. Nolen. It had developed as a sequel of typhoid fever. After the temperature had dropped to normal and the swelling of the spleen had gone down, the appearance of a new swelling of the spleen directed attention to the possibility of abscess, although fluctuation could not be elicited. When the abdominal cavity was opened a liter of dirty-brown pus was found with coagula suspended therein. Th. Kölliker reported a case of abscess of the spleen at the session of the Medicinische Gesellschaft, in Leipzig, on November 10, 1891. The patient was suffering from leukemia and

the spleen was very much enlarged, so that it extended below the costal arch. A diagnosis of abscess was made by the recognition of fluctuation, later through exploratory puncture. The operation was performed in two stages. On the third day after incision of the abdominal walls the abscess was opened with a trocar and thermocautery and then drained. In spite of an aseptic course of the disease the patient died of heart collapse and meteorism. On autopsy seven other abscesses were found in the spleen, which was very much enlarged, and, besides, two large abscesses in the center of the organ. Bacteriologic examination of the pus and staining with Gram's and Löffler's solutions gave negative results; cultures also remained sterile. Lauenstein reports a similar result in a case where splenectomy was performed for abscess; he found neither pus, cocci, nor typhoid bacilli in the contents of the abscess. His case, however, recovered.

ACUTE SPLENIC TUMOR.

Acute tumor[1] of the spleen can be defined clinically as an increase in the volume of the spleen occurring within, and lasting for a short time. The causes are always of an *infectious nature*, so that we find this condition in the infectious diseases; in fact, the occurrence of acute tumor of the spleen is almost pathognomonic of certain infections. It is found in a large number of acute diseases that have in common certain peculiar changes of the blood, changes that so far are not well understood. The swelling of the spleen begins with the primary disease and disappears with its cure. Anatomically, the tumor is characterized by the occurrence of hyperemia, followed in the later course of the lesion by a more or less pronounced hyperplasia of the pulp. It is probable that this hyperplasia occurs as a result of an irritation exercised on the elements of the spleen pulp by some infectious material circulating in the blood. It is a well-known fact that the spleen pulp reacts readily to irritation of infected blood; this is partly due to the fact that the spleen is so full of blood, but can also be attributed to the peculiar anatomic structure of the organ.

Within the spleen the arteries divide into a fine interlacing network of arterioles and capillaries; the blood flows from these vessels into spacious sinuses whose walls are without any lining membrane, but are formed by the substance of the spleen itself (the intermediary blood-vessels). The veins of the spleen start from these cavities, in the form of canals with cribriform walls. As a result of this arrangement the blood moves slowly and sluggishly through these wide intermediary lacunæ, and within these and in the perforated places of the vessels the blood comes in immediate contact with the lymph elements and the delicate network of fibers of the pulp. These tissues, as we know, respond readily to stimuli. In addition, the infectious matter circulating in the blood is more easily arrested in an organ constructed like this than

[1] It is, of course, understood that the word tumor in this and several succeeding instances is not used in the sense of a new growth or neoplasm.

anywhere else, so that, aside from the irritation produced by its passage through the organ, an additional hyperplasia of the elements of the spleen is produced by an excessive irritation, resulting from an accumulation of arrested blood-poison.

Certain experiments made by Ponfick[1] at the suggestion of v. Recklinghausen throw a great deal of light upon this property of the spleen to arrest and to incorporate within itself substances suspended in the blood. This author introduced suspensions of cinnabar into the abdominal veins and studied the deposit of these substances in the spleen. He describes the spleen of a frog treated in this manner as follows: In the loose tissues of the spleen, which had been teased with a 1 per cent. solution of salt, a comparatively small number of peculiar spindle-shaped elements were seen in addition to the fragments of normal capsule and of normal vessels. These elements were from 18 to 24 μ long, 3 to 4 μ wide, elliptically enlarged in the middle and drawn out to thin ends. They were finely granular and showed distinct, approximately oval nuclei. In addition, numerous colored corpuscles were seen that were not different from the ordinary elements of the blood, and a small number of rounded golden-looking bodies with round nuclear structures in their centers. These were probably derivatives of the red blood-corpuscles. Finally, an overwhelmingly large number of colorless bodies of different kinds and varying shapes were seen. Free cinnabar was never observed; this substance was inclosed only by members of the last-described group of cells, particularly by two of three subvarieties; first, round or oval cells, 6 to 10 μ in diameter, either typically granular or, at least, filled with a considerable number of large refractive granules, inclosing one or, rarely, two distinctly circumscribed, eccentrically situated nuclei; the nuclei were situated near to one of the non-granular poles, so near to them that the margins of the nuclei and of the cells were close together. Second, larger cells, from 12 to 20 μ in diameter, inclosing a varying number of round nuclei, sometimes as many as seven, and in addition large and small ball-shaped lumps of irregular outline; these are so-called blood-corpuscle-containing cells. In this second variety exceptionally large quantities of blood-pigment were found, so much at times that not only the numerous nuclei but also the colored blood-corpuscles, or rather their fragments, were completely obscured.

The retention of cinnabar by the pulp cells of the spleen could also be observed in the living cells. If a piece of the spleen removed from a frog some three days after the injection with cinnabar be examined a distinct movement within the cells containing the cinnabar can be distinguished, both in those inclosing red blood-corpuscles and in those that did not contain any. In order to make this examination the spleen should be quickly removed, teased in blood-serum, and examined in the moist chamber. The movements of the protoplasm within the cells are seen to agitate the pigment granules; the smaller ones especially participate actively in the rapid change of shape which the cells undergo. The larger particles, however, seem capable only of a sluggish to-and-

[1] *Virchow's Archiv*, vol. xlviii.

fro movement, so that they slowly oscillate and always return to their original position.[1]

Siebel[2] elaborated on these studies of Ponfick and, following v. Recklinghausen's original plan, injected indigo into the lymphatic channels of frogs. Considerable quantities of indigo were always found in the spleen, very unevenly distributed. The round cells of Malpighi's follicles, which in the frog are elongated and irregularly shaped, never contained indigo; here and there a few white blood-corpuscles containing pigment were seen within the vessels. The pulp of the spleen, on the other hand, contained a great deal of indigo, chiefly on the margin of these Malpighian corpuscles, where the venous network of the spleen pulp is particularly well developed; the center of the pulp contained much less indigo. An examination of the cellular elements of the spleen for indigo never revealed the presence of free granules of this dye, but the smaller cells of the pulp, however, contained some, and also those larger cells that enclosed red blood-corpuscles. The stain quickly permeates the cells of the spleen, so that a very few hours after injection the characteristic picture can be observed; this is due to the peculiar anatomic structure of the spleen.

Birch-Hirschfeld extended these experiments from stains to microorganisms, assuming that in this manner he might possibly throw some light upon the character of acute tumors of the spleen. His experiments[3] were made before modern bacteriologic technic was in use, so that his methods were technically inaccurate; nevertheless they have a great deal of significance, for they demonstrate positively that a relation does exist between invasion by bacteria and the occurrence of acute tumors of the spleen. Birch-Hirschfeld employed putrefactive organisms for his injection; he diluted some blood with water and allowed the mixture to stand covered for five days at a temperature of from 12° to 20° R. (15°–25° C.); the fluid, which had become cloudy and very malodorous, was filtered. "The filtrate contained numerous freely motile punctiform bodies, which were partly isolated, partly conglomerated into little heaps; the coarser masses (zooglœa) had remained on the filter. They were arranged in small chains of from 2 to 6 punctiform members (micrococci); occasionally, small rod-shaped bodies were seen in the filtrate." Of this fluid 2 to 10 gm. were injected directly into the blood of the rabbit, either into the jugular vein or into the carotid. All the animals (Birch-Hirschfeld experimented on rabbits) survived the operation by several days. The following two things were discovered: first, the spleen retains a part of the micrococci within its pulp; second, if the number of micrococci be sufficiently large a distinct swelling of the organ occurs. The spleen, which was removed immediately after the death of the animal, was clearly tumefied; its cut surface was mottled, owing to the presence of numerous punctiform hemorrhages of the spleen substance; Malpighi's corpuscles seemed to be obliterated. On microscopic examination the pulp and cells were found to be swollen and to contain

[1] Ponfick, *Virchow's Archiv*, vol. xlviii., p. 9. [2] *Ibid.*, vol. civ., p. 514.
[3] *Arch. f. Heilk.*, Berlin, 1872, vol. xiii.

micrococci. If the spleen pulp of the animals infected in this manner was examined in the moist chamber, movements of the cocci could be observed even after several days had elapsed.

The experiments of Posner and of A. Lewin[1] on auto-infection from the intestinal tract are interesting also, because they throw a great deal of light on the significance of the *spleen as a filter* for bacteria that have entered the blood-current. These investigators produced in rabbits complete occlusion of the intestinal tract by closing the anus, either by suture, by a tight bandage, or by ligation. Within eighteen to twenty-four hours after this operation the body of the animal was seen to be overwhelmed with Bacteria coli; they were found in the bladder, in the blood of the heart, the liver, the spleen, and the kidneys. In order to corroborate this finding, the above authors made a second series of experiments with cultures of prodigiosus. These were injected into the intestine of rabbits and the gut occluded; eighteen to twenty-four hours after injection the Bacillus prodigiosus could be cultivated from all the organs of the animals, including the spleen.

These experimental findings are, so far as their bacteriologic aspect is concerned, corroborated by pathologic and anatomic observations on man. Above all by typhoid fever, in which the Eberth-Koch bacillus is found in the spleen in large numbers.

The question is not yet settled whether the bacilli act purely mechanically upon the tissues of the spleen or whether their metabolic products, the toxins, also react upon the pulp. It is possible that both causes produce the swelling of the spleen. As we have mentioned above, Friedreich assumed that the increase of the pulp elements of a spleen swollen during the course of an infectious disease was the result of an irritation exercised upon the elements of the pulp by some "infectious material" circulating in the blood. It might be possible to determine this question by injecting into susceptible animals the toxins of those diseases in which we can isolate the poison.

According to all these researches the spleen must be considered as a filter which arrests the schizomycetes that enter the blood-current. As we have seen, fine particles of coloring-matter that have been introduced into the circulation of an animal are arrested in the spleen and there absorbed by the cells. The nature of these cells, and the retarded circulation of the blood within the spleen, are especially favorable for such a process. As we are justified in assuming that microparasites are the carriers of infection, it is readily understood that, especially in the spleen, these organisms would find a suitable nidus for deposit. The findings in typhoid, anthrax, and recurrent fever corroborate this assumption; in addition, the cells of the spleen react readily to the irritation exercised by the schizomycetes; we know this from the constant swelling of the spleen in infectious diseases.

Of all infectious diseases, *typhoid fever* is the one in which we most frequently discover a splenic tumor, and it is an exceptional occurrence to find a swelling of the spleen absent. Especially before the methods

[1] *Berlin. klin. Woch.*, 1895.

of bacteriologic clinical diagnosis had been elaborated, the presence of a splenic tumor was of the greatest significance in the diagnosis of typhoid fever. Particularly important was the observation that such a tumor could also be found in the lighter cases of typhoid and in so-called typhus levissimus and ambulatorius.[1] The fact that the spleen in typhoid fever begins to swell a very short time after infection has occurred is of particular importance. In fact, the tumor of the spleen is probably one of the first symptoms of typhoid. [The recently practised direct bacteriologic examination by cultures of the blood in typhoid fever shows the presence of the typhoid bacillus in the blood before the spleen becomes palpably enlarged. This should, of course, be the natural order of events—*i. e.*, first the bacteria in the blood and then the splenic tumor.—Ed.] Friedreich[2] describes the occurrence of a swelling of the spleen as early as the stage of incubation. One of his assistants informed him that he had discovered a tumor of the spleen in himself; Friedreich examined him and found the statement correct, for there was a tumor so large that it could be felt underneath the costal arch. The patient was apparently in the best of health. The next few days, however, revealed the true condition of affairs; fever set in and a severe case of typhoid fever developed, which lasted several weeks. The size of the tumor of the spleen in typhoid stands in no proportion to the intensity of the infection; large tumors are found in light cases, and *vice versâ*.

The occurrence of a tumor of the spleen during the incubation period of *syphilis* is probably as important and as regular an occurrence as in the incubation period of typhoid fever. However, cases occur in which the infected persons feel so run down and miserable before the appearance of visible signs of the disease that they present themselves for examination. In these cases, which are usually characterized by severe pain in the limbs, tumor of the spleen has occasionally been found, sometimes a considerable time before the appearance of the initial sore. The tumor of the spleen has been demonstrated with more certainty in several cases after the appearance of the chancre, a long time before the development of secondary symptoms, especially of the exanthem. For further particulars in regard to this point the writer refers to the section on Syphilis of the Spleen.

In typhoid a tumor of the spleen is found almost constantly, and in recurrent fever it is seen almost as frequently. In an epidemic which occurred in Breslau in 1872 and 1873 Litten found palpable tumors of the spleen in 96 per cent. of the cases. Similar relations have been discovered in malaria; it is very rare to find a tumor of the spleen absent in this disease. (Compare the section on Malarial Spleen.)

The relative frequency with which tumors of the spleen are found in other infectious diseases due to bacteria is varying. In regard to *diphtheria* we can state that, according to the autopsy reports on cases of diphtheria, tumor of the spleen is not often present; the reason for this may be that the tumor in diphtheria is always relatively small and

[1] Jürgensen, *Volkmann's Sammlung*, 1873, No. 61

[2] *Der acute Milztumor*, p. 4.

collapsed post mortem, so that it may be overlooked on autopsy. During life, however, tumors of the spleen are frequently found in diphtheria, which can be demonstrated by percussion, even tumors of such a size that they protrude below the costal arch; sometimes the swelling can be demonstrated while the local affection is still in process of development (Friedreich). It is not astonishing to find tumors of the spleen in different forms of angina, especially now that we know a true diphtheria may occasionally assume the form of a pharyngeal or tonsillar angina. Swelling of the spleen in diphtheria is different from that found in typhoid, the chief distinction being that in the former disease the tumor rapidly decreases in size as soon as the fever drops; in typhoid, on the other hand, the tumor persists during convalescence and sometimes afterward. [This is certainly not always the case if we rely upon palpation to determine the size of the spleen. In fact, so common is it to find that as the fever, spots, etc., disappear, the spleen diminishes in size, that where one finds the spleen distinctly palpable, even though convalescence seem to be well established according to all the other signs, one should feel that recovery is not complete and should be on the lookout for a relapse. We are inclined to agree with the author's statement on page 519 rather than with this one.—ED.]

In *erysipelas* as in diphtheria we have a tumor of the spleen which rapidly recedes. In this disease tumors of the spleen of considerable size are quite frequently observed, and are sometimes so large that they are palpable below the costal arch. In many of these cases albuminuria seems to accompany the swelling of the spleen.

Friedreich first called attention to the fact that swelling of the spleen seems to be a constant accompaniment of some forms of *pneumonia*, especially the so-called migrating pneumonia. In this disease he found "considerable swelling of the spleen during the first few days, and that in the course of a few days it developed to such a size that it protruded below the costal arch and could be clearly recognized by palpation. These tumors," he says, "are about as large as those found in typhoid fever; however, they are distinguished from these by the fact that they rapidly assume normal proportions as soon as the fever drops." This form of tumor of the spleen is caused by a hyperplastic swelling of the parenchyma, and occurs at a time when the hepatization of the lung has not progressed very far. Friedreich further calls attention to the fact that certain diseases considered as purely local processes should be counted among the acute infectious diseases on account of a marked swelling of the spleen that occurs in them, sometimes even before the local symptoms appear. He includes in this class, for instance, certain forms of coryza that are accompanied by fever.

Acute tumors of the spleen are found in the following diseases, in addition to those mentioned above: typhus, cholera, yellow fever, plague, dysentery, in all infectious catarrhs of the stomach or intestine, in mycotic diseases of the intestine, in ulcerative endocarditis, in pyemia, septicemia, acute inflammatory rheumatism, anemia, acute miliary tuberculosis, cerebrospinal meningitis, coryza, variola, scarlatina, measles,

erysipelas, scurvy, glanders, anthrax, puerperal fever, and in recent syphilitic infections. Occasionally a tumor of the spleen will be found in the newborn if the mother were affected with intermittent fever or syphilis during pregnancy; it is even possible that independent tumefaction of the spleen might occur, but no positive demonstration of such an event has so far been furnished.

The *anatomic findings* in acute tumors of the spleen vary widely in different cases. The degree of swelling, too, fluctuates within wide boundaries in different diseases and in different individuals afflicted with the same disease. Further, it has been noticed that different epidemics of the same infectious disease have been characterized throughout by the appearance of a greater or smaller degree of swelling of the spleen; this is especially noticeable in the case of typhoid fever. As the swelling of the spleen occurring in the course of infectious processes is primarily caused by hyperemia, and as this condition if it persist for a long time gradually gives rise to a true hyperplasia (consisting in an increase of the normal elements, a granular degeneration and an increase in the size of the pulp cells and, lastly, in the extravasation of numerous pulp cells containing red blood-corpuscles and pigment), we shall find, according to the presence of one or the other pathologic process, either an acute short-lived swelling of the spleen or a tumor that persists for a long time. The clinical findings in these cases will be found to correspond to these changes, inasmuch as we usually find very soft and scarcely palpable tumors in the beginning which later develop into larger, palpable swellings of considerable hardness. It is even possible to differentiate by palpation the tumors of different classes of infectious diseases; thus, for instance, recent tumors of the spleen in typhoid are very much softer than those felt at a corresponding stage in the course of remittent fever or of recurrent fever.

The most characteristic pathologic finding in acute tumor of the spleen is *hyperemia;* the organ is enlarged, the capsule distended, the lumen of the capillaries and veins is wider, and more tissue elements are found in the pulp. The pulp is very red and soft and pulp tissue can be easily scraped from the cut surface; the follicles of Malpighi are at times clearly visible as white nodules, and at other times are not visible at all. If the hyperemia persist for any great length of time the color of the pulp gradually changes, merging from a dark red to a grayish red or a pale grayish red, and the mass of the spleen grows progressively softer, until finally the tissue becomes mushy. These changes are accompanied by a constant increase in the size of the organ, so that occasionally rupture of the capsule and tearing of the tissues of the spleen occur. The microscopic examination shows that the vessels and strands of the pulp contain an abnormal number of colorless cells.

If the swelling persist for a long time, *hyperplasia* of the pulp, trabeculæ, the vessel walls, and of the capsule supervenes; diffuse or circumscribed areas of thickening occur on the capsule, assuming the form of nodules or small plates, and as a result of this perisplenitis the capsule of the spleen may become adherent to its surroundings. Accord-

ing to the quantity of pigment present in the pulp a section through the spleen will appear either of a light-red or brown to blackish-brown or of a slate color; the tissue itself is more solid, so that no pulp can be scraped from the cut surface.

Where the spleen is *pigmented* the colorless elements of the pulp, as a rule, contain the pigment in the shape of yellowish-red or brownish-red granules. Free pigment, besides, is found floating about. If black pigment be found in the spleen, the conclusion is justified, with a fair degree of certainty, that the patient at some time or another was afflicted with intermittent fever. Pigment granules are often found in the endothelial cells of the veins, or in some of the cells of the corpuscles of Malpighi: the system of trabeculæ is thickened to a varying degree, occasionally so much so that this change is visible with the naked eye. The reticulum of the spleen pulp is thickened only in those cases where the spleen is very solid and hard, but such thickening is occasionally seen to be converted into a striated form of connective tissue containing a varying number of cells. The walls of the arteries and veins also appear thickened and infiltrated with pigment, found either free within the tissues or incarcerated within cells.

The following changes are constantly observed in all *acute tumors of the spleen that have persisted for some time:* Enlargement and granular degeneration of the cells of the pulp; further, pulp cells that contain numerous blood-corpuscles and pigment; others that are of unusual size and packed with fat-globules. The writer has occasionally observed so-called *circumscribed focal lesions* of the spleen tissue that occurred in the course of acute infectious involvements of the spleen; in these cases were seen in the parenchyma of the organ circumscribed areas of a yellow color, or with a tinge toward red, usually dry and firm, though in part already degenerated into areas of puriform softening. These foci in some cases were isolated and scarce; in others they were found in great number, and varied in size from that of a pea to that of a walnut; usually they reached as far as the capsule, and sometimes sent out long processes, extending underneath the capsule and giving the appearance of narrow yellowish stripes on the cut surface of the spleen. In those cases in which these foci assumed larger dimensions they showed the characteristic wedge-shape of hemorrhagic infarcts, with the points directed toward the hilus; the bases of the wedges, however, did not always extend as far as the periphery of the spleen. In a few cases the writer has found that the puriform degeneration of these areas had progressed so far that cavities the size of a hazelnut had formed, containing either a spleen sequestrum that had been dissected off by the pus, or detritus very much resembling pus.

Besides this necrosis of certain parts of the spleen, abscesses and purulent degeneration of the whole organ may occasionally be observed.

The white wedges described above are most frequently found in recurrent fever, in typhoid fever, in intermittent fever, in cholera, and occasionally in other forms of infectious tumors of the spleen.

The **diagnosis** of acute tumor of the spleen is comparatively easy,

and is made with the aid of the well-established methods of percussion and palpation. Frequently inspection will reveal the presence of a tumor from the protrusion which is seen in the region of the spleen. It must be remembered that acute tumor of the spleen feels considerably softer than a so-called congested spleen or an amyloid spleen. An observer who has had much experience and practice should not be in doubt for a single moment whether he is dealing with one form of pathologic change or another; however, not to mention the individual variations and differences that are seen in different epidemics, a tumor which is originally soft and is simply hyperemic may change its consistence considerably during the course of the disease, so that, especially in typhoid relapses or in intermittent fever, where many relapses occur (notably in long-lasting attacks of intermittent fever), very hard tumors occasionally are felt. The harder the tumor, of course, the easier it is to palpate, especially where a corresponding increase in volume occurs, so that the normal indentations are more clearly marked. It may occasionally be very difficult, even on deep inspiration, to palpate a spleen in the initial stage of typhoid fever, because it is usually very soft and barely reaches to the margin of the ribs. We can more readily understand this upon seeing spleens from such a case on autopsy, and discovering that they are soft and mushy—so-called "spleen cakes"; and we may wonder that it is at all possible to feel so soft an organ during life. It is a peculiar fact, however, that the pulp of the spleen during life is not really as soft as it appears on the autopsy table. The changes observed are probably due to postmortem modifications, and are observed even when the tumor felt very hard during life. [Occasionally the spleen, though enlarged, may not descend so as to pass the costal margin even on deep inspiration, because adhesions from a preceding perisplenitis prevent.—Ed.]

The careful examination of the spleen is of such fundamental importance for diagnosis and differential diagnosis that we cannot insist too much upon it, especially upon palpation. In no part of the examination is the knowledge and skill of the physician put to so severe a test as in this manipulation; it is particularly important because so many cases are seen in which the presence or absence of swelling of the spleen may determine whether we are dealing with a serious infection in the stage of its incipiency, as, for instance, typhoid; and very frequently a positive exclusion of a spleen tumor will enable us to put the fears of the relatives at rest. A physician who cannot rely upon his examination in such doubtful cases—especially, for instance, in the gastric attacks of children, that often present such really alarming symptoms—and who can do no more than make a doubtful prognosis, will frequently be placed in a disagreeable position when a child, in which he had diagnosed a serious disease, is found to be perfectly well the next day.

Subjective signs of acute tumor of the spleen vary in different cases. Many patients complain of no symptoms at all that are attributable to a disease of the spleen; others again complain about pains in the region of the spleen, frequently stating that they seem worse on

inspiration. If the tumor be very large, its weight and volume may cause distress, so that the patients complain of a feeling of weight in the abdomen. [The strain upon the tense capsule or upon a spleen held by adhesions may also explain some of the pain.—Ed.] Sometimes the left half of the diaphragm is forced upward, causing some difficulty in breathing. Occasionally patients with acute tumor of the spleen complain of radiating pains. In judging of the value of subjective symptoms in acute tumor of the spleen, we must always remember that the primary disease (typhoid, malaria, recurrent fever) and the pyrexia that accompanies it may benumb the sensorium, so that the patient does not perceive the subjective symptoms with the same acuity as in health.

The **treatment** of an acute tumor of the spleen is usually identical with the treatment of the primary disease. As a rule, the tumor of the spleen is only an expression and one of the symptoms of some disease involving the whole organism. In order to cure a tumor of the spleen, therefore, we must attempt to cure the infection, so that the treatment of such a tumor will vary with the primary disease. Arsenic is frequently employed, and the new antipyretics—antipyrin, antifebrin, etc.—occupy a prominent place in the treatment of tumors of the spleen. Cold bathing is, of course, indicated in typhoid fever cases. Some clinicians have attempted to treat a tumor of the spleen directly; for instance, with the electric current. Chvostek [1] and Mader [2] have used the faradic brush over the region of the spleen in a case of intermittent fever. Botkin [3] and others, as Skorzewski, Tschulowski, Popow, and Schroeder, have used faradization with moist electrodes over the region of the spleen. They claim to have discovered an appreciable decrease in the size of the spleen. Schroeder and others claim that in some of the cases they were at the same time able to reduce the temperature. In the writer's own experience he has never seen more than very transitory effects from faradization of the spleen.

A complicating perisplenitis that causes violent pains and deprives the patient of sleep can be treated with cataplasms, cupping, or sinapisms. If no good results are obtained by these means or by hot applications, subcutaneous injections of morphin are indicated unless the nature of the primary disease or too great an elevation of temperature forbids its use.

Violent pain in the region of the spleen may sometimes call for an application of the ice-bag, a procedure which occasionally causes a diminution in the size of the tumor.

If after recovery from the original disease the acute tumor of the spleen persist and the organ do not assume its normal size and consistence, then quinin should be employed. In the chronic swelling of the spleen so often seen in intermittent fever this treatment usually leads to the goal; it is well sometimes to combine arsenic with it. If a considerable degree of anemia exist, iron preparations may be given with

[1] *Wien. med. Presse*, 1870. [2] *Ibid.*, 1880.
[3] *Faradization der Milz*, 1874.

great advantage, notably mineral waters containing iron (Levico, Roncegno, Guberquelle), combined, of course, with a nourishing diet. Preparations of iodin and iron, especially when given in the form of the syrupus ferri iodidi, are frequently useful.

PULSATING TUMOR OF THE SPLEEN.

C. Gerhardt, in 1882, first called attention to pulsating tumor of the spleen. Later, Prior found that Nicolaus Tulpius, in his *Observationes Medicæ*, published in 1652, described a case of pulsating tumor of the spleen, and called it "lien verberans." He saw it in the case of a man afflicted with "atra bilis," and describes his observations thus:

"Viro ab atra bile frequentius afflicto fecit nonnunquam lien tam vehementum impetum in castas circumpositas, ut . . . etiam longissima ab ipso remoti . . . numeraverint non semel singula verbera, et admota manu etiam coram tetigerint quoscunque ferientes lienis ictus. . . . Sed prout vel uberius vel parcius redundarent bilis atra, pro eo etiam, vel intendebatur, vel remittebat horum ictuum vehementia."

Gerhardt's case was that of a blacksmith, twenty-seven years of age, who was afflicted with aortic insufficiency and intermittent fever. The aortic insufficiency, which had probably originated in an attack of inflammatory rheumatism, seemed to be well compensated; the double sound of Durosiez over the crural artery could be heard, and a capillary pulse was visible in the skin. The intermittent fever was of a tertian type, and in this instance was a relapse from an attack contracted during the man's travels. Later on Gerhardt discovered a pulsating tumor of the spleen in two other cases of aortic insufficiency, in which, during the stay of the patients in the hospital, pericarditis had occurred; in both cases during the febrile stage of the disease. The spleen was very much more enlarged than it would otherwise have been under the same circumstances. Prior supplemented Gerhardt's observation by reporting two other similar cases of pulsating tumor of the spleen; one was a pulsating tumor that he saw in typhoid with well-compensated aortic insufficiency, his second observation has a most important bearing upon the explanation of this peculiar phenomenon; it was a case of hypertrophy of the left ventricle which had occurred as a result of overexertion. The patient, a laboring man, aged thirty-seven years, first developed the symptoms in the course of a croupous pneumonia. Still another case is reported by Drasche in a girl of seventeen with an aortic insufficiency. The phenomenon here was discovered during the febrile stage of an attack of inflammatory rheumatism complicated by croupous pneumonia.

Pulsating tumor of the spleen can be demonstrated both by palpation and inspection. On palpation of the spleen pulsation is felt; the tumor expands in all directions with each systole of the heart, gradually reaches its maximum volume and decreases in size with the diastole. Occasionally it is possible to grasp the point of the enlarged organ; if this be possible, a jumping of the edge of the spleen is felt recurring

with great regularity synchronously with the systole of the heart. The diagnosis through inspection is only possible if the volume of the spleen be very great and the pulsations very clearly marked.

In the same case the pulsations may not be of equal intensity during the whole course of the disease; the intensity usually varies with the intensity of the cardiac impulse. If, as in the case of pneumonia which Prior describes, or as the result of initial hemorrhage, as reported by the same author, the blood-pressure falls, then the pulsations of the spleen grow weaker. With a re-establishment of the force of the heart beat—as, for instance, in typhoid after bathing—the pulsation increases in strength. A pulsation of the spleen can only be felt in an organ that is very much enlarged, and as soon as the tumor of the spleen grows smaller the pulsation ceases.

All in all, a pulsating tumor of the spleen is a very rare occurrence. This is readily understood when we consider that it can be caused only through the complication of two pathologic processes—a chronic lesion of the heart and an acute infectious disease.

The heart lesion always is a hypertrophy of the left ventricle, sometimes idiopathic; in the majority of cases, however, complicated with aortic insufficiency. In all the cases the heart lesion was well compensated. This observation teaches us that increased arterial pressure is one of the essential conditions for the occurrence of pulsating tumor of the spleen. The other condition is the presence of an acute tumor of the spleen, as in intermittent fever, typhoid, and croupous pneumonia. The phenomenon is only observed in such an acute tumor during the febrile period of the disease, so that hypertrophy of the heart, acute tumor of the spleen, and fever are the three pathologic conditions productive of a pulsating tumor so far as observations go. The following theory can therefore be evolved: In an acute tumor of the spleen the organ is filled with blood; if fever supervene the tissues of the spleen are relaxed. In relaxed vessels that are filled with blood a strong pulse is more clearly perceptible, and the impulse of the heart is transmitted in all directions and perceived at the periphery of the organ.

SPLENIC TUMOR IN TYPHOID FEVER.

Tumor of the spleen, especially in *young individuals*, is an almost constant symptom of typhoid fever. The swelling may be very insignificant or very great. In some cases the spleen may be enlarged to six times its normal size. In rare cases, on the other hand, even in young individuals who have died when the disease was at its height, tumor of the spleen has been found absent. In older individuals, where the capsule is thickened or the tissues are sclerotic, tumor of the spleen is more frequently absent. [These cases of typhoid without enlargement of the spleen at some time during the illness are certainly exceptional. Where the swelling of the spleen is lacking, one feels like asking for indubitable bacteriologic proof that the diagnosis of typhoid is correct.—Ed.] The degree of swelling is dependent on the character

of each epidemic, and also to a large extent on individual peculiarities. A swelling of the spleen in typhoid fever, just as most of the other acute splenic tumors in infectious diseases, is primarily a hyperemia, followed later by hyperplasia of the pulp, as well as a new formation of other cells. Hemorrhages into the tissue and underneath the capsule also occur.

Histologic examination generally shows an increase of the normal elements and in many cases an enlargement of the pulp cells that are in a state of granular degeneration. Some cases, besides, are characterized by the presence of numerous spleen pulp cells containing blood-corpuscles and pigment; also by the presence of cells of unusual size that are filled with fat-granules. The swelling of the spleen usually occurs very early, and can be recognized clinically even in the stage of incubation; it reaches its maximum during the height of the first period of the disease. [One must take exception to this statement. Only rarely can a spleen be palpated in the incubation period of typhoid. As Litten himself says, percussion findings are unreliable. We agree with his statement, on p. 518, that usually by the fourth or fifth day of the *fever* the spleen can, as a rule, be palpated. In discussing the spleen in recurrent fever the author seems to contradict his statement just made, for he there refers to the fact that in recurrent fever splenic tumor can be palpated very early in the disease, thus sharply differentiating it from typhoid and malaria (see pp. 518 and 523).—Ed.] At this time the spleen presents the appearance of a brownish-red, spongy, easily compressible tumor, or of a mass of soft, gruelly matter, colored violet to dark red, and in which the corpuscles of Malpighi cannot be clearly distinguished. The capsule, as a rule, is delicate and very tense. In the second period, usually in the third or fourth week, the size of the organ seems to decrease rapidly without any perceptible connection with the course of the intestinal lesions. If death occur later on a large tumor is rarely found on autopsy; as a rule, only a very slight swelling or no enlargement at all is discovered. The capsule usually is relaxed and folded. The pulp is colored brown by the presence of pigment. In typhoid relapses the spleen usually swells again.

The *finer changes* in the spleen of typhoid fever have been studied, with particular care by Billroth.[1] He discovered within the veins a great number of large cells containing from 2 to 6 nuclei, and resembling those in the lymph glands in typhoid. These cells probably originated from the epithelium of the splenic veins. Very few cells were found within the corpuscles of Malpighi. The large cells mentioned above are undoubtedly carried away with the blood through the veins of the spleen, and may occasionally give rise to capillary emboli in the liver.

The writer has frequently observed *circumscribed lesions* in the organ in addition to a general hyperplasia. These lesions were either infarcts or necrotic areas. The writer has seen recent dark-red wedges, similar to those frequently seen in the spleen where there are lesions of the left

[1] *Virchow's Archiv*, vol. xiii.

heart. In these particular cases, however, no evidence could be found of any involvement of the heart or of any embolic process.

Repeatedly is noticed the occurrence of large, wedge-shaped, grayish-yellow infarcts, that resemble in a most striking manner those grayish-yellow wedges that are found so frequently in the spleen, and occasionally in the kidneys, in recurrent fever and cholera; they have not been satisfactorily explained so far, notwithstanding the frequency with which they are observed. The arterial channels in these cases were always found to be patent, and no thrombi were seen in the veins. The number of these wedge-shaped foci is different in different epidemics. In some epidemics as many as 7 per cent. of the patients are affected in this way.

Occasionally dissecting infarcts and abscesses are seen. They usually constitute cavities situated in the center of the swollen spleen; they are about as large as a walnut, lined with a so-called pyogenic membrane, and filled with a thin mass of pus or detritus containing sequestra of spleen substance. At the same time miliary abscesses are found in the kidneys and similarly dissected infarcts in the lungs.

In very rare cases the capsule of the spleen is seen to be torn (compare the section on Rupture of the Spleen); as a result of this accident blood is poured into the peritoneal cavity. Such *ruptures of the spleen* occur at the time of greatest swelling, particularly when the size of the organ rapidly increases. Rupture of the spleen has been found only in typhoid, intermittent, and recurrent fever. Peritonitis rarely results in these cases; the patients usually die soon after the accident, with the symptoms of internal hemorrhage and frequently in great pain. Many patients have described the feeling as to the bursting of something inside of them.

The natural termination of tumor of the spleen, provided death does not occur, is a gradual return of the organ to its normal size and consistence. In some cases, however, the tumor becomes chronic and may persist for many years, and occasionally for the rest of the patient's life; this only rarely happens in typhoid fever.

The writer has endeavored to demonstrate whether increase in the volume of the spleen occurs in a typical manner in typhoid—that is, whether the swelling of the spleen stands in any direct relation to the typical course of the fever or the changes in Peyer's patches. Some authors maintain that the swelling of the spleen continues as long as the infiltration of the intestinal glands progresses; the writer's own investigations directed toward an elucidation of this point do not seem to justify definite conclusions in one way or the other; if anything, they speak against the existence of such a relationship.[1] In the living the question cannot be satisfactorily settled, for the reasons that, first, it is often difficult to palpate splenic tumors in typhoid; second, we have no definite clues as to the exact condition of the affected glands, so that only postmortem material can be used in this investigation. Here, contrary to the prevalent opinion, the writer has been altogether unable

[1] *Cf. Charite Ann.*, vi.

to determine that the intestinal changes stand in any relationship whatever to the enlargement of the spleen. He has proved this beyond a doubt from the examination of a great many cases that died early in the disease, and has come to the conclusion that the *swelling of the spleen is independent of the changes in the intestine* and begins at a time when no swelling of the intestinal glands has occurred. On the other hand, that it reaches its maximum at a time when the cellular infiltration of Peyer's patches still continues. The volume of the spleen seems to be greatest toward the end of the first week ; whereas the swelling of the intestinal glands reaches its maximum during the second week and often continues for a long time thereafter. In relapses the swelling of the spleen also seems to reach its maximum at a very early stage, while changes in the intestine continue for varying periods of time. In some cases large tumors of the spleen are seen, although there is a complete absence or very slight manifestation of typhoid processes in the mucous membrane of the intestine.

[The later proof of the presence of typhoid bacilli in the blood during the febrile period, and their disappearance as the fever disappears, the spleen usually growing smaller as the bacilli fail to be found in the circulating blood ; also the fact that typhoid infection—*i. e.*, typhoid fever—may exist without intestinal lesions, puts a new light upon the relation of the spleen to the ulcers so long regarded as the all-important pathologic finding in the disease.—Ed.]

In 1880 Eberth demonstrated the *Eberth-Koch bacillus* in the spleen of typhoid. He found this micro-organism, however, only in some of the spleens of typhoid cases that he examined. Gaffky,[1] in 1881, demonstrated that this bacillus is constantly found in the typhoid spleen. He used solid culture media for his examinations. His method of procedure was as follows :

The spleen was first examined for evidence of putrefaction, and if it were found that no putrefactive process had occurred, the whole spleen was carefully washed in a 1 per cent. solution of corrosive sublimate. An incision was then made with a knife that had previously been sterilized by passing through the flame, and the whole organ divided in its longitudinal axis ; then with another sterilized knife a second incision was made through the first cut surface, extending deeply into the tissues of the spleen, but not reaching as far as the capsule ; on this second cut surface a third incision was made with a third knife sterilized as above. From the bottom of this last cut small quantities of blood or small pieces of spleen substance were taken with platinum needles that had been heated prior to contact with the organ. The material removed in this way was transferred to plates of solidified peptone-gelatin. These were kept in moist chambers at room temperature. The same portions of the spleen from which the material for these cultures had been removed were then examined microscopically in stained cover-glass preparations. In each specimen some bacilli which corresponded to Eberth-Koch's organism could be seen. Other species

[1] *Mittheilungen aus dem kaiserlichen Gesundheitsamt*, vol. ii.

were not found. In sections of the spleen that had been placed in alcohol the bacilli were also seen arranged in characteristic masses. Culture experiments with the blood and the substance of typhoid spleens always yielded positive results.

W. Kruse,[1] in reporting some very interesting findings significant in determining the importance of typhoid bacilli in the causation of abscesses of the spleen, found 1 case of abscess that contained only typhoid bacilli.

The Eberth-Koch bacillus has not only been found in the spleen of persons who have died of typhoid, but also occasionally in the spleen of living typhoid patients. Philipowicz,[2] Widal and Chantemesse,[3] and Redtenbacher [4] performed puncture of the spleen in typhoid fever with a Pravaz syringe. In this manner Redtenbacher could demonstrate the presence of typhoid bacilli in 10 out of 14 cases that were examined.

Clinical Symptoms.—The *swelling* of the spleen occurs early in the first week, and can clearly be recognized on the fourth or fifth day of the disease; the greatest swelling is established at the height of the first period of the disease. All observers seem to agree that the tumor of the spleen occurs very early in the course of typhoid fever and may be ranked among the first symptoms of the disease; on the second or third day the spleen is enlarged to such a degree that it protrudes very markedly underneath the arch of the ribs. Friedreich in one case by chance discovered a large tumor of the spleen in one of his assistants while the man was feeling perfectly well; he had had no intermittent fever nor any other disease that could possibly have left a chronic tumor of the spleen. In the course of the next few days the first febrile disturbances appeared, and a very severe attack of typhoid fever, lasting several weeks, resulted, at the termination of which the spleen returned to its normal size. In this case, doubtless, the spleen had already increased in volume during the period of incubation. From this observation and from the fact that frequently in the very first days of typhoid large tumors of the spleen can be demonstrated. Friedreich draws the conclusion that the swelling of the spleen in typhoid fever is really the first and only effect of the infectious material circulating in the blood during the period of incubation, and that consequently in this stage such a tumor may already assume large proportions. At all events, the determination of the fact that tumors of the spleen may occasionally occur in the incubation period of typhoid fever is very important, as we have thereby a means of frequently recognizing the disease before the fever and other symptoms of the disease have made their appearance. [Again this seems to us a rather exaggerated statement.—Ed.] Friedreich suggests in addition that it might very well be possible to recognize typhoid fever, for instance, in the inhabitants of a house or of a quarter of the city in which an epidemic of typhoid was raging before the later symptoms of the disease have made their appearance, and that such a discovery would be practically and therapeutically very valuable. Fried-

[1] Flügge, *Mikro-organismen*, vol. ii., p. 391.
[2] *Wien. med. Blätter*, 1886.
[3] *Archiv. de Physiol. Norm. et Path.*, 1887.
[4] *Zeits. f. klin. Med.*, 1891.

reich's report is the more important since we know that similar conditions exist in syphilis ; at all events the question whether infection, especially in case of an epidemic, can be recognized by the swelling of the spleen before the breaking out of the disease proper is a very important one.

We are not justified in drawing any conclusions from the size of the tumor in regard to the intensity of the disease. The writer has already mentioned that even in young subjects who have died at the height of the disease a tumor of the spleen may be completely absent, and that, on the other hand, very large tumors may occasionally be seen in mild cases. Jürgensen lays particular stress on the occurrence of considerable swelling of the spleen in typhus levissimus and in the ambulatory form of the disease—both variations of typhoid characterized by the short duration of the sickness. Even in the lightest form of typhoid, however, tumors of the spleen are found and are a constant symptom. In view of all these facts, which the writer can corroborate by numerous cases observed by himself, we learn that the *size of the tumor of the spleen cannot be used as an indication of the intensity of the infection.* We must assume individual differences in the resisting powers of the elements of the spleen against the action of infectious material.

In the same way that the spleen is one of the first organs to show changes in typhoid infection, it is also the last organ to resume its normal state. As a rule, swelling of the spleen persists after all the other symptoms of the disease have subsided and usually for a long time after convalescence has been established. [*Cf.* Editor's note on p. 508.—Ed.]. Clinical experience has demonstrated positively that relapses of typhoid occur only during the time that swelling of the spleen still exists, and hence a typhoid fever patient can be declared out of danger from relapse only after the spleen has resumed its normal size. It is not possible, in the present stage of our knowledge, to determine what significance in the genesis of typhoid relapses the presence of typhoid bacilli in the intestine and dejecta have. We know that they are present in the digestive tract for many months after the termination of the disease, and it is possible that the bacilli remain for just as long a time in the spleen, perhaps in this way causing relapses.

The clinical symptoms due to tumor are very insignificant, because the distress caused by such a swelling is not very great. Frequently the sensorium of the patient is too much benumbed for him to perceive or recognize that the spleen is at all swollen ; but from the writer's own experience he is able to state that even very large tumors of the spleen, as they are seen in recurrent fever, are hardly noticeable to the patient. An occasional attack of perisplenitis might produce more pain, but is so rare an occurrence in typhoid fever that it need hardly be considered here ; when it does occur, it is the result, as a rule, of the formation of the wedge-shaped foci described above, especially if their bases extend as far as to the capsule of the spleen. Once in a while a patient will complain of a dull ache which is increased by pressure, even if the capsule be not inflamed. In other cases it is difficult for the patient to lie on the left side.

The *diagnosis* of tumor of the spleen is easy if the point of the organ protude beyond the costal arch or move below it on deep inspiration. If meteorism be present, the demonstration of the tumor may be very difficult or impossible, because the distended intestine pushes the spleen upward or comes to lie in front of it. It is also due to this meteorism that the spleen in typhoid is usually situated more posteriorly than in intermittent fever. If the distention of the intestine be very great, it becomes altogether impossible to estimate accurately the variations in the volume of the spleen. Percussion in these cases is altogether without value, and we must rely exclusively on palpation. The spleen in the first part of the disease feels very soft, but is in reality harder than a normal spleen. On autopsy the spleen is usually found to be very soft and mushy, so much so as to be almost liquid; this, however, is a postmortem change and cannot be utilized when it comes to forming an opinion on the consistence of the organ during life.

In rare cases the swelling of the spleen becomes chronic and persists for years, sometimes during life. Such a tumor following typhoid rarely causes any trouble.

Acute tumor of the spleen is a frequent occurrence in "exanthematic typhus"—i. e., typhus fever—but is not constantly found even in young subjects. The tissues of the organ are dark violet, soft, mushy, even diffluent. Recent infarcts and wedges of fibrin are found more frequently and earlier in the disease than in typhoid fever. They are usually isolated, and no other metastases are found in other parts of the body. Occasionally numerous areas of inflammation are observed in the corpuscles of Malpighi, accompanied by copious exudation; these play a large rôle in recurrent fever and so-called "bilious typhoid." A swelling of the spleen is a phenomenon of irregular occurrence; in some epidemics it is found constantly, and the spleen may become so large that rupture of the organ occurs; in other epidemics or in other locations it occurs only rarely, and then only to a very slight degree.

It is easier to demonstrate the presence of a swollen spleen in typhus than in ordinary typhoid, for the reason that meteorism is nearly always absent.

TUMOR OF THE SPLEEN IN RECURRENT FEVER.

The spleen in recurrent fever is characterized by its enormous size; leukemia, pseudoleukemia, splenic anemia, and intermittent fever or malaria are the only diseases in which the organ is still larger. The increase in volume occurs in all directions; it is interesting to study some of the measurements that Ponfick made in cases of recurrent fever. In 1 case the spleen was 23 cm. long, 13 cm. wide, 4.5 cm. thick, and weighed 350 gm.; in another case, the corresponding figures were 21, 13, 4.5 cm., and 670 gm.; in a third, 15, 12, 5 cm., and 330 gm. The weight of the spleen, as we see, was considerably

augmented, for the average weight of the spleen, taken from figures obtained from 57 essentially normal subjects between twenty and sixty years of age, is only 154 gm.

The capsule is tensely stretched and shiny; the tissues softer and more fragile than normál, sometimes of almost fluid consistence; the pulp looks a dark bluish red, bulges, and shows enlarged or completely obliterated follicles; their color is usually gray, sometimes pure white or more yellowish. As the swelling of the pulp decreases in the later stages of the disease, the follicles stand out clearly. The enlargement of the spleen can be demonstrated at least for a month after the last attack of fever. If the pulp swell up very much in a very short time, the capsule may rupture, blood may be poured into the peritoneal cavity, and a peritonitis result. The swelling of the pulp is produced by two factors: first, the enormous distention and *engorgement of the vessels of the spleen;* and second, the great *increase in the number of cellular elements*, among which large multinuclear forms are especially conspicuous. In many of the pulp cells red blood-corpuscles are seen, which, depending on the stage of the disease, may be either fresh or in advanced stages of retrogressive metamorphosis. In other pulp cells larger or smaller quantities of fatty granules or fat-globules, often of considerable size, are seen; the capsule is small and sometimes thickened, and occasionally numerous areas of hemorrhage are seen in the parenchyma of the organ and underneath the capsule.

Aside from these general symptoms of affection of the organ, certain characteristic *localized lesions* are discovered in the spleen in recurrent fever. Two kinds of these focal lesions can be clearly differentiated—viz., those found in the arterial districts and those found in the venous areas. The venous lesions or infarcts are much more frequent than the arterial; they were found in about 40 per cent. of all cases of recurrent fever studied post mortem. They are distinguished from the arterial focal lesions by their size, sometimes occupying as much as two-thirds of the whole spleen, and are clearly circumscribed and of varying outline. The individual foci differ from one another in size; the largest are usually situated immediately underneath the capsule of the spleen and are usually of a more or less wedge-shaped outline. The smaller foci are round and situated nearer the center of the organ. In the beginning the foci are colored dark red and are spotted; this color gradually merges into grayish red, grayish yellow, and finally yellowish white. Corresponding to these changes in the color, the cut surface also changes its appearance; originally it is slightly granular and protruding, but gradually assumes a more smooth and homogeneous appearance. As the disease progresses the infarcts of the spleen become necrotic. The smaller foci are healed by absorption of the disintegrated tissue composing them, so that nothing may remain of an infarct but a hard cicatrix, colored yellowish brown by blood-pigment.

In the case of the larger foci things are usually different; around them a zone of reactive inflammation is formed, so that the infarct is surrounded by a capsule; a sequestrum is dissected off through the pus

formation and gradually becomes liquefied. Sometimes the peritoneal covering of the spleen is involved by continuity of tissue, and in this manner a circumscribed fibropurulent *peritonitis* may occur, which, in rare instances, may develop into a general inflammation of the peritoneum; as a rule, however, it remains strictly localized to the spleen and its immediate surroundings. It is not impossible, further, for this peritonitis to extend to the left pleura. Occasionally, too, that piece of the spleen which encloses the abscess cavity becomes disintegrated, so that if the pus burst the capsule, it pours into the peritoneal cavity and causes a diffuse purulent peritonitis. If adhesions existed between the diseased portions of the spleen and certain areas of the peritoneum, a circumscribed pus sac may develop; in these cases fever persists for a long time, until finally the pus becomes re-absorbed. In less favorable cases the diaphragm is involved in the process, so that abscess of the diaphragm occurs, perhaps accompanied with rupture into the diaphragmatic pleura and pleuritis. Ponfick even saw a communication established between the peritonitic abscess cavity and the left lung.

Arterial focal lesions of the spleen are not so frequently met. Ponfick saw such lesions in only 5 per cent. of his cases. They are always found in the follicular tissues; sometimes they are so numerous that they are disseminated all through the dark tissue; occasionally they are limited to a very small portion of the organ. The portion of the organ involved usually corresponds to the area of distribution of some artery; they are clearly distinguishable from similar foci that occur in the area tributary to the vein. They resemble little dull-white or yellowish spots or streaks, occupying a part, or the whole, of the follicle. The single foci are usually smaller than a pin-head, and only in rare instances a little larger. As the foci increase in size their color grows more and more yellowish, and their tissue becomes less and less solid and more purulent; finally a small cavity appears in the center of the involved district. Secondary phenomena in the region of these arterial foci are never seen.

Ponfick has demonstrated, by *microscopic examination* of these little foci found in the corpuscles of Malpighi, that there is to be seen in all these places an increased accumulation of the same small lymphoid elements that occur normally in the follicular tissue of the spleen. The peculiar opaque, dirty, yellowish-white color, and later the disintegration and complete dissolution of the area, is explained, according to this author, by the great tendency of these lymphoid cells to undergo fatty degeneration. In the latter stages, larger forms are seen in addition to the smaller cells, that are distinguished and characterized by the presence of large and small fat-granules; they are found partly in the follicular tissues and partly in the adventitia of the arteries. The media of the arteries may also be said to be involved, inasmuch as a large number of fat-granules are seen within its muscle fibers.

R. Koch discovered the relation of *Obermeier's spirillum* of recurrent fever to the tumor of the spleen in this disease; he repeated the experiments of Carter on the artificial transmission of recurrent fever to mon-

keys. Koch injected subcutaneously defibrinated blood containing the spirochete into two long-tailed Makaka monkeys. After an incubation period of several days a typical attack of fever occurred, during which spirilla in large numbers were found in the blood; before and after the attacks they could not be demonstrated. Koch killed two of the animals at the height of the disease in order to study the presence of spirochete in the different organs. He succeeded in demonstrating them in stained sections in the spleen, the brain, the lungs, the kidneys, the liver, and the skin.[1] In his report on the Breslau epidemic of recurrent fever, 1872 to 1873, the writer has published his own observations on the clinical phenomena of tumor of the spleen in recurrent fever. According to his findings, swelling of the spleen was the most constant symptom of recurrent fever; in 96 per cent. of the cases it could be demonstrated by percussion, and the enlarged organ could always be palpated.

The fact that the *tumor of the spleen* in recurrent fever can be *palpated very early* in the disease differentiates it clinically very distinctly from that of typhoid or intermittent fever. *Severe pain*, increased on deep inspiration, is usually complained of in the left hypochondriac region. The *indentations* on the spleen can very frequently be felt with great distinctness. A reduction in the swelling occurs very gradually; in only 2 of all the cases the writer examined did the tumors decrease very much when the crisis occurred; as a rule, the diminution in size occurs very slowly, so that even at the end of the fever the swelling can still be demonstrated by percussion. Usually from three to four days elapse after the crisis before it is possible to demonstrate a distinct reduction in the size of the spleen. The swelling seems to disappear primarily at the anterior margin. In case of relapse the organ enlarges again, and usually attains its former size. In some cases the enlargement of the spleen will be found several weeks after the termination of the disease.

It is comparatively an easy matter to determine whether an acute tumor of the spleen is caused by recurrent fever if we consider all the symptoms of this disease. In the first place, it is important to remember that recurrent fever occurs in *epidemics*. During the epidemic in Breslau, in 1873, one fact was very apparent—viz., that the inmates of asylums, and other persons who were forced to live in a narrow, overcrowded space, became easily infected. In other epidemics the observation has been made that recurrent fever seems to be especially transmissible in the hospital. The most striking symptom of the disease is the temperature curve, to which the disease owes its name; the fever recurs almost without exception after the passing of the first attack and its termination in crisis. Several peculiarities of the fever curve are worthy of mention; the temperature may reach very unusual degrees, so that temperatures of 41.5° C. (106.7° F.) are not at all rare; some temperatures as high as 42.2° to 42.5° C. (108.5° F.) have been reported. The fever, further, is remitting in character, the first attack usually

[1] *Deutsch. med. Woch.*, 1879.

lasting from five to seven days, rarely longer than from eleven to fourteen days, and terminating suddenly by crisis; the temperature drops 5° within eight or nine hours under violent perspiration. In the next few days the temperature rises again, and after five to eight, or sometimes twelve to fourteen days, the relapse occurs, lasting three or four days. Usually one or two relapses occur; occasionally three or four have been observed.

The blood-picture in recurrent fever is characteristic and constant. During the fever the spirillum is always found in the blood. This organism was first described by Obermeier in 1873, and bears his name;[1] it is a long, wavy, flexible, thread-like organism, with from 10 to 20 corkscrew twists, and varying in length from 16 to 20 μ; it is from one-fourth to one-third as thick as the comma bacillus. In fresh specimens the spirilla are motile; moving rapidly from place to place with apparent undulation, so that wave-like movements seem to run through the whole course of the thread. They are readily stained by dyes, particularly well by fuchsin, alkaline methylene-blue, and Bismarck brown. Owing to their thinness they can, as a rule, be seen only with a very high power and a strong illumination; if they congregate in masses, as they often do in the blood, they are readily seen in fresh and stained specimens. The spirillum of Obermeier has so far never been found in the secretions of recurrent fever patients, and all attempts to cultivate it have been unsuccessful. If kept in blood-serum or salt solutions outside of the body, the germ retains its motility for a time, but has never been seen to multiply.

THE SPLEEN IN INTERMITTENT FEVER.

[Instead of attempting to rewrite this section or to bring it in all details up to date, it has seemed best to translate it as it stands, and then add a brief note concerning some of the new facts in malaria discovered since Litten wrote this book.—ED.]

Our knowledge of intermittent fever has been greatly augmented since we have learned to recognize the specific cause of the disease. The grave forms of tropic malaria and the so-called blackwater fever that occurs in German East Africa and on the west coast of the Continent have recently been carefully studied, and throw a great deal of light on the nature of our own domestic form of intermittent fever. There are certain marked differences, however, between the two diseases; in our *domestic form the spleen is always involved* and always increased in size; in the swamp fevers, on the other hand, in warm countries and, notably, *in the tropics, swelling of the spleen is not constantly found* during the life of the patient nor, in fact, in the bodies of subjects who were dead after short and very violent paroxysms. Even in the most serious cases of pernicious intermittent fever and of blackwater fever, in which death occurred during or after the second attack, the volume and consistence of the spleen were found to be normal. Occasional exceptions to this rule

[1] *Centralbl. der medicinischen Wissenschaften*, and *Berlin. klin. Woch.*, 1873.

have been reported: thus, E. Stendel, in his interesting communications on this subject from German East Africa, reports that he has found the spleen so swollen and so softened that it was almost impossible to procure a small piece of it for hardening.

Some gastric disturbance, accompanied by fever, usually precedes the paroxysms of our *ordinary domestic intermittent fever*, and sometimes a slight swelling of the spleen can be demonstrated during this time. During the attack, and especially during the stage of the chill, the spleen always enlarges and may become very painful; with the access of the fever the swelling increases. No distinct inter-relationship exists between the intensity of the fever paroxysm and the size of the tumor in this disease, so that we have an analogy here between intermittent fever and typhoid. In very mild chills we may occasionally find very large tumors of the spleen; sometimes the spleen continues to enlarge after the attacks have ceased, so that we find cases of chronic malarial cachexia with large tumors of the spleen, in which paroxysms are hardly ever observed. In fever regions we even find tumors of the spleen in individuals who never have had any distinct manifestations of the disease, and there are certain districts, especially in the tropics and in swampy countries, that are noted for the intense malarial character of the region, the majority of the inhabitants, not alone the natives, seeming to be afflicted with a chronic intoxication and a chronic tumor of the spleen. Considerable swelling of the spleen has even been found in newborn children whose mothers suffered from intermittent fever during pregnancy.

Enlargement of the spleen is only slight after the first attack, and seems to decrease almost to normal during the first periods of apyrexia; after the subject has had a number of attacks the tumor sooner or later becomes chronic; even though it may become slightly reduced during the fever-free periods. The enlargement of the organ may progress very slowly, very rapidly, or in spasms, so that the volume of the spleen may become double its normal size within twenty-four hours. In quotidian and quartan fever the spleen seems to enlarge to a greater degree than in the tertian form. Individual differences are observed, and in *old people* swelling of the spleen is never very great, sometimes not demonstrable at all; this can probably be attributed to the reduced elasticity of the capsule, or to the thickening, even calcification, of this tissue. In *children*, on the other hand, the enlargement of the spleen is most pronounced; Griesinger reports tumors of the spleen, occurring three weeks after the beginning of the first atack of fever, that extended above almost into the axilla, and below to three fingers beyond the costal arch. These cases are accompanied by a severe form of *anemia* that seems to increase in severity with the size of the tumor and the rapidity of its development.

With the cure of intermittent fever the acute tumor of the spleen also becomes reduced; if quinin be administered in recent cases, this usually occurs very rapidly—that is, in the course of from three to fourteen days. If the disease be not cured, the spleen in many cases

continues to enlarge even after the paroxysms have stopped, and during the period of complete apyrexia; it is in these cases that the organ attains great size, becomes very heavy, and assumes a characteristic shape. In other cases the volume of the spleen may remain almost normal even though the paroxysms of fever may continue; or it may contract after having been enlarged, so that on autopsy the spleen is found atrophic and hard, and usually covered with adhesions.

It is difficult to palpate spleen tumors during the fever because of their softness; with a little practice, however, it is possible to feel them on inspiration as they project below the costal arch. At all events it is important to control the results of percussion by palpation. It is a well-known fact that the tumor of the spleen in intermittent fever is situated more anteriorly than in typhoid, and, as we have shown above, this is due to the absence of meteorism in intermittent fever, and its almost constant presence in typhoid fever. Old tumors of the spleen can form large masses, filling out the whole of the left hypochondriac region and extending far into the abdominal cavity, causing the abdomen to protrude. These tumors are usually movable with respiration; they can easily be palpated, and are characterized by their blunt, rounded margin and the crenæ lienales. The diaphragmatic ligament is usually stretched and pulled to such a degree by the weight of the enlarged spleen that it yields, and in this way, especially if the abdominal walls are flaccid, the heavy spleen sinks in the abdomen until it may reach the pelvis, or even the region of the symphysis. Such tumors are usually found in the left iliac region, where they may be confounded with tumors of the ovary. These *dislocated spleens* are exceedingly movable, and it is an easy matter to replace them into their normal location; they must be bandaged, however, or held in place by abdominal binders, because without such artificial support they will always drop back into an abnormal position. Occasionally inflammation of the capsule supervenes and they become anchored by adhesions in some abnormal place. The spleen of intermittent fever furnishes the greatest number of floating spleens. (Compare the section on Floating Spleen.)

Swelling of the spleen in many cases produces no *subjective symptoms*. Occasionally a slight degree of *pain* or, at least, a certain degree of sensitiveness on pressure is complained of during the attacks or shortly after they have passed away; this phenomenon is found rather regularly and is more pronounced in children. If there be constant pain in the region of the spleen, persisting for some time after the fever has been cured, it is usually due to perisplenitis or to its sequelæ, adhesions.

In regard to these tumors of the spleen, we can hardly consider a patient cured if a recent tumor of the spleen seem to persist, even after the fever paroxysms have ceased; in fact, we may in these cases expect relapses and secondary anemia. The quartan type of fever usually leaves a chronic tumor, and, as a rule, slight and irregular paroxysms continue for a long time and seem to baffle all treatment. In many cases, however, old tumors of the spleen are found, where gradually the

swelling diminishes in size, the symptoms disappear, and the patient seems well. This is especially seen in those cases where the patient has been removed from the fever district.

In our local form of intermittent fever the paroxysms can usually be cut short by the exhibition of *quinin;* this treatment, however, does not absolutely cure the disease, because very frequently relapses occur, and a chronic tumor of the spleen often persists even after all fever manifestations have ceased. We cannot, therefore, declare the patient completely cured until at least six weeks have elapsed after the fever paroxysm, and the spleen has assumed its normal dimensions.

There is no regularity in the duration of this disease during its acute stage. There can be no doubt that it often heals spontaneously as soon as the patients are removed from the fever district. On the other hand, this may occur if they remain; very frequently, however, a change of location does not produce a cure, and the process becomes chronic. In such cases the tumor of the spleen continues to increase, and gradually symptoms of cachexia make their appearance. Even this stage of the disease is curable if the patient be treated correctly; of course, it is better if the patient be removed from surroundings where the disease is endemic; however, cures may occur in the district itself. In the majority of cases, especially in malarial countries proper, the cachexia increases in severity and ultimately leads to incurable invalidism and death.

Typical *cachexia* resulting from intermittent fever is characterized by a peculiar earthy or grayish-green color of the skin, great pallor of the visible mucous membranes, waxy looking ears, murmurs over the heart and blood-vessels, thrills over the jugular vein, emaciation, edema, ascites, swelling of the spleen and of the liver (at times ending in amyloid degeneration), dyspepsia, albuminuria, symptoms of the hemorrhagic diathesis or of scurvy, possibly chronic diarrhea, and great psychic depression; occasionally irregular febrile paroxysms or a hectic type of fever are developed. Those cases that have not progressed too far and do not show symptoms of permanent injury of the mucous membrane of the colon, as shown by chronic diarrheas, are curable. Usually, however, the patients die with symptoms of general hydrops and anemia, or of pneumonia, pleurisy, follicular ulcerations of the intestine, dysentery, or Bright's disease.

Pathologic Anatomy.—The changes in the spleen consist, in the beginning, of simple hyperemia, notably congestion of the venous vessels. These *hyperemias,* which produce considerable swelling of the spleen during the attacks of fever, but are also found during the feverless periods, ultimately lead to permanent enlargement of the organ. The spleen is seen to be enlarged three or four fold, congested with blood, grayish to violet black in color, usually very soft, fragile, and mushy; later on *pigment* formation is observed throughout the spleen, caused by changes in the extravasated blood. This pigment is yellow at first, later becomes brownish red or black, and colors the whole spleen slate gray or almost black; or if it be present only in small quantities,

simply causes a slight darkening. The tissues of the spleen proper, even if they be filled with pigment, may otherwise be normal or simply hypertrophied, showing very little degeneration even after a long siege of intermittent fever. The pigment assumes the shape of granules and is seen either free in the vessel walls or enclosed in cells. In many cases, however, gradual hardening of the spleen occurs, with a steady increase in its circumference, so that the organ often assumes enormous dimensions and may weigh from 3 to 6 kg.; it is then solid, of the consistence of meat or liver, brownish red, smooth on its cut surface, and containing very little blood; here and there in spots its color may become lighter than the rest and its texture less moist. If these changes have not advanced far the spleen may frequently resume its normal dimensions again. However, after great enlargement and hardening of the organ has occurred, such a retrogressive change rarely occurs, and if it does, exceedingly slowly. The changes in the structure of the spleen, combined, as they frequently are, with chronic degeneration of the lymphatic glands, the liver, and the kidneys, cause deficient blood-formation, hydrops, cachexia, ultimately leading to death. In the course of very prolonged intermittent fever amyloid degeneration of the spleen is seen, in addition to degeneration of the liver, the kidneys, and the lymphatic glands. Following a simple hypertrophy of long duration, the spleen ultimately becomes more like the liver, hard, tough, and assumes a brownish-red color; its cut surface becomes smooth and shiny, its consistence waxy, its color a brownish red, its texture homogeneous; or we may find numerous grayish-white gelatinous bodies of the size of a lentil embedded in the brownish, smooth stroma, giving the cut surface a peculiar granular, roe-like appearance.

The *capsule* of the spleen is often inflamed and covered with cloudy areas, scars, or adhesions. *Focal lesions* assuming the shape of wedges are seen in this disease, just as in recurrent fever, and occasionally in typhoid, typhus, and cholera. These wedges are clearly distinguishable from the surrounding tissues of the spleen by their grayish-yellow color. Their base is directed toward the capsule, and their apex toward the center of the spleen. They are not due to embolism, and we know very little of their pathogenesis. In very severe cases they are found to be necrotic, so that abscesses and cavities filled with detritus are seen, containing sequestra of necrotic tissue. The capillaries near these areas are completely occluded by pigment, and the blood of the spleen also contains large masses of coloring-matter. If these wedges reach as far as the capsule a circumscribed area of perisplenitis will be found at the places of contact. Occasionally the necrotic areas will extend for a varying distance underneath the capsule. If we find perisplenitis, we can usually assume, even during life, that such localized necrosis has occurred within the spleen.

Billroth has devoted especial attention to the study of pigment in the spleen of intermittent fever. He considers the black pigment so characteristic for this disease that, if it be found in the spleen, we are usually justified in assuming that the patient at one time or another was a

sufferer from intermittent fever. In all other diseases of the spleen the pigment is always yellowish red or brownish red; the blackish pigment consists exclusively of grains and granules that are either gathered together in irregularly shaped conglomerates or are enclosed in cells or flakes of tissue. Within the spleen they are distributed so that they occupy the follicles, or are situated near the trabeculæ of the organ. In other cases pigment is present in such masses that the specimen looks grayish black to the naked eye; occasionally no pigment is found in the follicles, but occupies the sheaths of the arteries; in still other cases Billroth found the whole tissue of the spleen filled with pigment to such a degree that even with the lowest power or with an ordinary magnifying glass the openings and channels of the venous sinuses could be clearly seen. The trabeculæ and the intervascular reticulum in the spleen of intermittent fever are usually somewhat thickened and compact. The follicles of the spleen are usually well developed and almost normal in structure.

In regard to the *melanemic pigment* found in the spleen of intermittent fever, Arnstein and Kelsch have made careful investigation and have arrived at the conclusion that in melanemia the pigment found in the blood owes its origin to a destruction of red blood-corpuscles by the poison of malaria. This is the old view and the one that was generally accepted until Laveran, Marchiafava and Celli, Golgi, and others published their investigations and demonstrated that malarial infection is caused by certain specific micro-organisms penetrating the red blood-corpuscles and there causing the formation of pigment granules from the hemoglobin. There can be no doubt that melanemic pigment is formed from hemoglobin.

As we have seen, the chief difference between splenic tumors caused by malarial infection and those caused by other agencies is the presence of more or less black pigment in the former class. This coloring-matter is found within the vessels, in the vessel walls, and in the pulp cells. Its origin is known, and, contrary to what was formerly assumed, it is not formed within the spleen, but is deposited there from the blood. We might possibly think that the changes seen in the spleen during intermittent fever are caused by the deposit of such large quantities of pigment; however, the histologic changes observed are too considerable to warrant such an assumption. It is probable, therefore, that in malaria the organisms themselves are responsible for the pathologic processes seen in tumors of the spleen in that disease. This theory is the most probable one, for recent investigations on the natural history of these plasmodia (see below) have taught us that they disappear from the blood of infected subjects immediately before an attack, and that the parasites, especially those in process of division, are found in greater numbers in the blood of the spleen than, for instance, in the blood of the fingers; this seems to demonstrate that certain organs, particularly the spleen, are breeding-places for the malarial parasites in the body. According to P. Baumgarten, the bone marrow has the same function in this respect as the spleen, so that we find analogous changes in this tissue.

Within the spleen plasmodia are found in all known modifications. This has been shown by Councilman, of Baltimore. In the interior of the spleen the plasmodia are arrested and undergo retrogressive changes. The writer will have to recur later to these interesting and valuable experiments performed with blood removed directly from the splenic vein of living subjects.

Plasmodia of Malaria.—Different *micro-organisms* have for a long time been considered as the cause of malaria. The first reports that created general interest were those of Salisbury, who claimed that certain microscopic algæ belonging to the palmellæ were the miasms of intermittent fever; later, Klebs and Tomasi-Crudeli proclaimed a bacillus of malaria, announcing this organism to be the cause of the disease, without, however, adducing credible evidence in support of their statement. The honor of having discovered the true parasite belongs to Laveran and Richard, and to two Italian investigators, Marchiafava and Celli. Their findings have been corroborated so many times by German investigators in our domestic form of intermittent fever, and by the brilliant work of Golgi, that no doubt can exist as to their correctness. Golgi further showed correctly that these organisms have a paramount etiologic significance in the causation of the disease.

These genuine organisms of malaria, the so-called *plasmodia*, belong neither to the bacteria nor to the fungi, but to the lowest form of animal creation—*i. e.*, the protozoa. Investigations by Metschnikoff, Celli, and Guarnieri have made it very probable that the malarial plasmodia are genuine protozoa and belong to the class called sporozoa. The writer will base his further description of the plasmodia, and of the changes they can produce in the blood, on the excellent description of Baumgarten. According to this author, the germ of malaria enters the living human organism in a manner so far unknown, and selects exclusively the blood, and particularly the erythrocytes, for its habitat and for its place of development. The endoglobular parasite develops gradually from a very small primordial form, deriving its nourishment exclusively from the substance of its host and destroying the blood-corpuscles in this manner. Within the bodies of the hemoplasmodia small remnants of hemoglobin are occasionally found in the shape of small black granules, the so-called typical malarial melanin. This pigment contains no iron—that is, it does not contain iron in any form demonstrable by the usual chemic reactions for this element (E. Neumann). As soon as the plasmodia have devoured the red blood-corpuscles they appear in the plasma as free adult plasmodia. Former investigators have designated these organisms as leukocytes containing melanin. The pigment, which in the beginning was situated near the periphery of the malarial germ, gradually distributes itself more regularly all through the body of the parasite, and, as soon as the plasmodium is free, seems to concentrate itself near the middle. In this manner star-shaped pigment figures are created that, later on, show centrally located conglomerations of coloring-matter. As soon as the pigment begins to recede from the peripheral parts, the proc-

ess of segmentation becomes visible, consisting either in the separation of regular pear-shaped or spheric structures grouped in a radial arrangement, or in a wreath of peculiar roundish bodies. These products of division contain no pigment and gradually separate from the pigmented center of the parasite, and enter the blood-current; shortly before a new paroxysm they disappear from the greater circulation and become lodged for a time in different organs, especially the spleen, the liver, and the bone marrow. The pigmented remnants suffer the same fate and are also deposited in these organs, where they are taken up by the leukocytes. In the beginning of a new attack of fever and during its course, for a day or two the plasmodia return into the blood-current, again attack new red blood-corpuscles, and perform the same evolution as described above.

In the fresh blood we can frequently see the plasmodia exercising certain ameboid movements within the erythrocytes. The plasmodia that are floating free in the plasma occasionally have one or more long flagella, and in fresh preparations these can be seen to perform violent whip-like motions; if they are separated from the body of the plasmodium they shoot backward and forward with great rapidity. Laveran and Richard have designated those forms of malarial parasites having flagella as the genuine and essential species; in reality, however, they are rare forms representing those plasmodia that have developed within the erythrocytes. Golgi has demonstrated that a connection exists between the development of the malarial parasite in the blood of the patient and the sequence of paroxysms. He has also shown that in quartan fever the development of the plasmodia, as described above, occupies exactly three days from the time that the red blood-corpuscles are invaded until the matured plasmodium is completely subdivided and the daughter elements have again invaded the blood-corpuscles. This period corresponds exactly to the interval between two attacks of the regular quartan type; in tertian fever, on the other hand, this development occupies only two days. According to Golgi, this difference in the time of the developmental cycle is not an accidental difference in the mode of development of the same parasite, but is dependent on a difference in the species of the plasmodia which produce quartan fever on the one hand and tertian fever on the other. Both kinds of malarial parasites show distinct differences, both in regard to their biologic properties and to their morphology. In regard to the former differences, endoglobular plasmodia of tertian fever show much more violent ameboid movements than those of quartan fever; they also destroy the hemoglobin much more rapidly and much more completely, so that in tertian fever the erythrocytes become completely discolored, while the endoglobular parasite is still relatively small. In quartan fever, however, even after the plasmodium has reached its maximum size and occupies nearly the whole corpuscle, a fine rim of characteristically pigmented tissue remains. Finally the endoglobular plasmodium of quartan fever causes contraction of red blood-corpuscles, whereas that of tertian fever causes swelling. In regard to their morphologic characteristics, the parasite of

tertian fever has a much more delicate protoplasm and less clear and distinct outlines than that of quartan fever, besides the former contains pigment granules that are much smaller than the latter. Above all, fundamental differences exist between the two species in regard to their mode of division: thus, the plasmodium of quartan fever divides into from 6 to 12 daughter cells, whereas the germ of tertian fever divides into from 15 to 20 subdivisions.

Golgi further showed that in those cases belonging to neither of these two types of fever, still other species of plasmodia are seen; such types of fever are the quotidian, the double quartan, and the irregular type. In still another type of irregular fever a peculiar form of parasite is the probable cause; this plasmodium is characterized by the appearance of so-called crescent bodies. Golgi shows that these shapes represent stages in the development of a particular kind of malarial organism; he never found them in connection with the typical tertian and quartan fever parasites. "The crescents are found in very severe cases that are characterized by a very irregular fever. They are usually seen floating free in the plasma, and are further characterized by their great resisting powers against quinin, in contradistinction to the ameboid endoglobular form of plasmodia that rapidly disappears from the blood after exhibition of this drug."

In a paper read in 1887 before the Pathologic Society of Philadelphia, Councilman communicated his personal observations made on the abundant material in Baltimore. His investigations included all types of malaria, even the pernicious forms. He divided all forms of malarial parasites that he had found into ten groups, which the writer cannot enumerate here, but shall mention later on in the description of the disease. The writer only wishes to cite a few details in this place that were gleaned from a study of preparations made directly from the blood of the spleen. In this one case Councilman found a form (No. 10) that had the general appearance of the crescents, but showed an extraordinary, rapid, wave-like movement of its peripheral portion. He describes the crescents under No. 6 as follows: "These bodies can be readily distinguished from other forms of the organism by their shape, and particularly by their great refraction. They can readily be seen even with a relatively low power. They are crescent shaped in outline, have an average length of about one-and-a-quarter times the diameter of a red blood-corpuscle, and a width of about one-quarter of this dimension. Their ends are usually round, but may be pointed; the protoplasm is not granular, and the organism looks almost as shiny and translucent as a bacterial spore. They are pigmented, and the coloring-matter is nearly always found in the center in the shape of little rods; in some instances, however, the pigment was not present in the center, but extended in fine lines all through the body of the organism. A peculiar phenomenon seen in these bodies is a delicate line extending through their concave surface; it never runs from end to end, but in a certain direction over the center, and it is as clearly outlined and as refractive as the edge of the crescent itself. This

shape of parasite is never found within the white or the red blood-corpuscles." According to Councilman, they represent a much more resistant form of the parasite than the rest. This is made probable by their great resistance to quinin, which they are able to resist even when given in large doses or continued during a long time. One of his patients whose blood contained crescents in great numbers, and who had a typical cachexia, received 3 gm. daily for seven days, and for two days the dose was even increased to 4 gm. Nothwithstanding all this they persisted in undiminished numbers; in most of the cases their number gradually decreased, and in still others they disappeared completely, apparently, however, independently of any treatment.

In order to elicit more information in regard to the inter-relationship of these different forms, Councilman studied blood taken directly from the spleen; the spleen was selected because this organ seemed to be the one most affected by the poison of malaria. With a Pravaz syringe the blood, under aseptic precautions, was aspirated directly from the spleen; 25 cases were examined in this manner, and in 21 he was successful in procuring blood from the spleen. In 4 cases where he was unsuccessful the spleen could not be reached, or the syringe was defective. The first finding was that all of the forms of the parasites were found more abundantly in the blood of the spleen than in the blood of the finger; this applies particularly to the segmented forms that are found during the period of the chill. The most interesting discovery, however, was that the spleen seems to be the chief place of predilection for the flagellate forms. Of the cases examined, 9 were cases of intermittent fever and 12 of malarial cachexia; in 6 of the 9 cases of intermittent fever were found the flagellated bodies, and likewise in 10 of the 12 cases of cachexia. It was not found that the parasites occurred more frequently during the chill than in the intermediary period. In 1 case that was examined during a chill a free flagellum was found in the blood of the finger, but a careful analysis of the slide revealed no flagellated plasmodia. The blood of the spleen was then examined and flagellated bodies found in great numbers. As a result of these examinations Councilman attributes a much more important rôle to the flagellated bodies than do other investigators. In conclusion, he arrives at the important decision that there can be no doubt that all forms of malaria are particularized by some characteristic organism always demonstrable in the blood.

The writer quotes a paragraph from the publication of Albert Plehn, entitled, *Beiträge zur Kenntnis von Verlauf und Behandlung der tropischen Malaria in Kamerun*, 1896, in which the author assumes a position different from that of Councilman in regard to the significance of these crescent bodies: "The so-called crescent shapes of the malarial parasites that have been designated as the cause of chronic malaria are only occasionally found in the fever of Kamerun. Sometimes no such organism would be found for months, although blood-examinations were regularly made. I am of the opinion that they are probably an

inactive form of the malarial parasite, and I have found this structure in the blood for days, even weeks, after the paroxysms had ceased, and while the patient was complaining of no subjective symptoms. I never administered quinin in these cases, and possibly by chance these patients seemed to remain free from relapses. Here and there I have found crescent plasmodia within the body of leukocytes, and this finding probably points the way in which the organism gets rid of these parasites." We see, therefore, that in this respect this investigator differs with Councilman.

In cases of grave malaria the brain is frequently affected, the disturbances in the function of this organ manifesting themselves in pronounced coma. This symptom is very conspicuous in the picture of pernicious intermittent fever, so much so that those cases in which coma occurs have been called febris intermittans continua, and offer a very bad prognosis. Before the microscopic examination of the brain in typical cases of this comatose form of fever demonstrated that malarial pigment is never present in the capillaries of the brain, this coma was usually attributed either to the effect of the high temperatures or, above all, to the occlusion of brain capillaries with pigment. This was called melanemia and was considered a sequel of pernicious malaria. Since the discovery of ptomains and toxins many authors have attempted to prove that the coma in malaria is due to the action of specific malarial toxins elaborated by the microbes of malaria. This theory seemed particularly probable, as a great many products of microbic life capable of exercising a deleterious action on the central nervous system have been isolated. However, Marchiafava and Celli demonstrated that in febris comatosa the capillaries of the brain are constantly filled with young endoglobular forms of plasmodium, so that we need no longer assume some hypothetic malarial toxin to explain the coma. The presence of these parasites in enormous numbers in the blood-vessels of the brain constitutes a mechanical impediment to the circulation of the blood, and uses up or destroys a large quantity of the oxyhemoglobin of the red blood-corpuscles. In this way the oxidation processes within the brain are reduced, and, as a result, its function, in the absence of the stimulus normally exercised by a sufficient quantity of oxygen, produces symptoms of torpor of the brain or of "coma." Marchiafava's and Celli's investigations teach us, besides, that the presence of melanin in the arteries of the brain, which, as we have said, was formerly considered the chief cause of malarial coma, has nothing whatever to do with the disturbances in the function of the brain. They draw this conclusion from their observation of certain rare cases in which the formation of melanin from degenerated erythrocytes did not take place at all, so that the endoglobular plasmodia found in the vessels of the brain contain no pigment whatsoever. In these cases coma of the same intensity occurred as in other cases where the plasmodia were filled with pigment.

Treatment.—The treatment of the tumor of the spleen in intermittent fever and malaria coincides with the treatment of the disease,

so that we must give our attention chiefly to the measures at our disposal for treating intermittent fever and malaria; above all, a change of location and life in a healthy region free from fever are indicated; the higher and dryer the location the better. It is absolutely essential that the patient be removed from a district impregnated with the miasm of intermittent fever, and very frequently such a change will alone produce a cure. Of drugs, quinin and its derivatives, notably the hydrochlorate, occupy first place; it is necessary, however, to be persistent in the administration of this remedy, and to continue it until the enlargement of the spleen has completely subsided. Only in the case of very large tumors of the spleen with advanced cachexia is this medication useless. A combination of quinin with iron preparations is often useful if anemia persist and the digestive organs are unimpaired. In other cases, where quinin alone does not seem to be effectual, a combination with arsenic in increasing doses frequently leads to the goal. The objections that have been raised from time to time against the use of quinin are refuted by experience; only in those cases in which the exhibition of this drug fails to yield beneficial results, or where an insurmountable idiosyncrasy exists, is iron or its iodid indicated; these frequently do much good. The same drug is also useful if chlorosis exist, if the glands be swollen, or if complaint be made of anomalies of menstruation.

A valuable adjuvant to the treatment are baths, such as iron, alkaline or iodin waters, and mud baths (Carlsbad, Kissingen, Marienbad, Homburg, Franzensbad, Pyrmont, Kreuznach). Massage, douches, and electricity are also recommended, but their value, in the writer's opinion, is rather doubtful.

The experience of our German physicians in the German Protectorates in Africa gives us some information in regard to the treatment of the very grave cases of pernicious malaria and of blackwater fever, the most dreaded complication of malaria. The writer quotes from the reports of R. A. Plehn: "Whereas the physicians on the west coast of Africa treat the last-named disease with very carefully guarded doses of quinin, we in East Africa continue the use of 8 to 10 gm. per diem, and afterward, for weeks, of 5 to 6 gm. This therapy is the one originally recommended by Steudel.

"In Kamerun a difference is usually seen between the course of a first attack and of relapses. The former are frequently continuous or remittent types, and may drag along for many days if the specific remedy be not administered in sufficiently large doses. It seems that this first attack is particularly resistant against the action of quinin, and it is frequently necessary to give from 1½ to 2 gm. at each dose for several days before we succeed in bringing the temperature down to normal. Larger doses more frequently repeated do not lead to better results; on the contrary, they seem to increase the subjective symptoms and augment the danger of collapse.

"In continuous fever with high temperatures the cold bath seems to exercise a particularly good effect. On the other hand, sweat baths seem to act beneficially in remitting fever at the time of remission,

particularly if perspiration at this time be not as active as could be desired. Antipyrin and phenacetin are the drugs that seem to relieve violent headaches and pains in the limbs quicker than anything else. If vomiting cannot be controlled, hypodermic injections of morphia, of at least 0.02 gm., are indicated and help to relieve the distressing unrest and the dyspnea complained of so bitterly in the beginning of the attacks.

"The only true remedy, however, is quinin. In West Africa it is considered a very precarious procedure to administer this drug during or immediately before the attack of fever; one always waits until after the attack of fever, particularly in the case of intermittent. It must also be considered that the patient who takes quinin as soon as he feels the approach of the fever paroxysm seems to prevent the second attack, which always occurs in the fever typical for this neighborhood."

Plehn particularly warns against the expectant plan and condemns waiting for the fever to decline before giving quinin, because if this plan be carried out, it is frequently too late to derive any benefit. Under all circumstances Plehn gives from 1½ to 2 gm. of quinin when a continuous fever of high degree (39° to 40° C.) has lasted for forty-eight hours. In order to aid absorption in these grave cases he administers quinin subcutaneously; at the expiration of twenty-four hours he administers a second dose, and after another interval of the same length possibly a third dose of equal size, always subcutaneously. In rare instances the temperature fell by crisis and remained normal; more generally, however, the continuous type of fever was converted into an intermittent one, and several doses of quinin were required to produce a lasting cessation of the fever. The plasmodia that are seen in the peripheral blood in all stages in the beginning of this disease frequently disappear from the circulation some time before the temperature is reduced to normal.

There can be no doubt that such obstinate cases seem to call for very large doses of quinin; we must bear in mind, however, that such large doses may produce failure of the heart in a very sick patient, but we can employ a fractional method of sterilizing the body with moderate daily repeated doses of quinin instead of administering such very large doses at one time.

If, as usual, we are dealing with an intermittent type of fever, or possibly with the less frequent remittent type, the best plan is to administer quinin in a dose of 1 to 1½ gm. at the time when the temperature is beginning to drop. At this time two generations of parasites in two different phases of development are found side by side in the blood of malarial patients in Kamerun. The younger of these generations assumes the form of very small endoglobular ringlets, about one-twenty-fifth to one-fifteenth as large as a red blood-corpuscle; this is destroyed by the quinin, disappearing within a very few hours after the drug has begun to act. The second generation has usually passed into the second half of its development, or even beyond, depending on the proximity of the second attack. These plasmodia are about one-fourth as large as the erythrocytes and usually contain pigment; sometimes pigment

is absent. Their growth and sporulation are not arrested at this period by doses of quinin of 3 gm. and above; the usual dose of quinin of 1½ gm. retards the final development for a few hours only. Usually the second attack of fever is just as severe as the first, so that it is completely useless to bother the patient with additional doses of quinin during the time of comparative ease which he enjoys after the first attack. The second attack will come, anyhow; but if at the end of this second attack we administer a dose of quinin of from 1 to 1½ gm., then the young plasmodia that have developed from the second generation of spores are also killed, and the patient remains free from fever without further dosing with quinin. Occasionally, even after very severe attacks, the patient is up and about on the fourth and the fifth day—until the next relapse.

Examination of Fresh Malarial Blood According to F. Plehn.—Malarial blood is best examined, according to F. Plehn, by embedding the blood in liquid paraffin. A flat ring of varnish is painted on an ordinary slide about the size of the usual cover-slip; then a drop of liquid paraffin is placed upon the slip, and a second drop in the middle of the ring on the slide. The drop of blood to be examined is rapidly placed upon the drop of paraffin on the cover-slip, and spread in a narrow layer between the two drops by placing the slip upon the ring of varnish. The examination of the living parasite is carried on in the warm stage, at body temperature.

Alcohol is the best agent for fixing the preparation if it is to be stained later. In emergencies, heating over the flame is sufficient. The following solution is commendable for staining the blood-corpuscles and the malarial parasites:

Concentrated solution of methylene-blue	60
½ per cent. eosin solution in 75 per cent. alcohol	20
Distilled water	40

Add 12 drops of 20 per cent. potassium hydrate solution.

The specimens are placed in alcohol for from three to five minutes, and from there transferred directly into the eosin-methylene-blue solution, where they remain for from five to six minutes. The examination of the fresh blood on the warm stage should go hand in hand with the study of the stained specimen. The microscopic findings will vary with the kind of malaria; the domestic tertian type presents the simplest picture. If we examine unstained blood taken some two or three hours after the reduction of the temperature, a large number of very small, slightly refractive, pale bodies are seen rapidly moving about in the plasma. They have no very distinct outline, and the blood-corpuscles near them seem to be moving up and down in a seesaw manner. If the microscope be carefully adjusted and a suitable blind employed, minute dark dots, a little coarser than those of the blood-plasma, may be seen dancing around in a very lively manner within the organism; they seem to be connected with the body of the parasite by very fine refractive threads. The less motile the large bodies are, the better these threads can be recognized in the specimen.

An analysis of the stained plasma will readily explain the significance of this finding. It will be seen that these threads are stained blue like the malaria parasites, and are very delicate flagella about three to six times as long as they are broad; they are divided by from 2 to 5 very dark knotty swellings that in the living blood seem to be little granules running around the parasites; as many as 3 flagella are seen in each parasite. The plasmodium may be endoglobular or ectoglobular; the endoglobular are stained intensely blue, particularly along their peripheries, and assume outlines that resemble a seal ring. The parasite is usually situated somewhat eccentrically within the broad, pink-colored, red blood-corpuscle. It is difficult to recognize the flagella in this species. F. Plehn [1] describes the metamorphosis of the malarial plasmodia in tertian fever up to the morning of the first afebrile day and beyond, as follows: "The parasites have penetrated the blood-disks and have grown to be about half as large as a blood-corpuscle. Their bodies are studded with numerous scintillating, dark brown-red, refractive granules and rods that move about within the plasma with great intensity; this motion is caused by the movements of the blood-plasma. The locomotion of the parasites themselves is not as active at this stage as it was before. Whereas in the living parasite a very small difference can be seen between the marginal zone and the interior, an examination of the stained specimen reveals a great difference in this respect, due to a greater affinity of the marginal zone to the stain. The pigment granules are in great part if not exclusively found in this marginal zone. In the course of the day and the following night the pigmentation of the parasite increases, and the blood-corpuscle in which the parasite is seen grows correspondingly paler, paralleling in this way exactly the development of pigment within the body of the parasite. Finally, nothing is visible of the corpuscle but a barely perceptible marginal zone surrounding the parasite. Now the plasmodium has matured and looks like a pale lump of protoplasm as large as a blood-corpuscle, moving lazily around in the field; within this organism two pretty sharply outlined lighter spots are seen that are also readily discernible in the stained specimen, and contain from 3 to 4 dark spots. The parasite remains in this state until germination, which in typical tertian fever occurs every forty-eight hours."

If the blood in malaria be examined before an attack, certain very characteristic changes may be seen. Side by side with a number of half-matured or completely matured parasites that, in their peculiar movements and the active twirling of the pigment granules and the whippings of the flagella, resemble a swarm of gnats are seen certain forms of parasites characterized by a peculiar refractive phenomenon which gives them the appearance of being coarsely granular. F. Plehn has interpreted this phenomenon as a process of division. If such a parasite be brought into the middle of the field (and it is practicable to raise the temperature of the warm stage to 40° or 41° C. (104° or 105.8° F.)), the following changes can be seen: After an hour and a

[1] *Aetiolog. u. klin. Malariastudien*, 1890, p. 17.

half or thereabouts the movements of these pigment granules become more active, and, parallel with this increase in the other movement, the differences in refraction seen within the protoplasm and the parasite become more apparent. The pigment granules undergo various changes in their location and are gradually forced toward the periphery of the organism, where they accumulate in little heaps. While this is in progress a series of light refractive bodies are observable in the interior of the parasite, which gradually assume a distinct outline. These little bodies are held together by a finely granular matrix (protoplasm) that is less refractive. Shortly thereafter the little heaps of pigment become separated, forming a garland of light oval bodies.

The protoplasm now becomes obscure and these oval bodies (spores) scatter in all directions, and are distributed all through the blood-plasma (Plehn). In the stained specimen these spores look oval or egg-shaped, with unstained interior and intensely stained poles; occasionally fine flagella can be demonstrated.

Grave atypical forms of malaria, particularly the tropic type, are characterized by parasites shaped like half-moons and spindles, or sometimes like seal rings. The first appear like oval or half-moon-shaped bodies that are more or less twisted, with partially thickened ends and a hyaline body. The peripheral zone has a double outline, and in the center is usually seen a large quantity of dark pigment granules; the poles have a greater affinity for stains than the central zone, so that the latter is always less and more irregularly stained. The parasites are usually found near the margin of the blood-corpuscles. The seal-ring forms are conspicuous by their small size. Plehn [1] has reported another important finding from Kamerun—that is, that in very grave forms of remitting or hemoglobinuric fever a colored specimen often will yield a negative result, so that it is necessary in these cases to examine the fresh specimen in order to find a motile unpigmented ameboid organism, thereby clinching the diagnosis.

The scientific investigations carried on during the last few years in the German colonies have thrown a great deal of light upon the pathologic anatomy of tumors of the spleen in malaria and blackwater fever (fièvre bilieuse hématurique). E. Steudel [2] has published a report of 3 autopsies of blackwater fever. In regard to the spleen, he says:

CASE I.—Subaltern of the Imperial troops, received at the hospital on the 30th of November. Patient has been living in Africa for a year and three-quarters; during the first weeks he was infected with fever in Daressalem; later several times again in Mikindani; twice the fever was accompanied by coma. Since the 26th of September stationed in Bagamoyo; on the 28th of November fell sick and became incapacitated for service; early on the 30th vomiting and a temperature of 40° C.; pulse small, rapid; sensorium not quite clear; no heart murmurs. December 1st, administration of quinin, drop of temperature, slight unconsciousness, yellowish tinge of the conjunctivæ; December 2d, temperature 37° to 38° C., evening 38.4° C.; December 3d, blood in the urine, morning temperature 37.2° C., evening temperature 38.6° C.; December 4th, liver and spleen decidedly enlarged, no blood in the urine; December 5th, liver dulness not increased, splenic dulness

[1] *Arbeiten aus dem kaiserlichen Gesündheitsamte*, xiii., 1, 1896.
[2] *Pernicious Anemia in Africa*, 1894.

percussible, 16 cm. long and 9 cm. wide; at noon sudden rise in temperature to 40° C. December 6th, second attack; in the afternoon vomiting of bile; evening temperature 39.5° C.; December 7th, no blood in the urine, pulse very rapid and small; temperature 37.6° to 39.8° C. December 8th, frequent vomiting during the night, collapse, death.

Autopsy was performed twenty hours after death; here and there marked changes of decomposition in some of the internal organs; all the organs, even the white thrombi of the heart, colored icteric. The heart was enlarged, with large cavities, flaccid walls, pale muscles, and a yellowish tinge; small hemorrhagic points at the edge and at the base of the aortic valves. The lungs contained little blood, but were filled with air. The left kidney small, little blood, yellowish pigment; the right kidney larger, containing more blood; no hemorrhagic or embolic foci. The spleen very large, 19 cm. long, 13½ cm. broad, and 7 cm. thick; capsule adherent to the diaphragm in one place, otherwise smooth; parenchyma moderately solid, colored dark red like venous blood. Connective-tissue stroma could not be recognized macroscopically; the liver was not very large, rather diminished in thickness, though enlarged in width from the right to the left margin; 28 cm. from side to side, 18 cm. from front to back, and 6 cm. thick; the surface of the liver smooth, the color pale yellow, the parenchyma containing little blood, the single acini clearly distinguished by their color and by the fact that they protruded slightly; the impression is created as if the cells of the parenchyma had disappeared and the vascular connective tissue had become prominent; stomach and intestines present no abnormalities.

Case II.—Officer of the Colonial troops; four years (with interruptions) in Africa. Has had two light attacks of malaria, twice pernicious malaria with bloody urine; the last illness started with an alcoholic excess. Duration of the severe attack (repeated hematuria frequent vomiting, and several times threatened collapse), fifteen days. Although the patient was fat, the spleen could easily be palpated during life; it extended as far as to the umbilicus. On autopsy the spleen was found to be enormous, 26 cm. long, 15 cm. broad, 6½ cm. thick, mushy in consistence, and dark blackish red. On section it is diffluent, so that it is difficult to procure a small piece for the purpose of hardening; the capsule adherent here and there with surrounding organs, otherwise smooth.

Case III.—Subaltern in the Colonial troop; a year and a quarter in German East Africa. From the 4th to the 10th of April, 1893, remittent form of malaria; later very anemic, and had repeated attacks of a mild form of fever. In the beginning of March the patient participated in an expedition to the coast region, where, on account of the rainy season, much water was on the surface and the whole ground was very moist; here he suffered from repeated attacks of malaria. On the 22d of April fever and violent pain again appeared in the region of both kidneys; since April 24th bloody urine, that during the last three days has assumed a dark coffee-brown color; since April 24th great loss of strength, yellowish coloring of the skin, persistent vomiting, especially after each attempt to take food. When received in the hospital on April 29th he was very much emaciated, the skin slightly icteric, the mucous membranes very pale; unrest, half-coma, and great apathy; enlargement of the spleen could not be demonstrated; the abdomen was retracted, nowhere sensitive on pressure, anemic murmurs in the region of the heart, the pulse pretty strong and regular. During the night the patient dropped into a deep sleep that toward morning assumed the character of coma; breathing very violent, almost spasmodic, 24 respirations to the minute; pulse became slow and weak; death. Section performed three and a half hours after death; spleen only very little enlarged, very resistant; the capsule tense, but strong and smooth without any thickening; length of the spleen 14 cm., width 9½ cm., thickness 4½ cm., weight 330 gm. On transverse section the follicles are readily seen in the shape of large light dots; the substance of the spleen is solid, and only very little fluid can be obtained by passing the knife over the cut surface.

[In an article on the spleen in malarial fever one is not called upon to go into the details of the life history of the malarial parasite, its structure, the methods of staining, or even into the minutiæ of the

symptomatology of the disease. For such particulars works on malaria are to be consulted. (*Cf.* the volume on Malaria, etc., in this series.) But in the last few years many new facts have been learned that change in a measure the point of view. A few of these are here mentioned.

In the first place, the *mosquito—i. e.*, certain species of the genus *Anopheles*—has been definitely proved to be the conveyer of the parasite to man. An infected human being is bitten by the mosquito, the parasite enters the body of the insect with the blood, and the sexual forms copulate and, as the result of impregnation, a brood of young parasites, sickle-like in shape, are formed and ultimately are stored in the mosquito in the venenosalivary glands, whence they enter the body of man when he is bitten again by the infected mosquito. Thus there is an *asexual cycle in man, a sexual cycle in the mosquito.* It seems now definitely settled that some of the large ectoglobular forms in man are sexual forms; also the crescents in the æstivo-autumnal fever are sexual. Impregnation occurs, however, only outside man's body. The flagella, so often referred to by Litten, correspond to spermatozoa; they appear outside of the human body—*e. g.*, in the body of the mosquito—and may leave the male parasite, the microgamete, and enter and fructify the female, or macrogamete.

This relation of the mosquito to malaria modifies entirely the *prophylactic treatment* of the disease. Quinin, as already emphasized, is the *sine qua non* for active treatment, and is to be recommended also for prophylaxis. But measures looking to the destruction of the mosquito are of more avail. Drainage of swamps, pools, and ditches, pouring of kerosene over the surface of the water to smother the larvæ, screening houses, protecting the body from the bites of the insect, staying indoors after dark when the mosquito is abroad, all these methods of prophylaxis bid fair to rob malaria of much of its horror and to redeem to civilization and cultivations certain tropic lands in Africa, Italy, South America, etc. In this connection one may read with profit the reports of the Italian Malarial Commission, or Celli's work on Malaria, that has been translated into English, or the reports from the German physicians in Africa—*e. g.*, the Plehns.

On page 525 reference is made to the fact that many of the inhabitants, native as well as foreign, in some malarial districts have enlarged spleens, though the ordinary manifestations of malaria may not be, or have not been, present. Koch and others have found that in some tropic localities at least even the native children, who seem free from the disease, have enlarged spleens, slight fever, and plasmodia in the blood. Later, because of this preceding mild form in childhood, they are practically immune.

Much confusion has existed, and to an extent still exists, as to how many species of parasites shall be recognized. In general the consensus of opinion seems to be that there are three distinct species, differing morphologically and in the effects they produce in man. These are the *tertian*, *quartan*, and the *estivo-autumnal parasites*, the latter the cause of the greater number of the severer so-called malignant and tropic

forms. The quotidian form of fever is believed to be due to infection with more than one group of parasites and not to some different, special variety.

The symptoms of malaria are to be explained by the actual destruction of red blood-corpuscles inducing anemia, by toxemia, and by the mechanical effects resulting from plasmodial blocking of vessels. Some of the wedge-shaped and necrotic areas in the spleen may be explained by the plugging of vessels in this way. In the same manner hemorrhage from the stomach or bowel, and cerebral symptoms may result from circulatory disturbance from plasmodial thrombi. If we conceive of malaria as a *plasmodial sepsis*, as it was termed by Mannaberg, we can quite readily understand the phenomena of the disease.

For the best ways of examining the blood for plasmodia, by stains, etc., reference must be made to special articles or to such books on the blood as those of Cabot, Ewing, or Da Costa. There is rarely any difficulty in detecting the tertian or quartan forms or the crescents of the æstivo-autumnal forms in fresh unstained specimens. In fact, in many respects this method is the best. The æstivo-autumnal parasite, however, is not so readily recognized in the unstained specimen, and is more apt to be absent from the peripheral blood than the other two varieties. Here repeated examinations of the blood or the use of some stain may be necessary.

One word more may not be out of place as to the value of blood-examinations in malaria. Where there is leukocytosis one should suspect that the disease is something other than malaria. Also malaria does not cause an increase in the polymorphonuclear leukocytes, and if this occurs in the course of malaria a complication is presumably present.—Ed.]

CHRONIC TUMOR OF THE SPLEEN.

We call *chronic tumors of the spleen* enlargements of the organ that persist for a long time or during the whole life of the patient, in contradistinction to acute tumors of the spleen that persist for a short time only. Sometimes these chronic forms develop from acute tumors; in other cases they are chronic from their incipiency. As the spleen is only rarely independently affected, it will depend on the nature of the primary disease, having swelling of the spleen as one of its symptoms, whether a chronic tumor of the spleen will gradually develop from an acute one or will be chronic in character from the beginning. In acute infectious diseases, *acute tumors* develop in the first place and may gradually become chronic; for instance, in typhoid fever, recurrent fever, and intermittent fever. Here the question is complicated, because we do not know exactly to what extent other pathologic processes—as, for instance, changes in the blood—play a predisposing rôle; all in all, the development of a chronic tumor of the spleen from an acute one is comparatively rare. In intermittent fever we find peculiar conditions, for here the spleen not only enlarges during the course of the single attacks and

relapses, but frequently becomes chronically indurated after the disease is cured, at least so far as the occurrence of fever paroxysms is concerned. Swelling of the spleen in intermittent fever may be found in regions where this fever is prevalent, but in individuals who have never had any visible signs of the disease, and, further, in certain regions, particularly the tropics, a great majority of inhabitants, both natives and immigrants, are afflicted with a chronic tumor of the spleen.

The occurrence of tumors of the spleen that are chronic from the first, on the contrary, is very frequent, and the causes for such enlargement of the organ are very manifold; congestion, chronic infectious diseases, and diseases of the blood are the most important. Among the diseases that seem to predispose to the formation of a tumor of the spleen that may be called chronic from its incipiency are the following: chronic infectious diseases, syphilis, leprosy, rickets, tuberculosis, and scrofulosis; the following diseases of the blood: leukemia, pseudoleukemia [splenic anemia], scurvy, melanemia; amyloid degeneration, and finally all diseases of the spleen caused by congestion or stasis, especially those forms following [or accompanying] cirrhosis of the liver.

In view of the great difference in the etiology and the varying anatomic changes observed, it is best to discuss the representative forms of chronic tumor of the spleen separately, particularly as they are also different clinically. We shall begin with the so-called congested spleen.

CONGESTED SPLEEN.

Etiology.—*Congested spleen* is found chiefly in disturbances of circulation, notably when they affect the *portal system;* chronic occlusion of the portal vein, cirrhosis of the liver, chronic diseases of the lungs, and lesions of the heart that cause stasis may produce it. The swelling is usually moderate and may be absent, especially in children and very old people, even though the disturbances in the circulation persist for a long time; this may be true also when there is thickening or calcification of the capsule.

In looking over these different causes, *portal stasis* seems to be the most conspicuous. The splenic vein pours its blood, as we know, into the portal vein, and is one of the main branches of this vessel. It is immaterial whether the portal vein itself is occluded or whether a large number or all of its branches within the liver are obstructed; consequently we find the same degree of stasis in the spleen during cirrhosis of the liver (where it is found in from 50 to 75 per cent. of all cases) as in chronic thrombosis of the portal vein. Syphilis of the liver can also produce this effect, because connective-tissue hyperplasia starts from Glisson's capsule and extends along the small branches of the portal vein, ultimately producing a narrowing of the lumen of the interstitial veins within the liver. In addition, a narrowing of the vessels occurs as a result of the syphilitic process involving the endothelium of the intima, so that in this manner the lumen of the small branches of the portal vein is still more reduced.

Direct compression of the portal vein by enlarged lymph glands, neoplasms, gummata, chronic peritonitis with the formation of fibrocartilaginous plates inclosing the whole portal vein, and finally the traction of contracting connective tissue near the porta hepatis, can all lead to almost complete impermeability of this vessel. In two cases the writer has been able to diagnose by palpation the presence of gummata as large as apples on the under surface of the liver during the life of the patient; to do this he had to raise the liver, so to say, in such a manner that its under surface was brought to the anterior abdominal walls. Such a gumma, of course, produced compression of the portal vein and swelling of the spleen. On autopsy this diagnosis was corroborated. In another case the relaxation of all the organs of the abdomen occurring immediately after aspiration of a very large ascites (26 liters) made the examination very easy.

As the portal vein empties its blood into the inferior vena cava, all causes that can produce compression of the latter vessel will lead to stasis in the portal system and to congestion within the spleen; neoplasms here are the most important, especially if they compress the main branch of the lower vena cava above or below the diaphragm. In one instance the writer saw an aortic aneurism compressing the lower vena cava above the diaphragm.

Dilatation of the right auricle can produce the same congestion in the lower vena cava, although more gradually and less intensely. Whenever the *vena cava* becomes overfilled the effect is felt in the portal vein and all its branches, including, of course, the splenic roots, so that congestion of the spleen is the result. Such processes are found chiefly in valvular diseases of the heart and degenerations of the heart muscle. In the first class of cases this effect is strongest if those valves near the right auricle are diseased, so that, for instance, congenital valvular lesions at the ostium venosum dextrum produce the greatest amount of stasis. Next in importance are the valves of the pulmonary orifice, those of the mitral orifice, and lastly those at the aortic orifice, so that we find stasis within the spleen and other organs (liver and kidneys) in valvular diseases that are either not yet compensated or in which compensation is beginning to fail. Frequently a congestive swelling of the spleen will disappear if compensation be re-established.

Diseases of the lungs, finally, may cause congestion of the spleen, especially those forms in which the circulation within the lungs is impeded, either through lesions situated within the lung—interstitial pneumonia, emphysema, etc.—or through mitral diseases in which the venous blood of the lungs cannot empty itself rapidly into the heart. In one case the writer found the pulmonary artery completely lined with living echinococcus cysts extending the length of the stem and into both branches; as a result, narrowing of its lumen, congestion of the right heart, and, secondarily, of the spleen, were found. During life the symptoms of a complicated mitral lesion were present. In all these cases the right ventricle necessarily becomes engorged, and therewith the right auricle, so that finally the vena cava and the portal system become

congested. Finally, the writer must mention those forms of congestion in which the splenic vein itself is involved; such cases are rare and are only found in thrombosis or in cases where tumors press upon the vein. Here a very intense degree of hyperemia may develop that is most violent if the pathologic process seem to occur suddenly. Occasionally in such cases extravasation may occur.

Pathologic Anatomy.—In hyperemia of the spleen as a result of stasis the organ is usually enlarged. Sometimes, however, the size of the spleen does not seem to be increased over its normal dimensions. A diminution in its size is very rare. The enlargement may fluctuate within wide boundaries, but it is the exception to find very large tumors. The margins of the hyperemic organ are usually rounded, the whole organ somewhat twisted, and its consistence somewhat increased, so that it feels exceedingly solid and hard. On transverse section the trabeculæ are usually quite distinct, the capsule thickened and sometimes wrinkled. The spleen is *indurated* by the hyperemia, and the chief pathologic change seen is an increase of the connective tissue involving, in the first place, the trabeculæ, then the vessel walls and their surroundings; the corpuscles of Malpighi are distinctly visible to the naked eye and hyperemic. In old cases of congested spleen a network of numerous thick, white fibers seems to ramify throughout the pulp; a careful inspection will show that this impression is created by the presence of thick white fibrous layers around the blood-vessels. It is a peculiar fact that the *color* of a chronic congested spleen is not as dark red as might be expected; on the contrary, it is often found to be very bright. A congested spleen is different in this respect from all other congested organs; as, for instance, the liver and the kidneys, which are always colored exceedingly dark red. We shall see later that this peculiarity of the spleen is due to an increase of muscular tissue occurring in the course of chronic congestion. If the hyperemia be very intense, *extravasations* are formed underneath the capsule and in the tissues proper, so that the cut surface presents a mottled appearance, owing to the presence of numerous punctiform hemorrhages and larger patches of discoloration, which may attain the size of a lentil but are rarely larger. Such small hemorrhages may appear repeatedly during the course of a fever, so that recent extravasations are frequently seen near the remnants of older hemorrhages, which are characterized by the presence of pigment in the tissues or in the cells (pigmented cells), or by cells that contain red blood-corpuscles.

R. Nikolaides has carefully studied the *pathologic histology* of congested spleen. The organs were hardened in alcohol and Müller's fluid.[1] In order to understand these changes we must briefly recur to the connection existing in the spleen between the trabeculæ of the vessel sheaths, on the one hand, and between the latter and the meshes of the pulp proper.

As we know, the capsule of the spleen that surrounds the organ like a sac is folded inward at the hilus, where the vessels and nerves enter the spleen, and

[1] *Virchow's Archiv*, vol. lxxxii.

follows the course of the vessels into the spleen, forming their sheath; more of the capsule surrounds the arteries than the veins. Another part of the covering of the capsule assumes the shape of the so-called system of trabeculæ; these trabeculæ run through the tissues of the spleen in all directions, are divided and subdivided, and in this way form a very complicated structure. Finally these trabeculæ become attached to the vessels, and ultimately merge into them, particularly the veins. The reticulum of the pulp finally forms the sheaths and adventitia of the vessels, and surrounds the cavernous veins with a network of ring-shaped, anastomosing fibers, thus forming the boundary between the blood and the pulp. Lastly, the reticulum of the pulp becomes attached to the trabeculæ.

In congested spleen all the parts described above are irritated by stasis and increased blood-pressure, so that enormous *thickening of the blood-vessels* and of the sheaths of the vessel walls occur. If cross-sections through a congested, hardened spleen are examined under the microscope, the vessels, principally the arteries, are seen to be thickened. The adventitia and the sheaths of the vessels that are in intimate connection with it are chiefly affected, so that these parts are converted into a broad connective-tissue zone which merges into the adjacent reticulum of the pulp. Occasionally, in cases of congested spleen, broad connective-tissue strands are seen to pass from the sheaths of the vessels into the pulp, and between the fibers of the latter tissue-cell débris is frequently seen. The trabeculæ are enormously thickened, so that they form large areas of thickened connective tissue around the vessel walls wherever they are in contact with the sheaths of the vessels. From the trabeculæ the connective-tissue strands also pass into the pulp.

This thickening of the trabeculæ, the vessel sheaths, and their adventitia is found more or less developed in all cases of congested spleen, and the hardness of the organ is in a large measure dependent on the degree of this thickening process; the slower the congestion of the spleen develops, the more pronounced will be these changes.

Aside from the changes observed in the trabeculæ and the sheaths of the vessels, certain abnormalities occur in the intima and muscularis of the blood-vessels. The former change gives the congested spleen its characteristic appearance. The latter occurs very early in the case of the arteries, and only affects the veins if the congestion be of long duration. The intima of the arteries is affected in a different manner than that of the veins, for the latter show only a slight superficial fatty degeneration; whereas in the former a proliferation of all the connective-tissue layers—that is, a true endarteritis—is seen. Virchow has observed similar changes in the intima of the veins of the lung following valvular lesions of the heart; occasionally the portal vein is similarly affected in congestion of the liver. The intima of the veins is only changed if a considerable increase of blood-pressure exercises its effect upon the walls of the veins for a long period of time. Nikolaides has seen the muscularis of the vessels, notably the circular fibers of the arteries, very much thickened, and this author is of the opinion that this is due to a strengthening and hypertrophy of the muscles of the vessel wall occurring whenever the disease is protracted, so that this change would

constitute a compensatory effect, inasmuch as it would help counteract the congestion. Most authors agree that in congested spleen hyperemia from congestion never reaches such a degree as in analogous lesions of the liver and kidneys, and attribute this peculiarity of the spleen to the existence of a certain contractability. It is due to this, they hold, that the spleen frequently appears bright red and that its musculature is hypertrophied, so that a comparison seems possible between the hypertrophy of the spleen and the compensatory hypertrophy of the heart muscles. Rindfleisch is the chief advocate of this view, and Nikolaides opposes it chiefly on the ground that he has never succeeded in finding muscular fibers in the trabeculæ of the human spleen, so that, of course, muscular hypertrophy could not occur.

From these facts we can draw the following *conclusions:*

The characteristic lesion of congested spleen is a thickening of the trabeculæ and of the vessel sheaths connected with them.

The intima of its vessels, chiefly its arteries, is indurated at an early stage of the disease. In the case of the veins this change occurs only after congestion has lasted for a long time and considerable pressure has been brought to bear upon the walls of these vessels.

Symptomatology and Diagnosis.—It is an easy matter clinically to diagnose a congested spleen whenever it is possible to feel the spleen as an *enlarged hard tumor* beneath the costal arch, and whenever the cause of the stasis can be found. Usually we are able to palpate the spleen when it is congested; in case the organ does not protrude below the costal margin, we can usually succeed in palpating it if we instruct the patient to take a deep breath. The consistence of the spleen is so characteristic in these cases, its lower margin so rounded and blunt, that we rarely have any difficulty in recognizing a chronic tumor. Pain is never present, not even on ordinary pressure. Occasionally, if the tumor assume very large dimensions, a feeling of weight and tugging may be complained of in the left hypochondriac region.

In making clinical examinations of this organ we frequently encounter a large number of chronic swellings of the spleen, the cause of which cannot be discovered despite the most careful anamnesis. The writer has noticed this fact for a great many years. Within the last five or six years he has been able to corroborate it in the examination of his large polyclinic material (5000 cases a year), every case of which was examined for the presence or absence of enlargement of the spleen. If we consider the spleen enlarged in those cases only where the organ can be felt by palpation, and do not include those tumors that are recognized by an enlargement of the splenic percussion dulness, we find that from 20 to 25 per cent. of all cases observed have a more or less developed tumor of the spleen, this altogether independent of the patient's age, present or past occupation, and former diseases. We were unable to find a cause for this relatively frequent occurrence of chronic tumors of the spleen, and in many cases we had to be satisfied with the explanation that the individuals had been sufferers from chronic *constipation* for many years. There can be no doubt that such conditions can lead to

chronic congestion in the veins of the spleen, and in this way produce stasis within its vessels. No explanation has so far been offered for the cases in which this history could not be elicited.

It is rarely difficult to discover the *cause of congestion*. We can assume that a local cause (compression, thrombosis) is acting on the splenic vein if we find no other symptoms excepting a large tumor of the spleen. In all other cases the tumor of the spleen is only an isolated, comparatively insignificant symptom among a large number of other clinically recognizable phenomena. Above all, such tumors are rarely found alone, but, as a rule, are accompanied by the general symptoms of stasis, nutmeg liver, induration of the kidneys, cyanosis of the skin and mucous membranes, possibly albuminuria, hydrops of the body cavities, and anasarca.

In considering different groups of lesions that can produce stasis in the spleen, we find that *portal stasis* again is the chief cause. It is manifested clinically and anatomically by congestion in all the roots of the portal vein. We find in these cases, aside from congested spleen, catarrh of the intestine, of the stomach, possibly with hemorrhages, ascites, dilatation of the external veins of the abdominal wall, so-called caput Medusæ, and, above all, enormous varicose enlargements of the veins situated in the lower third of the esophagus. These vessels may be so dilated that they rupture and occasionally cause sudden death; this formerly was always attributed to hematemesis. The writer has been able to demonstrate in a number of cases of diseases of the liver in which a narrowing of the lumen of the interstitial veins within the organ occurred (cirrhosis and syphilis) that the "hematemesis" ending so frequently in profuse and fatal hemorrhage is not a real hemorrhage of the stomach, but can always be attributed to a rupture of these esophageal veins. [Preble,[1] from a study of 60 recorded cases of fatal gastro-intestinal hemorrhage due to cirrhosis of the liver, found such hemorrhage to be an infrequent but yet not rare complication of cirrhosis. The first hemorrhage may be fatal, and may precede other subjective or objective phenomena of cirrhosis, so that a positive diagnosis at the time may be impossible. In 80 per cent. of the 60 cases esophageal varices were demonstrable. In only a small percentage of these cases showing esophageal varices was the cirrhosis typical—*i. e.*, showing ascites, enlarged spleen, and abdominal varices. In a few cases of fatal hemorrhage no esophageal varices were demonstrable, the hemorrhage apparently being due to simultaneous rupture of many capillaries of the gastro-intestinal mucous membrane.

It is well to refer here to the fact that the element of congestion is not regarded as explaining satisfactorily the splenic enlargement in all cases even of atrophic cirrhosis of the liver, to say nothing of the hypertrophic form (Hanot's cirrhosis), where portal stasis is of minor importance. The influence of chronic toxemia in some of these cases, the toxic substances acting directly on the spleen, cannot be entirely overlooked.—Ed.] Tumor of the spleen is not a constant

[1] *Am. Jour. Med. Sci.*, cxix.

occurrence in portal stasis, but is found in one-half to three-quarters of the cases.

In direct *compression of the lower vena cava* above and below the diaphragm, either by neoplasms or aneurism of the aorta, we again encounter a congested spleen, but only as one of many symptoms. The chief signs of this condition are again ascites, with dilatation of the superficial veins of the abdomen, and usually considerable edema of the lower extremities. This picture is distinguishable in many respects from the analogous symptom-complex observed in portal stasis, so that it is usually an easy matter to differentiate the two conditions. In the former the abdomen is distended and enlarged owing to the ascites, and the legs, too, are edematous and swollen; in portal stasis the abdomen is also distended, but the legs are very thin. This difference is exceedingly characteristic. Further, in portal stasis the anastomotic venous circulation is usually grouped around the navel, so that the veins radiate from the umbilicus toward the periphery, in this way producing the appearance of the caput Medusæ and the "circomphalos." In compression of the vena cava inferior the lateral veins of the abdomen are chiefly dilated, notably the inferior epigastric veins that anastomose with the superior veins of the same name and their lateral branches that extend from the inguinal region to the costal arch. The appearance of the dilated veins is characteristic in each case, and often enables us to distinguish the primary cause of the dilatation. In disturbances of the circulation in the inferior vena cava we usually see varicose veins in the lower extremity, which may be very pronounced. In portal stasis such varicosities are never seen. Additional symptoms of stasis in the cava system are generally cyanosis of the skin and mucous membranes (the lips, the conjunctivæ) and of the terminal phalanges of the hands and feet; also occasionally albuminuria. [It is well to keep these points in mind, and they will be found of great help in the differential diagnosis between obstruction in the portal vein and the inferior cava. Yet the distinction is sometimes hard to make at the bedside. And edema of the lower extremities may occur early in cirrhosis of the liver (edema præcox).—Ed.]

If *valvular lesions* are the cause of this stasis, analogous conditions to those found in the spleen are seen in the liver and the kidneys. During the period of disturbed compensation, edema, cyanosis, and albuminuria are rarely absent. The most severe degrees of stasis are found in valvular lesions of the right heart; these are usually congenital and accompanied by cyanosis of high degree. In this condition the drumstick swellings of the terminal phalanges of the hands and feet are characteristic. In disturbances of compensation following valvular lesions a congested spleen is very frequently found, but not always, however; if it be present, other symptoms of stasis are usually observed, principally edema of the lungs and hydrothorax, and altogether a general picture of an uncompensated valvular lesion. As soon as compensation has been re-established through rest and proper treatment, the tumor of the spleen disappears. The same applies to muscular insufficiency of

the heart. [Muscular insufficiency may be the result of the valvular lesions just referred to or of primary myocardial disease—*e. g.*, chronic fibrous myocarditis or of pericardial adhesions. In some cases of the latter condition—adhesive mediastinopericarditis, concretio cordis cum pericardio—the stasis in spleen, liver, etc., is extreme. This is notably true in the so-called pericarditic pseudocirrhosis of the liver (Pick's disease, multiple serositis).—Ed.] Congested spleen is found least frequently in aortic insufficiency. This lesion is the one that can exist for the longest time without producing serious symptoms. If in such a case an acute disease supervene—for instance, pneumonia—a well-marked pulse can often be felt in the spleen. The same applies to those *diseases of the lungs and pleura* that can cause congestion (chronic pneumonia, particularly the interstitial form, tuberculosis, emphysema, compression by pleuritic exudates, and contractions, atelectasis, etc.). In these cases stasis in the vena cava inferior will be produced with all those disturbances already enumerated—namely, congested liver, congested kidneys with albuminuria, congested spleen, hydrops, cyanosis, and possibly one-sided or unilateral hydrothorax.

Treatment.—The treatment of congested spleen is dependent on the treatment of the cause, so that our first indication is to find this cause and, if possible, remove it. Treatment of congested spleen, therefore, is identical with the treatment of almost all internal diseases. One or two points may be emphasized. If we have diagnosed a compression by neoplasm and suspect gummata, antisyphilitic treatment is indicated. If disturbances of circulation are found as a result of disturbed compensation in valvular diseases, digitalis [and rest] are indicated; in weakness of the heart, stimulants (musk, camphor, ether); in other cases, nerve sedatives (valerian, bromid of potassium). It is useless and unnecessary to treat the tumor itself, for the reason that it will certainly disappear if we succeed in removing or moderating the disturbances of circulation that cause it.

AMYLOID DEGENERATION OF THE SPLEEN.

History of Amyloid Spleen and its Chemistry.—Virchow was the first in Germany to study amyloid degeneration of the spleen. The writer quotes from his memorial oration on Johannes Müller, as follows: "In the year 1846, when I was prosector in the Charity Hospital, I frequently encountered a pathologic form of spleen that I later designated as sago spleen. I gave the explanation of this phenomenon a great deal of thought, and for a long time could not find out more than that granules consisting of homogeneous flakes had been formed in the place of the spleen follicles. This explanation, such as it was, was attacked by others, who did not consider that the follicles were affected. One day I took a spleen of this kind to Müller in order to elicit his opinion in regard to the follicular origin of these granules. He had devoted especial attention to the structure of the spleen, but did not recognize these changes. He was himself in doubt whether

they originated from the follicles, and said, 'This is a very peculiar thing, and you must examine it.' When I told him that I had already done this, but that I was not satisfied with the results of my investigations, he said, 'Then you must examine some more. I am sure you will find it interesting.'"

It was not until 1853 that Virchow succeeded in interpreting the significance of sago spleen. He first recognized in a "waxy" spleen the so-called corpora amylacea, that he designated at first as colloid, then as albuminate, and later as plant cellulose. Apparently in this sago spleen the *corpuscles of Malpighi* were the seat of all the important changes. Virchow,[1] in summing up the results of his first examinations, says, "The whole spleen increases in volume and solidity, and at the same time grows anemic. In the outer parts of the follicles a homogeneous, translucent, either colorless or grayish or yellowish zone is seen, that gradually increases in size, so that ultimately the whole content of the follicle is converted into a mass about as large as a pin-head or a grain of hemp. On cross-section this grain looks gelatinous, and it is prominent and somewhat larger than a follicle, so that the comparison of these grains with grains of sago floating around in soup is well chosen. Occasionally a white central portion is distinguishable within the gelatinous granule which represents the unchanged remnant of the contents of the follicles."

This pathologico-anatomic description of Virchow's is valid to-day. It is interesting to follow the course that he took in order to establish the character of amyloid degeneration of the spleen. He says, "At first I looked upon these grains as amyloid; later they seemed to me to be solid albuminate. I discovered that they grew pale on addition of acetic acid, and that they became granular when exposed to the action of potassium ferrocyanid; nitric acid, especially when hot, colored these bodies yellow, and when ammonia was added they changed to orange, and finally gave the reddish-blue color of the xanthoproteid salts. This led me to suspect either a fibrinous exudate or an albuminous degeneration. With it all, however, the exact interpretation of the process remained doubtful to me, and I could not bring it in connection with any of the other known forms of elementary degeneration. Recently I had an opportunity to examine a spleen of this kind, and while studying it carefully I was struck with the great resemblance of these sago-like granules to the corpuscula amylacea of the brain. It is true they do not have the concentric and striped arrangement of the latter, but they resemble them in their pale color and their dull, shiny, soft-looking structure. Usually they are round or angular bodies, homogeneous throughout, somewhat larger than the ordinary lymph bodies seen within the follicles, closely packed, pavement-like; yet the addition of nitric acid reveals the presence of unchanged nuclei between the different grains, which seem to form part of a fine reticulum. *On addition of a watery iodin solution a characteristic yellowish-red coloration appeared with great rapidity; I had never seen this before; and on addi-*

[1] *Archiv*, vol. vi., p. 269.

tion of sulphuric acid, further, a pronounced violet color appeared. This reaction occurred much more rapidly in these bodies than in the so-called ependymal granules, and if very much sulphuric acid were added a dark-brown color appeared in a short time; if little was used, the bluish or violet tint was very apparent."

Meckel v. Hemsbach [1] attempted to prove, in opposition to Virchow, that the blue coloration given by the pathologic tissue of amyloid spleen on addition of iodin or of iodin and sulphuric acid was attributable to the presence of cholesterin; he showed further that in an amyloid spleen cholesterin was found in considerable quantities. Virchow, however, refuted Meckel by demonstrating that a marked difference existed between the staining reactions of amyloid substance and of cholesterin if both substances be treated in the same manner.

Virchow's opinion that animal amyloid is similar to vegetable carbohydrate was verified in 1859 by Friedreich and Kekule,[2] who demonstrated by their analysis that amyloid contained nitrogen. According to these investigators the amyloid substance of the spleen gives the following reactions: Water, either hot or cold, does not change the substance, but extracts traces of an albuminous substance. Alcohol and ether produce no changes; the extract with these two solvents showed the same color test with iodin and sulphuric acid. If small pieces of amyloid spleen are boiled for some time with very dilute sulphuric acid they are dissolved to a clear fluid in which a few ramified structures, remnants of blood-vessels and lymph vessels, are seen floating. From these structures all the amyloid substance has been extracted. A clear solution of amyloid substance reduces alkaline copper solutions (it contains no sugar), but if the reaction be made after Trommer's method they give a violet-colored tint (similar to solutions of proteid). In dilute alkaline solutions the substance swells up, becomes translucent, and finally dissolves on prolonged boiling. In this procedure a few of the branched structures mentioned above remain undissolved. On addition of acids this alkaline solution gives a white flaky precipitate, acting similarly to a solution of albuminous material.

Friedreich and Kekulé have determined the *chemical composition of amyloid of the spleen.* They proceeded as follows: The waxy parts of the amyloid spleen were carefully excised, divided into fine pieces, and repeatedly macerated and extracted with cold water in order to remove the soluble albumin. They were then successively extracted with hot water, dilute and absolute alcohol, and finally repeatedly with ether. As these solvents had extracted comparatively little, all the extracts were united and evaporated to dryness in a water-bath, and this residue then extracted with ether. The part that remained consisted almost exclusively of proteid material, but also contained considerable quantities of salt, and, as it seemed, some leucin. On slow evaporation of the ethereal solution cholesterin remained in the shape of well-formed crystals, and in so considerable a quantity that it could be recrystallized white and pure. Besides cholesterin, small oily drops of a fatty sub-

[1] *Alte Charité-Ann.*, iv., 2, 1852. [2] *Virchow's Archiv*, vol. xvi., p. 50.

stance were found in the ethereal solution, some of which crystallized into fine needles on cooling (the origin of this fat was probably the connective-tissue corpuscles of the amyloid trabeculæ that had undergone fatty degeneration). The chief portion of the white waxy part of the spleen used in this experiment remained after all these extractions; after the evaporation of the ether it presented the appearance of almost snow-white bodies and lumps, that, examined under the microscope, seemed to consist almost exclusively of shapeless glassy flakes. Only very few remnants of larger vessels were seen within the mass.

This substance gave the same reactions as did the spleen originally when brought in contact with iodin and sulphuric acid. In the case of the smaller granules, however, the blue color disappeared much quicker than in the larger flakes, changing from blue to green and then paling off to yellow. The vessels mixed with the mass did not give the amyloid reaction and were colored reddish yellow. It was impossible to separate the shapeless flakes from the vessel remnants, because they reacted almost equally to all chemical agents, but mechanically it was possible to separate them in part. The extracted portions of the spleen were macerated with ether, and by decantation a large part of the shapeless flakes could be procured containing almost no vessel remnants. In this form the amyloid part is a white, mealy powder, in which only very scanty remnants of vessels could be discovered, even under the microscope. As this amorphous substance could not be purified any further, and as the blue-color reaction of the amyloid spleen seemed to be in fact a property of it, this substance was subjected to an elementary analysis after drying at 100° C. The results of this analysis were as follows: 0.1978 gm. burned with chromate of lead gave 0.3890 gm. carbonic acid and 0.1246 gm. water; 0.2451 gm. yielded 0.5894 gm. of platinum-ammoniumchlorid, corresponding to 0.0369 gm. of nitrogen. From these figures the following percentage composition can be deduced:

C = 53.58
H = 7.00
N = 15.04

If these results are compared with the figures obtained from the analysis of albuminous substances, it will be found that they are sufficiently similar to warrant the assumption that they belong to the group of albuminous substances; thus, the elementary analysis of egg albumin gave the following results:

	After Dumas and Cahours.	
C = 53.5	53.4	53.5
H = 7.1	7.2	7.3
N = 15.8	15.7	15.7

After Lieberkühn.	After Rüling.
C = 53.5	C = 53.8
H = 7.0	H = 7.1
N = 15.6	N = 15.5

From this analysis Friedreich and Kekulé draw the following conclusions in regard to the composition of amyloid spleen: First, amyloid

belongs to the group of albuminous substances; second, waxy spleen contains considerable cholesterin, but this is not the substance that causes the iodin-sulphuric acid reaction (in opposition to Meckel); third, waxy spleen contains no body chemically related to amylose or cellulose.

[The origin and nature of amyloid are still far from settled. Its chemical composition is still the subject of much study and investigation. The latest views concerning its chemistry can be found in Neuberg's article in *Verhandl. der Deutschen Patholog. Gesellschaft*, 1904, No. 1. His investigation leads him to believe that amyloid may have a composition varying according to its origin, perhaps also according to its age; that it is absorbable, belongs probably to the basic albumin bodies, and is in many respects much like histon.

The iodin reaction is best obtained if the cut surface of the organ to be examined be first washed with water to free it of blood, then made acid by pouring over it a little acetic acid. The solution of iodin in iodid of potassium (iodin 1 part, iodid of potassium 10 parts, distilled water 100 parts) is then poured over the surface, staining the amyloid material a dark reddish-brown or mahogany color, the non-amyloid parts staining light yellow. Hardened amyloid tissues will also show the iodin reaction. If after the iodin solution has been applied a 5 per cent. sulphuric acid be used, the amyloid tissue shows a dark-brown, greenish-blue, violet, or blue tint. This color reaction is extremely inconstant and variable. In sections for microscopic examination excellent results are obtained by taking tissue hardened in formalin or alcohol, staining for a few minutes in a watery solution of methyl-violet, washing in a weak acetic acid solution, mounting, and examining in glycerin. Non-amyloid tissue stains bluish violet, while the amyloid parts are bright pink or red.—Ed.]

Jürgens[1] first discovered a second reaction characteristic for amyloid. Independently and at the same time Heschl[2] and Cornil[3] made the same discovery. A watery solution of iodin violet, 1 : 100, is placed upon a section of the amyloid tissue. This reagent is a combination formed from the union of methyl iodid and anilin; it first colors the whole section uniformly violet. Very soon, however, the color of the tissue, if it has undergone amyloid degeneration, is changed to a brilliant red, and in the majority of cases the violet tint of the normal parts assumes a more bluish shade. Both these changes can be seen very distinctly after ten minutes, or continue even after this time to increase in intensity. The methyl anilin reaction was found to be particularly useful in the microscopic examination of tissue that had undergone amyloid degeneration.

Pathologic Anatomy.—From the point of view of pathologic anatomy three forms of amyloid spleen can be distinguished.[4] In one of these forms, the so-called parenchymatous degeneration (Kyber) or

[1] *Virchow's Archiv*, vol. lxv., p. 189.
[2] *Wien. med. Woch.*, vol. xxv.
[3] *Arch. d. Phys.*, 1875, p. 671.
[4] Eberth, *Virchow's Archiv*, lxxx.; Kyber, *ibid.*, lxxxi., p. 1.

"diffuse degeneration" (Förster, Billroth), the parenchyma of the spleen has undergone amyloid degeneration. As this process seems to involve the whole organ even in mild cases of degeneration, the entire organ apparently forms a mass of degenerated tissue. The second form, the so-called sago spleen (Virchow), "focal degeneration" (Förster), or "degeneration of the lymphatic sheaths" (Lymphscheidenentartung) (Kyber), is characterized by a peculiar amyloid degeneration apparently involving particularly the adenoid sheaths and the lymphatic apparatus [the Malpighian follicles]. The third form of amyloid spleen is a combination of the first two; according to Kyber, it should be called a combined or a general degeneration.

In the early stages of *parenchymatous degeneration* no microscopic changes can be seen in the spleen; the whole organ is of a fleshy consistence, very similar to that seen in chronic congestion. Occasionally the spleen contains almost fluid, soft tissue (Kyber). Abnormal size of the organ is rarely found in this condition. The reaction (Virchow's) gives only doubtful results in the gross specimen. As soon, however, as the blood has been completely removed from the organ the characteristic color appears. Distinct dark-greenish parts on the parenchyma are distinguished among the pure-yellow trabeculæ and lymphatic strands.

Microscopically, the first thing that is recognized in hardened specimens treated with iodin-sulphuric acid is that two kinds of tissue seem to alternate with great regularity; even with a low power it is easy to see that one of them is partly greenish blue, the other yellow throughout. From the tortuous shape of these blue strands, and the circles and bands formed by the yellow parts, it is readily observed that the tissue of the spleen proper has undergone amyloid degeneration, and that the Malpighian bodies have not participated in this change.

If parenchyma that is undergoing this partial degeneration be examined with powers of 100 to 200 diameters, it will be seen that the amyloid reaction is most distinct in the neighborhood of the numerous little canals of the spleen that have been described as capillary veins. These vessels frequently appear to be soft, engorged with blood-corpuscles, and on transverse and longitudinal section seem to have narrow blue margins 2 to 4 μ in diameter. The trabeculæ and vessels forming the lacunar system of the spleen are colored yellow, as are also the lymphoid follicles; here and there, in exceptional cases, a fine artery (from 20 to 30 μ in diameter) shows amyloid degeneration. With a power of 400 diameters all the cells forming the walls of the capillary veins appear yellow and show no abnormalities. In preparing the specimen these cell walls frequently become loosened from their surroundings and protrude into the lumen of the vessels, looking very much like ragged shreds. In the immediate vicinity of these cell walls a blue substance is seen, which, with a high power, resembles an extremely contracted covering of the venous channels, clearly outlined against the lumen of the vessels; toward the other side, however, a gradual transition is seen from the blue to the yellow parenchyma. This blue margin here and there appears altogether homogeneous, with a ragged periphery; in

other places it seems to have a structure, and to be composed of the same elements as the normal parenchyma of the spleen.

The lymphoid cells that give the reaction are partly homogeneous, partly larger or smaller than normal; they seem either fused together where they are in contact or united by a bluish, finely granular or homogeneous, intracellular substance. The majority of the blue cells present very few morphologic changes, so that the protoplasm, the nucleus, and the nucleoli can often be clearly distinguished. Occasionally solitary, blue, round cell-nuclei are seen within a yellow or even a bluish granular area. The matrix occasionally is colored diffusely blue, even in places where the lymphoid cells still appear yellow. The same changes that are found in a chronic congested spleen, only to a lesser degree, are seen almost everywhere in the parenchyma; the cells are either closely pressed together and more closely connected with the tissue, or the intermediary substance is overdeveloped and the matrix replaced by narrow strands of fibrous connective tissue passing between the different cells of the parenchyma. Occasionally small clumps of a finely granular mass are seen; sometimes fat-globules or yellow pigment. The Malpighian bodies that have not undergone amyloid degeneration frequently exhibit a thickening of tissues; this is particularly apparent in the smaller arterial branches.

If the parenchymatous degeneration of the spleen be more advanced, the organ will usually, though not always, be found to be enlarged; the capsule is tense, the margin of the spleen blunt and rounded, its cut surface pale red and somewhat shiny. Small sections that can easily be made of the cut surface, when held against the light are seen to be translucent like wax, particularly at their margins. On pressure they have a peculiar rubber-like resiliency and elastic hardness. In the main branch of the vein and its larger roots occasionally areas of amyloid degeneration are seen, and microscopically it is easy to recognize, even with a low power, that a part of the arterial branches give an amyloid reaction. The smaller branches of the veins, into which the capillary veins enter, are usually stained greenish blue over large areas, just as the smaller trabeculæ. With a higher power the cells forming the walls of the capillary veins are seen to have retained their yellow color. In the immediate surroundings of these veins the parenchyma is replaced by a large mass of homogeneous amyloid substance; further toward the periphery a large number of round cells are distinctly visible, colored blue and embedded in the matrix, which is also blue. The shape of these round cells is partly preserved, in part they are converted into homogeneous swollen bodies, connected in groups of two and three wherever they are in contact; further, they are united with the homogeneous amyloid substance lying in close proximity to the veins. In other places the whole parenchyma seems to be converted into a uniform blue mass that can be readily split; parts of the parenchyma, on the other hand, have retained their yellow color. In different places fatty degeneration and deposits of yellow pigment are seen, and the smaller arterial vessels, particularly in an organ that has undergone advanced grades of amyloid degeneration, are, as a rule, changed in the

same manner. A slight reaction can usually be seen in the main stem of the artery, which, however, is not observed in the branches; as soon as finer divisions of the vessel have occurred, the reaction is again seen to a slight degree in arteries that are from 120 to 180 μ thick. As the smaller arteries are examined, it will be found that the degeneration is more clearly visible. The arterial capillaries are partly degenerated, partly atrophied and destroyed by pressure, and partly intact.

The cellular walls of the capillary veins are almost without exception yellow. The walls, however, of the venous radicles into which the capillary veins are poured are frequently seen to be amyloid. The smallest trabeculæ, if the degeneration have progressed, frequently give an amyloid reaction in spots, occasionally all over. The larger trabeculæ give the reaction only very slightly or remain yellow; they are usually thinner than normal and more or less atrophied. The capsule very rarely gives the amyloid reaction, and, as a rule, shows the degeneration only in isolated places or in very small spots.

Kyber, whose description of the pathologic anatomy of parenchymatous degeneration of the spleen we have followed, summarizes his remarks on the matter as follows:

"Even in the earliest stages of the degeneration the organ shows with more or less clearness the changes that are produced by the chronic irritation. The amyloid degeneration seen in the immediate surrounding of the capillary veins consists in the gradual transformation of the parenchyma of the spleen into amyloid substance; a part of the round cells and of the remaining parts of the parenchyma are destroyed by atrophy; whereas a greater part of the round cells of the matrix and of the reticulum, also a part of the arterial capillaries, do not undergo amyloid degeneration. The strands of parenchyma usually increase in diameter, or may appear in other cases as very narrow strands, similar in their appearance to those seen in indurated spleen in which amyloid degeneration has not occurred. The peculiar cells in the walls of the capillary veins act differently, and only in the most advanced degrees of degeneration a small number of them are seen to have been converted into amyloid substance. The adenoid sheath of the arteries is seen to be in different stages of simple retrogressive metamorphosis altogether independent of the degree of degeneration found in the parenchyma of the spleen; occasionally these sheaths may be well developed and hyperplastic. The blood-channels show interesting changes that are in no relation to the changes seen within the parenchyma."

In very severe uniform amyloid degeneration of the spleen the degenerated organ is enlarged, more solid, and if the disease assume a diffuse form, of a uniformly transparent lardaceous appearance. In cases where the disease occurs in *spots* only, certain small portions of the spleen show this appearance, and the sago-corn appearance is noticed. *Sago spleen*[1] is of normal or increased size. The parenchyma on cross-

[1] Virchow, *Cellular Pathologie;* Meckel, *Charité-Ann.*, vol. iv.; Billroth, *Virchow's Archiv.*, vol. xxiii.; Cornil, *Arch. de Physiol*, vol. vi.; Kyber, *Virchow's Archiv.*, vol. lxxxi., p. 21.

section appears more or less bloodless, the solidity is only slightly increased, or the tissues are found to be fleshy, and tough in consistence, as in chronic congested spleen. When degeneration has progressed very far the follicles of Malpighi are seen to be shiny, transluscent, and similar in appearance to boiled sago grains; in other instances it is very difficult to observe the Malpighian corpuscles; certainly they are not any more distinct than in a normal spleen. It is usually possible, however, to lift them out with the point of a knife; this cannot be easily done in the normal organ. Macroscopically and, of course, much more readily microscopically, an amyloid degeneration, not only of the Malpighian corpuscles, but also of the whole adenoid arterial sheath, is seen as soon as the specimens are treated with iodin and sulphuric acid. The circles and bands that border the small arteries are blue and surrounded by parenchyma that is distinctly yellow.

The degenerated corpuscles if treated with iodin and sulphuric acid seem to consist, microscopically, of blue homogeneous multiform flakes that may be either round or angular, having an average diameter of from 10 to 60 μ; they are either isolated or closely packed together; in specimens that are very carefully prepared they are seen to be connected with one another. In the fissures left between the different flakes small yellowish grains and granules are seen here and there if, in a very fine section, the flakes are carefully teased apart and the specimens examined with a power of from 400 to 900 diameters. On addition of iodin and sulphuric acid nothing will be seen between these blue flakes but occasional yellow granular masses and small yellowish nuclear structures that are partly isolated, partly in close proximity to the surface of these flakes. The network of the corpuscles of Malpighi has completely disappeared and the small arterial vessels are degenerated to varying degrees. As a rule, the change is not widespread, so that occasionally a completely normal artery may be seen passing through a corpuscle that has undergone complete amyloid degeneration. As a rule, a part of the small arteries of an amyloid spleen will give the iodin-sulphuric acid reaction. The parenchyma of the spleen shows varying degrees of atrophy and of conversion into fibrous connective tissue.

General degeneration of the spleen, the third form of amyloid spleen, is characterized by the appearance of parenchymatous degeneration combined with that of a sago spleen.

Etiology.—Amyloid degeneration of the spleen, and of other organs that are participating in this process, notably the liver, the kidneys, and the intestine, is usually a part of the symptom-complex presented by some constitutional disease. This fact has been so often corroborated by experience that the diagnosis of amyloid degeneration during life must be guarded if we cannot find the causative disease. Among all diseases capable of producing a deposit of amyloid substance in the vessels of the different organs, *pulmonary tuberculosis* occupies first place. This disease the writer found in 70 per cent. of all his cases of amyloid; 31 per cent. of whom had tuberculous ulcerations of the intestine. Those cases of chronic pulmonary tuberculosis that are accom-

panied by large ulcerative processes and the formation of cavities are the most important in this connection. Scrofulosis and *chronic suppurative processes*, particularly when they involve bones or joints, are other forms of predisposing constitutional maladies. Occasionally chronic ulcer of the skin may also be made responsible for amyloid degeneration. Chronic spondylitis, with ulceration and resulting deformities, may cause amyloid degeneration in early childhood; suppuration of glands comparatively rarely produces the disease. In other cases chronic suppurative processes of the soft parts and of the bones, with the formation of fistulæ, are found, and Bartels lays especial stress upon a communication between such a pus focus with the external air or with cavities containing gas. The later forms of constitutional *syphilis* are also a prolific cause; here again the ulcerative forms that lead to chronic diseases of the bones and skin are especially important. In one case that merits particular attention the writer found gummata of the esophagus in a man of middle age as the cause of amyloid degeneration of the spleen and kidneys; during life the symptoms of carcinoma of the esophagus were present.

Carcinoma is regarded by many authors as a not uncommon cause of the complication under discussion. In the writer's opinion this view is wrong; only a few well-established facts are on record, particularly in the case of carcinoma of the uterus. Personally he has observed this complication three times in ulcerating carcinomata of the stomach, once in combination with chronic pulmonary phthisis and once in an old syphilis, in both of which cases the carcinoma could hardly be regarded as the cause proper of the amyloid degeneration, because undoubtedly the older lesions of phthisis and syphilis were sufficient to explain its occurrence. In the third case a soft carcinoma of the stomach was found. The disease is sometimes seen following malaria, but probably in only very severe and inveterate cases.

Among the less frequent causes the following can be mentioned: dysentery of the colon, empyema without tuberculosis, varicose ulcers of the leg, chronic ulcers of the stomach, chronic erysipelas, and leukemia. In a case of diffuse bronchitis in a patient with emphysema, the writer observed the complication once, and repeatedly in extended bronchiectasis with profuse discharge of pus; once also in a case of genuine gout.

It would be an easy matter to multiply single observations that have been at times made responsible for amyloid degeneration; the only point, however, that is of importance in practice is, that general amyloid degeneration is to be considered as a sort of dyscrasia; so far it has only exceptionally been found as an idiopathic affection, and, as a rule, is but a secondary affection following in the course of some chronic cachexia of an entirely different kind. Some authors have stated that amyloid may follow chronic Bright's disease, both if it assume the shape of a large white kidney or the less frequent one of contracted kidney. Aside from the fact, however, that amyloid degeneration can develop in healthy kidneys, such cases are usually complicated with one or another

frequent cause of amyloid degeneration—as, for instance, syphilis or tuberculosis—so that in nephritis and amyloid degeneration we shall have to distinguish two independent co-ordinated disturbances involving the same organ at the same time, and, as a rule, depending on the same primary cause. The above-named diseases are capable of producing both an amyloid degeneration of the kidney and a chronic nephritis, so that if such patients are afflicted with lesion of the kidney we can expect to find one or the other sequelæ, or both. So far, uncomplicated cases of chronic nephritis with amyloid degeneration have only exceptionally been observed in perfectly healthy individuals. Probably the chronic cachexia existing is the source of the general amyloid disease, and we can assume that the blood-current is the carrier. On the other hand, no facts have been adduced that would demonstrate that a general amyloid degeneration can be considered as a symptom of some change within the blood, or that the amyloid substance is carried to the organs through the blood. If amyloid or its mother substance were in solution in the blood we ought to be able to find it there, and that has so far not been done. Some investigators think that the amyloid substance is formed from the tissue elements and is manifested within the cells of the affected tissues. Even in this case we would have to assume that amyloid is attracted from the blood and, so to say, fixed by the cells, analogous to the deposit of calcareous matter in bone tissue, so that the important and essential part of the disease would be a degeneration of the cells and not the infiltration of the latter.

As no one has, so far, succeeded in producing amyloid degeneration in animals (Litten), we are dependent exclusively on clinical observation for information in regard to the length of time required for its development. [Some experiments, however (Czerny, Krakow, Maximow, and Davidsohn), seem to show that amyloid can be produced artificially, as by the repeated injections of cultures of Staphylococcus pyogenes aureus.[1]—Ed.] We are fortunate in having bedside observations of such precision that they are equal in value to any experimental data. For these observations we are indebted chiefly to Cohnheim, who made his observations on young soldiers who had been wounded at Mars la Tour and Gravelotte, and who were afflicted with gunshot wounds of the bones with complicated fractures and serious suppurative processes or putrid suppuration of large joints. In these patients he could demonstrate that degeneration of the spleen, or of the spleen and kidneys, never appeared earlier than four months nor later than six months after the wound.

The writer was able to determine the beginning of amyloid degeneration of the spleen by the increased swelling of that organ and characteristic changes in the urine in an uncomplicated case of empyema of the pleura in an adult, and of spondylitis in a boy of five years, that came under his observation from the first day on which their disease had been diagnosed. In the former of these cases amyloid degeneration appeared in two and a half months; in the latter, in about three

[1] *Cf.* Krakow, *Arch. de méd. Exp. et d'anat. path.*, x., 1898.

and a half months; this probably is the minimum time that must elapse before the first signs of this complication can make their appearance. In many other cases, particularly in insidious cases of pulmonary phthisis, the general deposit of amyloid in the vessels of many organs seen so frequently, probably takes a much longer time. We must also remember that in the cases described either the spleen alone, or the kidneys and the spleen, had undergone amyloid degeneration and that no chronic nephritis had developed, and that all the other organs were still sound.

From these observations we also learn that the spleen and the kidneys are the first organs to become affected, and particularly the spleen. In all the cases mentioned above this organ was the first to be diseased and the one most seriously involved; whereas in the writer's cases at this period the kidneys were just beginning to show the degeneration. This is probably the rule, to which there are undoubtedly exceptions. The writer has occasionally seen a case in which the kidneys, and even other organs, showed the degeneration, whereas the spleen remained completely free from any complication. The same applies to the kidneys; and here also we must consider the absence of general amyloid degeneration as a pathologic anomaly.

In the year 1879, when the writer was an assistant in Friedreich's Clinic, he treated a merchant of fifty-three, who was afflicted with erysipelas in the lumbodorsal region following a chronic varicose ulcer. This patient had lived for varying periods of time in America and in London, and had suffered repeated attacks of malaria; besides, he indulged pretty freely in alcoholic liquors. Among the clinical symptoms profuse diarrhea, chills, and fever of about 39.7° C. were particularly prominent; no urinary abnormalities were discovered. Quinin did not seem to influence the paroxysms of fever, and the diarrheas and frequent vomiting seemed to remain uninfluenced by the usual remedies. The erysipelatous process extended to the scrotum and continued to extend over other parts of the body, until, after several days, collapse and death occurred. On section a chronic mitral endocarditis, a fibrinous pneumonia of the left upper lobe, a chronic splenitis, an insignificant interstitial hepatitis, and a slight degree of contracted kidney were found. The most important finding was a pale edematous condition of the mucosa of the intestine with widespread amyloid degeneration; all the other organs of the body, including the spleen, were free from any signs of amyloid degeneration. This is the only case of exclusive amyloid degeneration of the intestinal mucosa that the writer has been able to discover in many years, although he has given particular attention to this subject.

In another case a woman suffering from advanced pulmonary phthisis was brought to the clinic; this was in 1878. No symptom of any complication was elicited. At the end of four weeks considerable pain was complained of in the region of the liver, and at the same time the organ began to swell. The surface of the enlarged liver was smooth, its margin rounded, its consistence abnormally hard. An

examination of the other organs yielded a negative result; diarrhea occurred, which could have been due to tuberculous ulcerations of the intestine, just as well as to amyloid degeneration; albuminuria did not appear. When the patient died an autopsy was made, and a widespread amyloid degeneration of the liver and intestine was found; the spleen and the kidneys were intact.

Among 100 cases of amyloid degeneration the writer found the spleen affected in 98 per cent., the kidneys in 97 per cent., the liver in 63 per cent., and the intestinal mucosa in 65 per cent.

Symptomatology and Diagnosis.—Amyloid degeneration of the spleen itself only rarely produces symptoms; occasionally a dull continuous pain is felt, and if inflammation of the serous covering of the spleen or distention of the same through rapidly increasing swelling of the organ occur, the pain grows more severe, but even then rarely so violent that it cannot be easily borne; in addition, a feeling of fulness and weight is complained of in the left hypochondriac region. In the majority of cases, however, pain is completely absent. The larger the tumor and the longer it has been present the less sensitive it is, as a rule, to outward pressure, and even in the very largest tumors it is usually impossible to elicit pain by pressure. Lying on the right side is usually uncomfortable, and sometimes impossible, so that generally the patients prefer the left decubitus. Sago spleen causes less discomfort, as it is only slightly enlarged; an increase in this form of tumor occurs only in the transverse diameter; the consistence, too, may be changed. On the other hand, in lardaceous spleen proper enormous degrees of enlargement are occasionally seen, occurring so rapidly that the capsule of the spleen is greatly distended and stretched. In such cases the writer has found great sensitiveness of the spleen, necessitating the administration of narcotics. He has in rare instances observed the same phenomenon in amyloid degeneration of the liver.

Slight degrees of amyloid degeneration of the spleen remain unrecognized, as we can readily understand; the diagnosis can be made only when a hard tumor of the spleen with rounded edges, having an increased transverse diameter and being readily palpable on deep inspiration, is found in the course of a general disease capable of leading to amyloid degeneration. The diagnosis is strengthened if at the same time hard swellings of the liver, hydrops, and albuminuria are present. The latter symptom may be absent even if degeneration of the kidneys be present; in the great majority of cases, however, one of the typical symptoms of amyloid kidney is albuminuria. Obstinate diarrheas are frequently noticed as a complication. Cachectic conditions are also frequently seen, but in this it is often difficult to determine in how far they are attributable to the degeneration of the spleen or to the primary disease.

The interesting observations made by Fürbringer in Friedreich's Clinic showed that the diagnosis of amyloid degeneration is frequently not made despite the most careful clinical study. Four cases of chronic, widespread and far-advanced ulcerative pneumonia were observed, in the

course of which hard tumors of the spleen and the liver, and at the same time albuminuria, occurred; in addition, hydrops and diarrhea were present and could not be stopped by the administration of either styptic enemata or of opiates and strong astringents. On autopsy it was found that the spleen and the liver, as well as the kidneys (that showed chronic nephritis), were not affected with amyloid degeneration, which, of course, had been diagnosed during the life of the patient.

Fürbringer expresses the opinion that in this case a deposition had occurred in the organ of a new-formed substance closely related to amyloid and forming, so to say, a preliminary stage in the development of the latter. He assumes that this substance, like amyloid, can infiltrate the tissues, but does not give the characteristic reaction. In the writer's own investigations on amyloid substance he arrived at analogous conclusions altogether independently and uninfluenced by Fürbringer's studies, and believes that a substance exists which is different from amyloid proper, inasmuch as it does not give the reactions with iodin-sulphuric acid nor with iodin violet and methyl anilin. It resembles amyloid, however, very much in its physical properties; for instance, it is altogether similar to amyloid in its homogeneous consistence, its great powers of refraction, its solidity, its resistance to the influence of water, alcohol, ammonia, and acid solutions. This substance, that the writer will call "hyalin," seems under certain conditions to be able to form amyloid. Further, he feels justified in concluding from his studies that an amyloid substance under certain conditions (for instance, if a piece of the amyloid organ remain for a long time within the abdominal cavity of an animal) can be reconverted into this hyaline substance, so that it must, he thinks, be looked upon as the mother substance of amyloid.

Prognosis and Treatment.—The prognosis of amyloid degeneration of the spleen is altogether dependent on the prognosis of the general disease, and as this latter is, as a rule, very unfavorable, and as it is difficult to make predictions regarding the probable outcome, it is clear that the additional serious involvement of the spleen, accompanied as it usually is by similar lesions in other organs, makes the prognosis still worse. That it is possible for the degenerative process in the spleen to be arrested, or even to progress toward a relative improvement, is demonstrated by cases of syphilitic amyloid degeneration of the spleen, or the degeneration following chronic sores on the leg, diffuse bronchial catarrhs, and those forms of degeneration of the spleen which seem to occur idiopathically.

So much, however, can be positively stated, that organic tissue that has once acquired the properties of amyloid can never again perform its function, but must be considered, as Virchow says, as dead protoplasm. On the other hand, experience teaches us that amyloid degeneration of the spleen can be borne for years provided that the general disease and the other complications do not directly threaten life.

[If, as Neuberg[1] contends, amyloid material is absorbable, it is con-

[1] *Loc. cit.*

ceivable that in milder cases at least, a partial or even complete restitutio ad integrum might take place in an organ, like the spleen, that is the seat of amyloid degeneration. For while some of the tissues have perhaps undergone a complete and irreparable destruction, other cells may be but partially involved, or may be through pressure only slightly damaged by atrophy, etc., and the disappearance of the amyloid might be followed by a more or less successful attempt at repair. Observations on this point are needed.—Ed.]

In regard, finally, to the treatment of amyloid degeneration of the spleen, we can only indicate that it must be carried out according to general therapeutic principles; syphilis, of course, will most readily yield to treatment. In the management of this disease the problem is not to incorporate as many antisyphilitic remedies as possible, but to use the remedies in a manner that is appropriate and sensible. The writer has found, for instance, that hot sulphur baths—particularly Burtscheid-Aachen, Baths at Vienna and Zürich, Herkulesbad at Mehadia in Hungary, Trencsin-Teplitz in the Carpathian Mountains—combined with appropriate mercurial treatment (inunction, injection, internal administration of corrosive sublimate or of the iodid of mercury or of other iodin preparations), are much more suitable for the removal of the cause of this disease than one-sided medication at home. What holds good for syphilis holds good mutatis mutandis for the removal of the indicatio causalis in other diseases that predispose to amyloid degeneration —as, for instance, chronic diseases of the lungs, gout, etc. We should act on these principles wherever amyloid degeneration has begun to make its appearance; and even if we are unable to combat the latter, we should, at least, attempt to treat the symptoms so far as possible and to counteract the bad influence on the blood that any degeneration of the spleen is likely to produce. We can accomplish this with various preparations of iron, above all the iodid of iron (preferably in the form of the syrupus ferri iodidi) with manganese and arsenic and, further, with a vigorous diet (Meat, milk, wine, porter etc.); finally, by promoting the activity of the skin through bathing.

TUMOR OF THE SPLEEN IN LEUKEMIA.

[So much has been added to our knowledge of leukemia since Litten wrote this section, that a complete rewriting might seem best. However, in accordance with the plan adopted in the rest of the volume, the author's words are allowed to stand as he wrote them. But certain corrections and additions have been made by the editor, bringing the subject more nearly up to date. A full discussion of all points is not attempted, because the subject under discussion is the *spleen* of leukemia rather than leukemia itself, and again because the topic is exhaustively treated by Ehrlich, Lazarus and Pinkus in another volume of this same series, which is edited by Dr. Stengel.—Ed.]

Definition.—Leukemia is a disease of the blood-forming organs leading to permanent and steadily increasing flooding of the blood with

white blood-corpuscles, and a decrease in the number of the red blood-corpuscles. We distinguish three kinds, and call them splenic, lymphatic, and myelogenic (or medullary), according to whether the spleen and lymphatic glands or the bone marrow are the original seat of the disease. In nearly all cases the spleen is affected (in 109 cases 95 times); not always alone, but more frequently in combination with one of the other organs mentioned above. We have not sufficient experience to allow us to make any definite statements in regard to the frequency of isolated bone-marrow involvement. We know, however, that it is extraordinarily rare, the rarest by far of the three forms of leukemia.

[There is not always the steadily increasing flooding of the blood with white corpuscles that is referred to in the definition just given; marked variations in the number are met with during the course of the disease, and even at the time of death the number of leukocytes may not be extremely great. The changes in the blood are not alone quantitative or numeric, but *qualitative*. In leukemia the characteristic increase is in the mononuclear forms; the granular forms—myelocytes—in myeloid leukemia; the lymphocytes—large and small forms—in the lymphatic leukemia. Numerically great increase in the white cells may exist without leukemia, as in the ordinary leukocytosis, where as high as 50,000 to 100,000 white blood-cells may be found in each cubic millimeter of blood; but the increase here is in the polymorphonuclear neutrophiles and not in the mononuclear forms. On the other hand, leukemia may exist with no enormous increase in the leukocytes. Thus, in lymphatic leukemia counts of 50,000 leukocytes are not unusual. But the qualitative change, the lymphocytosis, is the striking feature, and marks the case, taken with the clinical manifestations to be sure, as one of leukemia.

The splenic form is now seldom spoken of. Bone-marrow changes are common to all forms of leukemia, even the lymphatic. Pure myelogenic leukemias—*i. e.*, cases with no changes in spleen, lymphatic glands, etc., merely in the bone-marrow—are, to say the least, rare, and the cases thus far reported as of this type are not clearly enough of this character to warrant the forming of a special class. The classification that best meets the demands of the clinician, and that so far as pathogenesis is concerned is as scientific as any, is to divide leukemias into the two groups of (1) lymphatic leukemia and (2) myeloid (splenic-myelogenic) leukemia, and to recognize under each group an acute and chronic variety. Unfortunately, no etiologic basis for classification is known, nor is there any really sharp dividing line from an anatomic standpoint. And even clinically mixed forms are seen—*i. e.*, forms with the blood-picture and clinical symptoms partaking of the characters of the myeloid (myelocytes in numbers) and of the lymphatic types (lymphocytes increased, lymph glands enlarged, etc.).—Ed.]

History of the Disease.—We are indebted to Virchow for the discovery and recognition of leukemia. In the year 1845 he performed an autopsy on such a case, and interpreted it correctly by declaring the white bodies found in the blood to be leukocytes, in contradiction to

other investigators before his day, particularly Bennet, Velpeau, Bouchut, who had looked upon them as pus corpuscles, interpreting the disease as suppuration of the blood (pyemia). In 1849 J. Vogel, in Dorpat, recognized the disease during life, for the first time, and diagnosed it correctly. We are indebted to Wunderlich, Friedreich, Mosler, and others for the development of the general symptomatology of the disease; and to Neumann, and after him Bizzozero, for the elucidation of the pathologico-anatomic basis of the disease, as these investigators discovered the blood-forming function of the bone-marrow.

Litten was the first to describe a pure uncomplicated case of exclusively myelogenic leukemia. Later Béhier attempted to establish a fourth class of leukemia, which he designates as enteric. As this author, however, did not examine the bone marrow in his case, in which hyperplastic changes of the lymphatic apparatus of the intestine and a normal spleen and lymph glands were found, nothing was proved, particularly as the glands of the intestine are found swollen in a variety of other diseases. Very probably this was a simple leukocytosis.

Etiology.—We have no direct information in regard to the etiology of the disease. Attempts have been frequently made to identify it as an infectious disease (notably by Klebs).

In 4 of the writer's cases blood, spleen, and lymph fluid were removed from the patients during life and examined, under Pfeiffer's direction in Koch's Institute, for *microparasites;* these investigations, as well as experiments with the injections of leukemic blood, yielded negative results. Such experiments have been frequently repeated, the blood being taken from acute cases that rapidly progressed to death within a week, but nothing was ever elicited to show that leukemia was at all infectious. Claudio Fermi has discovered in the leukemic spleen short, thick rods with rounded ends that remained unstained in the middle. We shall recur to this later.

In studying the etiology different things have been considered, but none of them gives us any clue; for instance, heredity, pregnancy, long-lasting lactation, poor nutrition, previous attacks of anemia (Litten), chronic diarrheas, and others. Occasionally the disease follows an infectious disease, especially malaria and typhoid. The writer has seen one case that followed four and one-half days after an attack of influenza and rapidly terminated fatally. During this same epidemic 2 other cases of the same kind were observed by other investigators. In another case the writer saw a severe acute leukemia with fatal issue following a case of pernicious anemia. Such observations have since been frequently published. Trauma seems to have a certain etiologic significance, and the external conditions of life are not without influence, as we notice that the lower working-classes are particularly frequently affected. Men are more frequently leukemic than women (67 to 33 per cent.); persons of middle age seem to be particularly predisposed, but the disease is also seen in early childhood. Those cases occasionally seen in children, in which a leukemic blood-picture develops several days after the discovery of a tumor of the spleen,

are probably attributable to a previous attack of anemia. [The attempt of Löwit[1] to prove leukemia due to a protozoan (*Hæmamœba leukæmia*) has not been regarded as successful. Türck and others have failed to find the supposed parasite, or they regard it as an artefact. One who has seen many cases of acute lymphatic leukemia, however, will not wonder at the persistence with which investigators hunt for a microbic cause. The resemblance of this form of leukemia to an infectious disease is certainly striking.—Ed.]

Pathologic Anatomy.—Virchow, in his classic studies on leukemia, made in the middle of the forties, has determined the pathologic anatomy of leukemic spleen so carefully that no one has since contributed anything essentially new to this subject. In the first case of leukemia, which has since become historic,[2] Virchow reports of the spleen as follows: "Enormously hypertrophied, nearly a foot long, very heavy, dark-brown red, of bread-like resistance, fragile, bloodless on transverse section, consisting of an apparently homogeneous tissue; the cut surface shiny, waxy, and resembling a large fever spleen." Virchow later[3] summarizes his findings in regard to this condition as follows: "In leukemia the spleen is usually very much enlarged, weighing frequently 3, 5, or 7 pounds—that is, fifteen times more than in its normal condition. In the majority of cases very pronounced signs of *perisplenitis* are seen. The capsule is nearly always thickened, opaque, and whitish, sometimes colored by pigmented spots, and covered usually with large, flat, cicatrized or round, semi-cartilaginous areas of thickening. As a rule, adhesions with neighboring parts are found, particularly with the diaphragm, the retroperitoneal tissues, and the mesentery. The specific weight of the organ is also increased and the spleen feels resistant; this resistance can particularly be felt when an incision is made. On transverse section the tissues usually look bloodless and are constantly colored light or pale red or yellowish red, sometimes flesh color, and occasionally brownish red. The *cut surface* is smooth, comparatively dry and homogeneous, and only the larger blood-vessels, which are usually dilated, are seen in the shape of patent holes. The follicles are usually very small, and not very distinctly outlined, and consequently not readily seen; if a careful examination be made, however, they can always be found, as they are differentiated from the red spleen pulp by their whitish color. The pulp is usually very abundant, exceptionally dense, sometimes almost elastic in resistance, and very tough, so that it is hard to tear and to penetrate. Within it the thickened trabeculæ are seen as white strands; they are particularly prominent near the capsule.

"*Microscopic examination* reveals the normal elements all very closely pressed together, so that the matrix of the pulp cells seems to be more abundant and more solid. Occasionally pigment is found, varying in shade from yellow to red, to gray and black. We are, therefore, in these cases dealing chiefly with a hyperplasia and an induration, and the

[1] "Die Leukæmie als Protozoeninfektion," Wiesbaden, 1900; also several other articles in journals.

[2] *Froriep's Neue Notizen*, Nov., 1845.

[3] *Gesammelte Abhandl. zur wissenschaftl. Med.*, 1856, p. 205.

condition is best differentiated by this latter property from the corresponding swelling of the lymph glands. It is a rare thing to find these changes alone; and, as a rule, more or less extended areas of a thicker consistence are found toward the outer surface of the organ that are differentiated, especially when recent, by their intense reddish color. Later this redness assumes a more hemorrhagic character, and the focus that originally was situated immediately under the capsule spreads out in a wedge-shaped manner, penetrates more toward the center of the organ, and is seen to have the characteristics of a *hemorrhagic infarct*. The older this grows the thicker and dryer it appears; it is of a dark-red color, changing gradually into a lighter yellow or into a dirty reddish yellow or grayish yellow, the whole mass becoming cheesy like a tubercle; if it persist for a long time, finally a yellowish orange or rust colored, occasionally a greenish-yellow or red scar is formed. Microscopic examination of such a focus reveals the normal elements of the spleen in a condition of general contraction and retrogressive metamorphosis. The blood-constituents have been converted into irregular flakes, into pigment granules and crystals, and even into connective tissue." Virchow saw only once a suppurative focus within the spleen; this spleen is described as follows:[1] The spleen weighed 1½ pounds, was 8 in. long, 4 in. wide, and 1½ in. in thickness; its capsule was thickened irregularly, with several large white spots, between which yellowish-brown pigmented areas were seen; it was altogether inelastic. On transverse section the pulp was seen to be of a peculiar yellowish red; it was pretty solid, but could be readily crushed on pressure, although it was not diffluent. It contained numerous very small white bodies and in different places were seen red spots like ecchymoses, about as large as a flea bite, from 2 to 3 lines in diameter, enclosing, as a rule, whitish spots in their centers. In some places larger resisting nodules about as large as a nut were visible; these contained solid white spots looking like connective tissue or muscle, surrounded by dark-red areas. On microscopic examination nothing was seen but closely packed nuclei, between which yellowish pigment heaps and cells with large granular nuclei could be distinguished. In one place near the center of the spleen a small pus focus about as large as a pea was observed, surrounded by a fine membrane and containing a yellowish mass of pus that under the microscope was dissolved into large polynuclear cells that had undergone partial fatty metamorphosis.

The pathologic findings in leukemic spleen teach us that the great enlargement of the organ is due to hyperemia and new formations. The blood-current is retarded and flows more sluggishly through those channels that have been called by Billroth cavernous splenic veins. An exceptionally large number of red blood-corpuscles are seen in addition to colorless spleen cells. The corpuscles of Malpighi are larger than normal. Later the cellular elements increase more and more, the cells themselves become very much larger, and the vessels and stroma also increase. In the course of time two stages can be distinguished, one a

[1] *Virchow's Archiv*, vol. v., p. 58.

softer, cellular stage, the other a harder, more indurated stage. The greater the degree of hyperplasia the less, as a rule, the amount of blood. The cut surface assumes a fleshy brown or grayish-red appearance. On the other hand, the younger the tumor the smaller the difference between its parenchyma and that of a normal organ; in such cases the parenchyma is more engorged with blood, and the follicles of Malpighi and the fibrous stroma are more conspicuous. We must assume that the development of the leukemic process in the spleen begins with an increased influx of blood; to this are added hypertrophy and hyperplasia of the normal elements of the spleen. This process, therefore, resembles an irritative process. As the disease progresses the fibrous stroma becomes more and more apparent. In different places numerous small knots and nests of colorless, round, granular and cellular elements develop that have been called *lymphoid new formations*. They are found in the liver, the kidneys, and the retina, in addition to the spleen, and usually appear in foci, rarely diffusely disseminated throughout the whole organ. The older the tumor of the spleen, the dryer, harder, and more anemic becomes the parenchyma. The follicles of Malpighi are relegated to the background and are not so easily recognized, and the whole parenchyma seems infiltrated with colorless elements. After this production of colorless elements has reached a certain point they may undergo retrogressive metamorphosis and be converted into amyloid or fat.

Kelsch and Vaillard[1] and Claudio Fermi have examined the spleen in leukemia bacteriologically. Fermi's case was that of a man of fifty-five, who had died of "leukemia, tumor of the spleen, and enlargement of the peritoneal, mesenteric, and axillary glands." Fermi[2] found the following: On gelatin plates made from the spleen, the liver, and the lymphatic glands a pure culture of the same bacterial species was seen at the expiration of three days. Microscopic examination of the plates showed round or oval, whitish, non-liquefying colonies. Stab cultures in gelatin showed the development only of a milk-white, prominent growth on the surface; the growth was pretty rapid, and in time a partial liquefication seemed to occur. In the slides made from these cultures short thick rods with somewhat rounded ends were seen, that were particularly characterized by their staining-properties, inasmuch as they remained unstained in the center. Sometimes several members were seen to be in connection with each other. By way of control other dead bodies were examined in the same manner (cases of pleurisy, meningitis, nephritis, sarcoma, diphtheria, tetanus, typhoid) and never revealed the presence of these rods. [In brief, it may be stated that no parasite vegetable or animal has yet been identified as the cause of any form of leukemia.—Ed.]

Chemistry of Leukemic Spleen.—Scherer was the first to occupy himself with the chemistry of the leukemic spleen; later E. Salkowski, G. Salamon, and others. Bockendahl and Landwehr have done the most exhaustive work in this direction. These authors proceeded as follows:[3] The spleen was macerated to a fine consist-

[1] *Ann. de l'institut Pasteur Année IV.*, vol. iv., No. 5, p. 276.
[2] *Centralbl. f. Bacteriol.*, vol. viii., p. 553.
[3] *Virchow's Archiv*, vol. lxxxiv.

ence and extracted 4 times with water of from 40° to 50° C.; then filtered through linen and the residue pressed out and washed; the extracts were acidified with acetic acid and boiled. The coagula of albumin were flaked, and it was an easy matter to filter the fluid through large folding filters. The filtrate represented from 5 to 6 times the weight of the spleen substance employed. With potassium ferrocyanid and acetic acid clouding was observed in the upper part of the fluid only. Millon's reagent gave a red color, and copper sulphate a well-marked biuret reaction. The extracts were evaporated to a thin syrup, first over the free flame, then on the water-bath. A small quantity of tyrosin was precipitated, the fluid allowed to grow cold, filtered, and the clear fluid saturated with double its volume of alcohol of 96 per cent. The mixture was permitted to stand for several hours, and a precipitate that had formed filtered off; the sticky yellowish filter residue was let stand over sulphuric acid for a short time until it became a whitish powder. This was dried in the drying oven at 105° to 110° C., forming a yellowish mass resembling dry gelatin. This was boiled with water on the water-bath, when it dissolved, leaving only very little residue.

As the solution became cloudy with potassium ferrocyanid and acetic acid, and with nitric acid gave clouding that disappeared on heating and reappeared on cooling (Kühne's hemialbuminose), it was mixed with iron chlorid and sodium acetate, boiled, filtered, concentrated, and then examined as follows: (1) A part was boiled for several hours with dilute sulphuric acid; leucin was formed, but neither tyrosin nor glycocoll. (2) A part was mixed with small pieces of putrefying pancreas and allowed to stand for some time at 46° C. At the expiration of twenty-four hours the solution was mixed with sodium carbonate and distilled. In the distillate considerable quantities of phenol could be demonstrated with bromin water. (3) A part was treated according to Hofmeister's method of converting peptone into albumin—that is, it was heated for six hours at 160° C. The bulk became transformed into albumin, which gave the characteristic reactions with potassium ferrocyanid and acetic acid, and could be converted into syntonin and precipitated by careful neutralization. (4) It was found that the substance had levorotatory properties; the yellow fluid absorbed very much light, so that it was necessary to employ dilute solutions. Bockendahl and Landwehr employed solutions of 1.938 per cent. of the spleen—peptone and the half-shadow apparatus [polarimeter] for the determination. On account of this great dilution the errors became so large that Bockendahl and Landwehr did not feel justified in making any other statements than (+) D = —60° —70°. A control estimate made with a good saccharimeter and a 1.8 per cent. solution of blood-peptone gave the same result. The alcoholic filtrate was evaporated, and by filtering after cooling, separated from the leucin which had been precipitated on cooling; it was evaporated to the consistence of a thin syrup, then dilute sulphuric acid was added, and the mixture repeatedly shaken with ether; the whole was placed in a separating funnel, the ether carefully pipetted off and distilled. The residue was further evaporated to a syrupy consistence on the water-bath, and placed over sulphuric acid; long needles crystallized out. The syrup was then diluted with water and saturated with sugar of lead solution. A precipitate was formed, which redissolved in the surplus of the lead solution, but fell out in crystalline shape on boiling and shaking. This precipitate was decomposed with sulphuretted hydrogen; the solution freed from sulphid of lead by filtering, and the filtrate boiled with nitric acid and neutralized with ammonia. The surplus ammonia was driven off, silver nitrate added to the solution, and the precipitate thus formed dried and weighed. The acid that was freed from its silver base by the action of sulphuretted hydrogen crystallized over sulphuric acid in beautiful four-sided prisms. This acid could be sublimed, and with a clear solution of barium chlorid and ammonia in alcohol gave white precipitates; when boiled with carbonate of magnesium, filtered, and saturated with neutral solution of chlorid of iron a voluminous brown precipitate resulted. Those parts of the succinic acid that were not used for this reaction were recrystallized from water and their melting-point determined; it was found to be 179° C.

The filtrate of the lead salt of succinic acid was freed from the lead by sulphuretted hydrogen, evaporated, boiled with the carbonate of zinc, filtered, and the filter residue washed repeatedly with boiling water. The filtrate was evaporated and placed over sulphuric acid and crystallized. A drop placed upon the slide showed the characteristic crystals of lactate of zinc. These crystals were dried

and weighed. The total quantity of lactate of zinc obtained from the liver, the spleen, and the blood was washed with absolute alcohol in order to remove the light-yellowish coloration. It was then recrystallized over water, dried on filter paper, and weighed for the determination of the water of crystallization; 13 per cent. of water was found. The crystals were then heated until their weight remained constant, and 33.4 per cent. of oxid of zinc remained.

In the residue of the alcohol washings that were taken up with water, phosphoric acid could be demonstrated with an ammoniacal solution of magnesia. The syrup was freed from organic acids by ether and saturated with ammonia. The precipitated phosphates were filtered off, and the filtrate reprecipitated with ammoniacal silver solution; the precipitate was insoluble in ammonia. This precipitate was carefully washed and redissolved in boiling nitric acid of a specific gravity of 1.1; on cooling a few crystals were formed; these were filtered off, and the solution again precipitated with ammonia. The crystals showed all the reactions of hypoxanthin (Salkowski). The precipitate produced in the nitric acid solution by the addition of ammonia never contained any guanin, which is insoluble in water. The hydrochlorate and the nitrate showed the crystal shape of the corresponding xanthin compounds. On addition of copper acetate the solution gave a blue-green precipitate only on heating. If the nitric acid was added and then evaporation carefully performed the mass turned yellow, and if potassium hydrate was added, red.

Bockendahl and Landwehr summarize the results of their anaylsis as follows: 1600 gm. of a spleen that weighed 3250 gm. were placed at our disposal. One piece of the spleen was boiled with water one hour after extirpation and examined for glycogen (with a negative result). For the other examinations 1400 gm. of the spleen substance were used. Tyrosin was not present, but leucin was found in considerable quantity. 14.5 gm. of peptone were obtained. The quantity of lactic acid was 0.168 gm. (0.012 per cent.); that of succinic acid, 0.029 gm. (0.002 per cent.); hypoxanthin and uric acid were not found, but 0.548 gm. of xanthin was present.

Symptomatology.—Owing to the characteristic changes in the blood, the skin and the mucous membranes of the patients are very *pale;* this symptom is rarely absent; the fat and muscles, however, are well preserved for a long time; ultimately the fat disappears and the enormous emaciation is in striking contrast to the distended abdomen.

After this the most striking phenomena observed in the disease are the *enlargement of the spleen* and of the lymphatic glands. The former is, as a rule, affected in this disease, as we have seen above and forms a hard, solid elastic tumor with a smooth surface; it is hardly ever painful, only occasionally tender on pressure. [With perisplenitis there may be considerable pain. And not infrequently patients complain of the feeling of weight and the dragging sensation due to the great size of the organ.—Ed.] It frequently reaches enormous dimensions and may even fill the whole abdomen, so that the belly is very much distended through this immense tumor. Very frequently an increase in the volume of the organ causes its ligaments to become loosened, so that the spleen sinks downward in the abdomen, and splenic percussion dulness is no longer found in its normal place in the left hypochondriac region. The upper outline of the spleen in these cases is usually very distinctly marked in the epigastric region, where it can be seen to move upward and downward with respiration. This is a step in the direction of float-

ing spleen, and it is only due to the enormous size of the organ that this condition does not fully develop. For the spleen in leukemia is usually wedged tightly between the sacrum, the symphysis, and the crest of the ilium, so that it simply cannot move any farther downward. The notches on the anterior, and occasionally the lower, margin of large tumors of the spleen are particularly well palpable, owing to the size of the organ and the bluntness of its margins; the writer has felt as many as four. In palpating the usually smooth surface, especially when rubbing over it with the finger-tips, a peculiar *crepitating* or *grating feeling* is often elicited, that, as the writer has repeatedly found on autopsy, is due to adhesions. These are seen in the shape of long, thin threads that are interwoven, so to say, with each other, and produce this peculiar sensation when they are touched and moved. They undoubtedly originate from ordinary inflammatory adhesions of the capsule that have become drawn out in this manner on account of the frequent respiratory movements of the spleen, the organ being thus prevented from becoming anchored, and by the forming of broader and firmer adhesions. Different from this symptom is the friction sound proper that can usually be heard and felt here and there over the surface of the spleen, but only synchronously with respiration. This may be very soft, or loud and grating, like the creaking of new leather ("*Neulederknarren*"); on auscultation it can readily be heard. Perisplenic inflammations are frequently found in leukemic tumors of the spleen; they are usually localized and strictly circumscribed. In other cases they may change their location, but do not, as we have seen above, generally lead to adhesions between the spleen and the abdominal walls. They may become very painful and cause a great deal of distress.

The enlarged *lymphatic glands* may become as large as an adult fist. Sometimes they are seen under the skin as large swellings, causing considerable deformities, particularly if they appear in the region of the neck. Their chief sites of predilection, aside from the neck, are the axilla and the inguinal region. They are not sensitive to pressure, nor adherent to the skin, exhibit no tendency to inflammation, cheesy degeneration, or suppuration. Occasionally the bronchial and tracheal lymphatics enlarge and compress neighboring parts, causing bronchial and tracheal stenoses. Other glands of the body situated more deeply may also become enlarged; as, for instance, the retroperitoneal and mesenteric glands or the glands of the tongue, the tonsils, and the thyroid, or, in the intestine, Peyer's patches.

We recognize from the blood that the *bone marrow* is involved and, according to some authors, from the pain that can be elicited over the bones on percussion, particularly over the large marrow bones (sternum, ribs). The writer has always denied the significance of this symptom, for the reason that it cannot always be elicited in true cases of involvement of the marrow and that it is not characteristic when it is found.

The constitution of the *urine* is, as a rule, not typically changed, although Salkowski claims to find a regular increase in the uric acid excretion.

Anemic murmurs are heard over the heart, and an anemic thrill in the jugular veins; *edemas* are frequent, and occasionally there is observed a great tendency to *perspiration* that may be very annoying to the patient. Loss of appetite and excessive thirst are frequently complained of; other disturbances of digestion appear, producing eructations, vomiting, and obstinate diarrheas; the latter may persist for so long a time, uninfluenced by any therapy, that they lead to collapse and death. Leukemic patients, further, have a great tendency to the *hemorrhagic diathesis;* hemorrhages, frequently of great severity, occur into the skin and mucous membranes of the mouth, the nose, the digestive tract, the retina, etc. As the coagulability of the blood is, as a rule, reduced, very slight injuries may frequently produce grave hemorrhages, so that all surgical operations are very dangerous. Simple epistaxis may be serious, owing to the large quantity of blood that is shed, and the writer has even seen obstinate hemorrhages result from a small prick with a needle, made in order to get a drop of blood for microscopic examination.

The *changes in the skin* that are found in leukemic patients have so far been very little considered. They usually appear in the form of characteristic wheals, so that the affected area is infiltrated; this causes hard, quite voluminous, whitish swellings, surrounded by hemorrhagic areas. In addition, petechiæ and sugillations are seen that may be found in the skin of any part of the body, with bloody spots that assume the shape either of large confluent spots attaining the size of the palm of the hand, or of little specks that are seen on the periphery of the white infiltrations mentioned above. The writer can best characterize these latter lesions by comparing them to the appearance of the skin in a badly executed subcutaneous injection—that is, where the needle has not, for instance, penetrated through the whole skin, but has entered slantingly, so that the fluid injected is forced into the tissues of the cutis. This causes the injected part of the skin to be raised in the shape of a white infiltration; such hard, I might almost say "boardy," infiltrations are seen over a great part of the body in some leukemic cases, and, as stated above, are sometimes as large as the palm of an adult hand. These changes in the skin are of the same origin as the retinal changes seen in leukemia, to be described presently.

In addition to this form of subcutaneous tissue change found in leukemia, the writer has observed another form that, it seems, is particularly rare; this lesion is found in the *upper* and *lower eyelids.* In looking at the patient or examining a photograph the impression of an existing edema of the lids is given; most observers have assumed that an infiltration has occurred; in reality, however, this is something altogether different. One of the writer's patients with such a condition was suffering from splenic-lymphatic leukemia that could in this case readily be diagnosed from the swelling of the lymph glands and of the spleen. All along the lymph channels strings of tumors were found that were about as large as small nuts; in addition, a bilateral, hemorrhagic, pleuritic exudate was present that, on aspiration, was seen to

consist of a light-reddish fluid containing nearly as many white as red blood-corpuscles. An analysis of the blood, moreover, showed leukemic changes, consisting chiefly in an increase of the lymphocytes. A participation of the bone marrow in the process could not be determined. In the retina of the left side the typical leukemic lesion was found—*i. e.*, white spots, and here and there hemorrhagic areas; the whole fundus had the characteristic orange tint. This was without doubt a case of splenic-lymphatic leukemia of long standing. The patient's eyelids seemed enormously swollen and protruding; this condition was due to the presence of numerous small tumors between the skin and the subcutaneous tissue, and of such irregular shape that the eyelids seemed to be infiltrated and appeared typically edematous. The skin over these little tumors could be lifted without difficulty, and underneath a moderately soft tumor mass could be distinctly palpated, that seemed to consist of different parts. They could be felt best if the lids were grasped between the fingers from above; in this manipulation it was even more apparent that the whole tumor mass consisted of a conglomeration of single small tumors. The same phenomenon was apparent in the lower lids, although the swelling was not so plainly marked here.

The lesions of the skin that the writer has seen in leukemia assume either the shape of rather soft, regularly formed, round or almond-shaped tumors, as in the above case; or that of the tense circumscribed infiltrations which he has previously described. These latter are characterized by their sinewy, shiny color and by the impression they create of their consisting of hard infiltrations similar to a swelling that would be produced if a subcutaneous injection were made into one of the lymphatic vessels. The first kind of tumor is characterized microscopically as a lymphatic tumor; the skin over these growths is never adherent. The latter forms of leukemic infiltration are arranged exactly like the corresponding lesions in the retina, and are always, like these, surrounded by hemorrhagic areas.

In the *retina* changes are found that are characteristic for leukemia. The lesion here is retinitis leukæmica, and is seen in one-quarter to one-third of the cases. The retina is usually pale and orange-colored, its veins wider than normal, tortuous, of a bright-red color, and occasionally surrounded by white margins or hemorrhagic infiltrations. The arteries are narrow and also less red; the reflex band of the veins is less distinctly marked than normal. The following localized changes are observed: Yellowish prominent spots frequently surrounded by hemorrhagic areas, and seen chiefly in the peripheral parts of the retina between the equator and the ora serrata, and also occasionally near the macula lutea. Numerous hemorrhages with white centers and bloody margins around the blood-vessels, particularly the veins. Occasionally the retina looks cloudy, and the outlines of the optic papilla indistinct. Visual disturbances are frequently altogether absent, but become manifest as soon as the pathologic changes appear near the center or in the vicinity of the macula lutea; in such cases it may happen that visual disturbances are the first recognizable symptom of the disease, so that

these patients may consult an ophthalmologist before the examination of the blood has ever been made. The diagnosis of leukemia is frequently made in this way with the ophthalmoscope.

Of other symptoms that merit chronicling are the *pleuritic exudates.* These are relatively frequent, and are usually bilateral, the fluid slightly bloody in color and filled with corpuscular elements of the blood. The writer has occasionally centrifuged such transudates and exudates, and found a cellular residue that showed the same numeric proportion between leukocytes and erythrocytes that obtains in the blood itself.

The Blood.—Among the lesions of leukemia, the changes in the blood are the most important and the most conspicuous, for the reason that they really characterize the disease and are peculiar to it. All the other symptoms may be found in other diseases. The diagnosis is easy and the microscopic examination calls for no special preparation. Frequently the color of the blood is so characteristic macroscopically that diagnostic conclusions are almost justified; it is light, watery, and resembles coffee and milk, and may occasionally be so pale that a drop fails to stain linen. [One should rely rather on the microscopic examination, a point referred to by Litten below. Confusion with chlorosis, severe primary or secondary anemias can readily occur if reliance be placed on the macroscopic appearance.—Ed.]

In order to obtain a drop of blood for examination, the finger is thoroughly cleansed, pricked, and a drop of the blood placed upon a carefully prepared slide, at once covered with a cover-slip of appropriate thickness that has also been carefully cleansed, so as to be free from all fatty or oily matter. In this form the specimen can be immediately examined. While it is true that, in order to make more delicate examinations of the blood, stained specimens are necessary, still the microscopic examination of such a fresh uncolored specimen is sufficient to make a diagnosis, and in many cases even to determine the nature of the different corpuscles seen in the blood. [The ear is by many preferred to the finger. Cover-slips and slides are best cleaned by alcohol, acidulated alcohol, alcohol and ether, or even by soap and water. They should be so clean and free from fatty matter that the blood "spreads" quickly and freely.—Ed.]

The most important question that the examination of the blood must decide is whether the white elements are at all increased. If this is found to be the case, the degree of increase must be determined. For this purpose we have a number of counting devices (Vierordt, Nalassez, Gowers, and others), of which the Thoma-Zeiss variety is the most convenient.

Method of Counting Blood-corpuscles.—An apparatus should be procured with which a dilution of the blood can be correctly made. For this one employs a shaking mixer; it is a small glass instrument shaped like a pipet and carefully graduated. The point of this pipet is dipped into the blood and suction performed through a little rubber tube until the blood rises to the mark $\frac{1}{2}$ or 1; the point of the instrument is then carefully wiped off and a 3 per cent. salt solution aspirated

to the mark 101; the mixer is then vigorously shaken and the mixture made uniform. The small glass ball found in the bulb of the pipet facilitates this mixing. If blood were drawn to the mark ½, this mixture is as 1 : 200; if to the mark 1, it is as 1 : 100.

In order to count the corpuscles, this diluted blood is placed into the counting chamber of Abbé and Zeiss, consisting of a glass cell 0.1 mm. deep, the bottom of which is divided by rulings into squares; this little chamber is glued to a slide, and for examination must be covered with a cover-slip. When covered each square is $\frac{1}{4000}$ of a c.mm.; the corpuscles found in one of these squares are counted, and the number obtained multiplied by 4000, the result being the number of blood-corpuscles in 1 c.mm.; this figure must be multiplied by 100 or 200, according to the dilution used. In order to be more certain of the result, several squares should be counted and the average taken of all the figures obtained.

If it be desired to count the white blood-corpuscles alone in the counting chamber, the blood is diluted with 10 parts of a ⅓ per cent. acetic acid mixture, which dissolves all the red blood-corpuscles (Thoma).

In the healthy adult 1 white corpuscle is seen for every 400 to 500 red ones; in leukemia the former may be numerically so much increased that they are equal to the red. The designation "white blood" is very appropriate, because in these cases it is frequently necessary almost to hunt for red blood-corpuscles. [!—Ed.]

[The details of the technic can be found in works on Hematology (Cabot, Ewing, DaCosta, etc.) or in books on Diagnosis. Toisson's solution[1] can be used instead of the salt solution, and it enables one to differentiate more readily between red and white corpuscles. The white corpuscles are stained by this solution in about ten minutes.

In order that results should be fairly accurate, not several, but *many*, squares should be counted, at least 100, preferably 300 to 400. It is also a good plan to make 2 preparations and take the average of the 2 counts. It is only in this way that blood-counts that are even approximately correct can be made. It is easy to see how an error in the average number becomes of great importance in the final result, because with a dilution of 1 : 200 the average number is to be multiplied by 4000 × 200, or by 800,000.

For the counting of the white corpuscles a special mixer permitting of an accurate dilution of 1 : 10 is generally employed. The average number per square would in this instance be multiplied by 4000 × 10, or 40,000, to give the number per cubic millimeter.—Ed.]

The next task is to determine the varieties of these white blood-corpuscles and their origin. So long as only 2 forms of leukemia (splenic and lymphatic) were known, the distinction was made between mononuclear cells—smaller than red blood-corpuscles, containing one large nucleus almost completely filling the cell and leaving only a narrow margin

[1] Toisson's solution: Methyl violet (5 B) .025 gm., sodium chlorid 1 gm., sodium sulphate 8 gm., neutral glycerin 30 gm., distilled water 160 gm.

of protoplasm—and large polynuclear cells, containing from 3 to 5 nuclei arranged in clover-leaf fashion. The latter cells were thought to come from the spleen, and the former from the lymph glands, and according to the prevalence of the one or the other form the leukemia was characterized as a lymphemia or a splenemia.

With the discovery of the hematopoietic function of the bone marrow certain red blood-corpuscles (normoblasts) were discovered that were called myelogenous—that is, derived from the bone marrow; these cells contain nuclei and are probably antecedents of the ordinary erythrocytes. Soon after this discovery the period of color analysis of the blood began, and with these new methods it became possible to differentiate not only the various forms of white blood-corpuscles, but also their granulations, which up to this time had never even been seen. Ehrlich has accomplished most in this direction. At the same time it must be remembered that the work in this field has so far not led to any final and conclusive discoveries; moreover, that a certain confusion of different details, particularly of the terminology, has been produced, chiefly owing to the fact that each investigator introduces his own particular methods of staining and of nomenclature.

By the methods of staining it became possible to recognize mitotic figures in the nuclei of leukocytes in leukemia. In addition a certain form of leukocyte was discovered that had been described, it is true, but had never before been considered characteristic for myelogenous leukemia; this is the large mononuclear cell, conspicuous by the large nucleus containing little chromatin, and a narrow surrounding cell body. Ehrlich, who called these cells *myelocytes*, could demonstrate neutrophile granulations within them with his triacid stain.[1] Other authors have called these structures "Markzellen." It is very probable that leukemia consists in an increased production of these white cells of the bone marrow, although this assumption does not in any way explain the origin of the disease.

Another form of blood-corpuscle must be mentioned, the *eosinophile* cell, so-called by Ehrlich on account of the great attraction their granules have for eosin. Ehrlich has called these granules alpha granules or eosinophile granules; they are distinguished by their intense staining properties with acid stains. They can readily be demonstrated as follows: A dried and fixed blood-slide is stained for a short time with 1 drop of a glycerin-eosin solution, then washed with water, dried again, and mounted in Canada balsam. The eosinophile cells are readily visible owing to their intense red color; in an unstained specimen they can often be seen because their granules are so coarse and refractive, and may be conglomerated so closely that they obscure the nucleus. As these cells are undoubtedly derived in great part from the bone mar-

[1] This is a solution of: Orange G 120 to 135 c.cm., acid fuchsin 60 to 85 c.cm., Methyl green (cryst.) 125 c.cm., water 300 c.cm., absolute alcohol 200 c.cm., glycerin 100 c.cm. For these solutions a temperature of 105° to 110° C. is sufficient for from one to two minutes. [This refers to the temperature at which the specimen or "smear" is fixed.—Ed.]

row, some investigators thought that this was an unmistakable sign by which the myelogenous nature of the disease could be recognized with certainty from an examination of the blood. While it is true that they are increased to a great degree in leukemia, they are also found in increased numbers in a variety of other diseases; occasionally they are even found in augmented numbers in otherwise normal blood, and, on the other hand, there are undoubtedly cases of leukemia in which they are absolutely increased with all the other white blood-corpuscles, but not relatively. Again, the writer has seen cases in which the blood seemed to be crowded with eosinophile cells, so that they were particularly conspicuous.

In one of these cases that was dissected later it was found that not alone the blood was crowded with these cells, but also the bone marrow, and a specimen made of the marrow looked, so far as these cells were concerned, exactly like a blood-specimen. In this case (one of pure myelogenous leukemia), the lymph glands were not involved at all, and the spleen only to a very slight degree. The writer was forced to make a diagnosis from the blood-examination alone, as the bones were not at all painful, even when considerable pressure was exerted. Another case of pure splenic leukemia, however, has taught him that these cells are not at all characteristic for myelogenic leukemia, because in this case eosinophile cells were found to be as numerous in the blood, and post mortem in the red bone marrow, as in the other.

Eosinophile cells were formerly considered to be white blood-corpuscles that had undergone fatty degeneration. Jäderholm was the first to describe them in a case of splenic leukemia; he states that in one case of this disease he found 5 per cent., in another 15 per cent., of the leukocytes in fatty degeneration. Mosler further describes a case, and states that he saw white blood-corpuscles for the first time that seemed to be completely filled with small refractive granules that were shown to be fat-droplets when placed in contact with chloroform. Budge observed that these cells were present in overwhelming numbers; in addition he found them in the so-called red bone-marrow, but only isolated specimens in the spleen pulp. Neumann placed himself on record as believing that these cells originated from the bone-marrow. The sternum of his case was punctured later, and the same cells were found in the matter aspirated. In another case of splenic and medullary leukemia Sticker found white blood-corpuscles that seemed to be filled with a large number of very refractive granules and droplets.

The appearance of "*Mastzellen*," described by Ehrlich, in leukemic blood does not seem to be exclusively characteristic for this disease.

Basing on these examinations we are enabled to answer the much-discussed question as to the extent to which the number of white blood-corpuscles must be increased, or what the proportion between red and white blood-corpuscles must be in order to enable us to diagnose leukemia, as follows: It is altogether indifferent whether the leukocytes are absolutely or relatively increased. The distinguishing diagnostic factors are the various forms. We say that a simple leukocytosis exists if the

blood contain many normal cells of the polynuclear neutrophile type; a leukemia exists when there is a specific increase of the myelogenous, mononuclear neutrophiles (myelocytes[1]), possibly combined with a great increase in the eosinophile cells or of the lymphatic cells (small, mononuclear leukocytes with a large nucleus, so-called lymphocytes). In the first instance we diagnose a myelogenous, in the second a lymphatic, form of leukemia.

The findings in regard to the red blood-corpuscles are simpler; only isolated cases of leukemia are reported in which an oligocythemia of the red blood-corpuscles does not exist; as a rule, it exists, though not to such a degree as Quincke and Litten have described it. The small form of nucleated, red blood-corpuscles [normoblast] is a frequent occurrence in leukemia, particularly in the myelogenic form; sometimes they are found in extraordinary numbers. The large form of these cells, however, is very rarely found; these have been called by Ehrlich gigantoblasts; they are probably found in leukemia only when complicated by an anemia of great severity.

The writer has always been able to find a certain number of cells containing blood-corpuscles in leukemia; sometimes their number is very great. They were very conspicuous in one case in particular, in which a myelogenous form of leukemia developed on the basis of a pernicious anemia. They are, however, not at all characteristic of leukemia, and are found in a variety of other diseases, both of a chronic and of an acute character; for instance, typhoid, phthisis, carcinoma, pneumonia, septicemia, tabes, pleuritis, syphilis, paralytic dementia, etc., and possibly in still other diseases. Occasionally these cells contain red blood-corpuscles with nuclei; they are found occasionally in considerable numbers in the bone-marrow of persons who have succumbed to a variety of diseases, and their appearance here is not dependent on the presence of lymphoid marrow nor on the previous existence of any kind of disease or any group of affections. These cells probably become converted into pigment-containing cells, which are also found under similar conditions in the bone marrow, both pathologically and physiologically. Normally, both forms of cells are found regularly, and are particularly prevalent in the atrophic gelatinous marrow of old people. Orth and Litten succeeded in demonstrating pigment cells in the bone-marrow in 37 per cent. of the cases that they examined.

The blood-plaques in the blood of leukemics have been counted by Pruss. This investigator is the only one who has made these examinations, and he reports that in 4 of his cases he found them increased fourfold. Litten has devoted special attention to this question for a long time, and has always found the blood-plaques to be increased in number. He has also found in fresh blood that was immediately examined certain structures that he called white blood-cylinders in all forms of leukemia.

The last finding of importance is that of the Charcot-Leyden crystals. They are not constantly found in leukemic blood and never

[1] These occur constantly in large numbers in the normal bone marrow, but are washed out into the blood-stream only in cases of myelogenic leukemia.

immediately after the blood has been removed, so that they are not visible in a fresh specimen. They only appear after a considerable time, and crystallize out of the blood in varying numbers and in different sizes. The writer has found them only in blood that contained many eosinophile cells, particularly in the myelogenous form of leukemia. These Charcot-Leyden crystals are found in different disease products of man wherever eosinophile cells are found in increased number in the blood, as in the sputum of asthmatics that is expectorated immediately after the attack; the longer such sputum is examined under the microscope, the more the crystals will be seen to form under the very eyes of the observer and the larger will they grow. At the same time eosinophile cells are found in large numbers in the blood and in the sputum of such cases. The same applies to nasal polypi; if these are examined, numerous crystals and eosinophile cells, the latter also found in the blood of such patients, are seen. The writer has noticed that in these cases, as in leukemia, the Charcot crystals appear in the same proportion as the decrease in number and consistence of the granules of the eosinophile cells. If this observation can be corroborated, the assumption can be made that the Charcot crystals are derived from the granulations. In the bone-marrow they are found normally, and it is probable that they are found in the spleen. In leukemic cases they frequently form after death, and cover most of the organs—for instance, the liver and the spleen—with a shiny, crystalline, scintillating covering of varying thickness. Nothing definite is known in regard to their chemical constitution. According to Schreiber, they are a combination of phosphoric acid with an organic base.

E. Neumann,[1] in regard to the nature of these crystals in leukemia, has recently expressed himself as follows: "I should like to direct attention to an observation that I have made that seems to favor the theory that these crystals originate in the bone-marrow. There are certain cases of leukemia in which the bone-marrow, which is pathologically changed, loses the faculty of forming these crystals when decomposition begins. In these cases, too, although a hyperplastic swelling of the spleen and of the lymph glands may exist, crystals are not found in the blood. It is true that some authors have looked upon the formation of these crystals as a regular occurrence in leukemia, and Zenker, for instance, has placed himself on record as stating that in every case of leukemia these crystals can be found if they are only carefully looked for, and Cohnheim, too, speaks of the remarkable constancy with which they are found in leukemic blood. These observations, however, do not correspond to the facts of the case, and I have frequently emphasized that the appearance of these crystals is limited to those cases in which the mononuclear or polynuclear leukocytes of the blood are conspicuous by their size and the quantity of protoplasm that they contain, and in which these elements appear in the coagulated blood after death as pus-like conglomerations of a greenish-yellow color. Formation of crystals, on the other hand, is not found in those rare cases in which

[1] *Virchow's Archiv.*, vol. cxvi.

the blood contains chiefly lymphocytes with a scanty protoplasm, and in which the coagula have a more whitish or pale-red color. It is true that the former class of cases forms the majority."

Relation of the Blood to the Blood-forming Organs.—It is probable that the increase in the number of the white blood-corpuscles and the decrease in the red stand in some relation to each other. Virchow and others assume that in this disease the conversion of the white elements into the red is prevented; Neumann and Litten claim that leukemia can develop on the basis of an anemia. The appearance of nucleated red blood-corpuscles is evidence of the participation of the bone marrow in the process. In addition, the appearance of marrow cells in leukemia demonstrates that in this affection these marrow elements enter the blood-stream in larger numbers than normally. These cells migrate from the marrow, where they are formed, into the blood and here undergo either a reconversion or are transformed into eosinophile cells. Biesiadecki and Kottmann have formulated a theory of leukemia that is radically different from all our ideas on the pathogenesis of this disease. They consider it an independent disease of the blood, whereas all other investigators consider it primarily an affection of the blood-forming organs. Their conception of the disease is based principally on the well-known case of Leube and Fleischer, mentioned above, in which the blood showed all the characteristic findings of leukemia, and the lymph glands and the spleen were at the same time found intact. The bone-marrow in this case was red and hyperplastic and contained many nucleated red corpuscles and marrow cells. Neumann interprets this case as signifying that a compensatory exaggeration of the bone-marrow functions had occured as a result of the existing anemia. This increase would ultimately become excessive and lead to pathologic hyperplasia and to leukemia. It is worthy of mention, finally, that in leukemia a decrease in the number of leukocytes is occasionally observed if acute infections occur intercurrently, especially pneumonia, typhoid, etc.

Course of the Disease.—The course of leukemia is, as a rule, *chronic*. The average duration is from one to two years. Yet cases with an acute course are frequently observed. Ebstein has collected the case records scattered through the literature and has described them as acute leukemia; this separation of the rapidly fatal cases from the others has not thrown any new light upon the nature of the disease. The writer himself has probably described the most acute cases so far reported; one, following pernicious anemia, that terminated fatally in three to four days with the symptoms of myelogenous leukemia, and was verified on autopsy; the second developing immediately after an attack of influenza, and also leading to death in a very short time, with the formation of metastatic foci in the brain, in the retina, and in the skin.

Diagnosis.—Leukemia can only be recognized with the aid of the *microscope*. It should not be confounded with the blood-picture of an ordinary leukocytosis, particularly as the latter affection is never lasting nor progressive as leukemia. We have already stated all that is neces-

sary in regard to the forms of leukocytes that are characteristic of leukemic blood. After the diagnosis of leukemia has been definitely made microscopically, nothing remains but to determine the kind; this is not difficult in the case of the splenic and lymphatic form. However, it may be difficult at times to recognize the involvement of the bone-marrow; here, too, the microscopic examination will have to decide, as the painfulness of the bones, especially on percussion, is not a reliable criterion. On the other hand, we shall be able to diagnose the myelogenous form of leukemia if with the increase in white corpuscles we find the spleen and lymphatic glands normal.

[Without going into details, which, as we have said, do not seem called for in an article on the *spleen* of leukemia, it may clarify some points if we give a brief statement of the blood-findings in the two varieties of leukemia that are commonly recognized.

The Blood in Myelogenous Leukemia.—*Red cells* show diminished number (oligocythemia), averaging about 2,500,000. Nucleated forms are common. Megaloblasts are not at all rare. At times "blood-crises" (v. Noorden) occur as in other severe anemias, and enormous numbers of nucleated red corpuscles may be seen.

Hemoglobin diminished (oligochromemia), generally out of proportion to the diminished number of red cells—*i. e.*, the color index (per cent. of hemoglobin divided by per cent. of red corpuscles) is below 1, averaging about 0.7.

White cells numerically increased, averaging from 200,000 to 600,000, although great variations are seen, even in one and the same case when examinations are made at different times. *Myelocytes* are numerous, averaging about 30 per cent. Eosinophiles are absolutely and often relatively increased, making at times as high as 28 per cent. of the white corpuscles (Cabot). Generally about 3 to 5 per cent. of eosinophiles are found. Lymphocytes are relatively diminished, averaging, say, 10 per cent. Polymorphonuclear neutrophiles are, of course, absolutely increased, although relatively diminished, averaging about 45 per cent.

Lymphatic Leukemia.—In the *chronic form* red cells, as in chronic myeloid form, though nucleated forms are not so numerous. White cells increased, the number usually being in the neighborhood of 100,000. Of these the majority, usually over 90 per cent., are lymphocytes, generally of the small variety, although exceptionally the larger forms are numerous. Polymorphonuclear neutrophiles, myelocytes, and eosinophiles, especially the latter two forms, found very sparingly.

Acute lymphatic leukemia deserves a word, as in a sense it differs quite sharply from all other forms. In many respects it resembles an acute infectious process, often starting in with an angina or symptoms like those of an ordinary "cold." Chills and general aches and pains may be present. The lymphatic glands at the angle of the jaw and in the neck enlarge quite rapidly, although seldom reaching a great size, rarely that of a hen's egg. Other glands, as the axillary, cubital, inguinal, etc., enlarge, as does the spleen. The latter organ may be 2 or 3 finger-

breadths below the costal arch. A fever is present that may be low or may rise to 104° F. Hemorrhages into the retina, under the skin and mucous membranes, as well as bleeding from the nose, gums, stomach, etc., show the marked hemorrhagic diathesis that makes such a striking feature of these cases. The bones may show tenderness. Edema may appear. The patient grows weaker and may lie as in a typhoid state. Albuminuria is common. The color of the patient at once suggests a high grade of rapidly progressing anemia. The red cells may within a few days fall to 1,000,000 or lower, the hemoglobin dropping with them or even more rapidly. Nucleated forms are rare, yet at times are seen in considerable numbers, as the writer has observed in 2 instances out of 10 cases of the acute lymphatic form. The white cells are increased usually to about 75,000 to 150,000, and the increase is seen at a glance through the microscope to be in the non-granular, mononuclear forms, the lymphocytes. In the acute leukemia the larger forms commonly predominate, although exceptions to this rule are seen, as the writer can testify. Myelocytes are not found, or only in small numbers, although at times they are abundant enough (2–6 per cent.) to make one feel like speaking of a mixed (myeloid and lymphatic) form of acute leukemia, a form recognized by some (Grawitz). Intercurrent infections (staphylococcus, streptococcus, etc.) are often seen, and may lower the count of the white cells or induce a change in the picture by causing an increase in the polymorphonuclear forms (ordinary leukocytosis). Death occurs generally inside of three or four weeks, although this type of case may last a few weeks longer.

The writer has been struck by the resemblance of this acute lymphatic leukemia, with its fever, hemorrhages, rapid anemia, etc., to cases of rapidly progressive fatal anemia apparently due to sepsis, but in the blood of which no absolute lymphemia is found, although a relative increase in the lymphocytes—a lymphocytosis—is present. Three such cases the writer has seen : one following a tonsillar abscess, another a criminal abortion, and the third a tuberculous ulcer of the bowel. Leube refers to the condition as lymphanemia. Were there only lymphatic enlargement with a greater number of lymphocytes, the pictures would be the same as that of acute lymphatic leukemia.

Acute myeloid leukemia is much rarer than the acute lymphatic forms, yet cases are occasionally seen. The literature has recently been collected by Billings and Capps, who report a case.[1]—Ed.]

Prognosis.—Nearly all clinicians make a *fatal prognosis*. Some authors, particularly Mosler, do not do this, but consider the case curable, provided the patient has received the appropriate treatment early in the stage of the development of the disease. In the writer's own experience of the great number of cases that he has treated he has never seen *one* recover ; all have died.

Treatment.—From a *prophylactic* point of view we must treat all those diseases that may lead to leukemia with particular care, in order to diminish as much as possible the danger of this sequel. This is

[1] *Am. Jour. Med. Sci.*, cxxvi., Sept., 1903.

particularly the case in anemia, intermittent fever, influenza, injuries of the spleen and bones, scrofulosis, glandular swellings, intestinal troubles, and possibly syphilis.

[One should treat all diseases of whatever kind as carefully and conscientiously as possible, in order to insure a prompt and complete recovery, as well as to avoid any unfortunate consequences. Toward the prevention of leukemia as a sequel there is, however, nothing that can be called a special or specific treatment.—Ed.]

Dietetic treatment is the most important when the disease has developed, for the reason that one of our chief indications is to preserve the strength of the patient. Most authors recommend an albuminous diet. The metabolism of leukemic patients, particularly the proteid metabolism, is very important. It is impossible for us to enter into this subject in detail; we shall limit ourselves to emphasizing the most important facts: Pettenkofer and Voit found that in the milder cases no considerable increase of proteid metabolism occurred; in grave cases, however, and especially in cachexia, it was far different, the elimination of nitrogen being undoubtedly increased. The fundamental principle in feeding leukemic patients must be to refrain from giving them anything that they cannot assimilate. This is particularly important in this disease, because leukemic cases frequently are afflicted with dyspepsia and intestinal troubles; for this reason only easily digestible food should be prescribed. In addition care should be taken that all the different classes of food should be present in proper proportion, and that indigestible substances, as cellulose, too much starch, etc., should be avoided. We must not overtax the digestive organs of such patients; on the contrary, their function and work should be facilitated as much as possible. For this reason it is good to put them on an animal diet, preferably milk, koumiss or kefir, eggs and meat, particularly raw scraped beef, scraped ham, game, poultry, meat peptone, and oysters; possibly the following vegetables, wheat bread, rolls, zwieback, leguminous flour, cocoa, asparagus, artichokes, cauliflower, spinach, and watercress; further, claret, good beer, meat broth, Valentine's meat juice, Brand's meat essence, etc. In cases of serious marasmus nourishing enemata are indicated. All in all, the writer would prescribe the following method of feeding in leukemia: a plentiful meat diet and a restriction of the starches and sugars, as these retard metabolism.

A second important factor in the treatment of these cases is *mental* and *bodily rest*.

Cold *bathing*, particularly sea-bathing, has been recommended; it can only do good in the beginning of the disease—that is, in cases suffering from serious nervous disturbances. In more advanced cases, in which the albuminates are being consumed in excess, such bathing is certainly contra-indicated, if for no other reason than that it withdraws some of the heat of the body. The warm bath, on the other hand, is to be recommended in case it does not weaken the patient; at all events, it should not be of too long duration.

Transfusion.—It seems natural to attempt a cure of a disease of

this kind, which chiefly affects the blood, by transfusion. Blasius tried it for the first time in 1863, with an unfavorable result. Mosler later tried it in 2 cases and had passing success. In the treatment of this disease tranfusion has not been followed by any important improvement, so that it has gradually been dropped in Germany; later in England and America. In the writer's opinion this is right.

Treatment by Medication.—For a long time it was thought that *arsenic* was destined to play an important rôle in the treatment of leukemia. Unfortunately these expectations have not been verified, although we must say that transient improvement has been noticed; especially the proportion of the red to the white blood-corpuscles has been increased; the spleen and the lymph glands, even, have been seen to decrease in size. For these reasons this remedy is certainly indicated in early stages of the disease. In addition to a decrease in the number of the leukocytes and an increase in the number of the red blood-corpuscles, it has been found that the hemorrhagic diathesis, the night sweats, and even the tumor of the spleen, have shown improvement. Personally the writer has seen good results follow the administration of this remedy, but never a cure. The same applies for the very acute cases. As arsenic preparations affect the digestive organs, it is necessary to be very careful in their administration. The best form in which to give the drug is the liquor potassii arsenitis (Fowler's solution). The maximum dose is 0.5 gm. (7 minims), practically a dose of 2 gm. *pro die;* the dose can be gradually increased as the organism becomes accustomed to the drug, but it is best not to exceed the maximum dose even though the organism may stand larger quantities without symptoms of intoxication. [By many Fowler's solution is given in gradually increasing doses up to 12 to 20 drops at a time. When the limit of tolerance has been reached, as shown by nausea, vomiting, diarrhea, puffiness under the eyes, etc., the amount can be lessened.—Ed.]. Subcutaneous injections of arsenic are of no special advantages in the treatment of leukemia. In several cases the writer has prescribed the use of the arsenic waters of Levico that contain the drug in the form of arsenous acid; if this water be taken for a long time, occasionally the size of the spleen may be reduced. This method of administration, however, has no particular advantage. Ebert found the administration of Fowler's solution combined with sulphate of quinin very effective in a patient suffering from splenolymphatic leukemia. He observed a considerable detumescence of the spleen and lymph glands, and saw the proportion of red blood-corpuscles fall from 1 : 12 to 1 : 124, until, finally, a normal condition of the blood was established. Other communications are too incomplete to merit more than passing mention. It is certain that this method of treatment is worthy of consideration, particularly in view of the utter hopelessness of all our other therapeutic measures.

Quinin and its salts have frequently been considered in the therapy of this affection, and large and long-continued doses of quinin in alternation with oil of eucalyptus and piperin have been recommended by Mosler.

It is certain that a great many of the cases of leukemia reported cured by quinin were in reality other diseases, particularly cases of malaria, of anemia, or of scrofulosis, with a leukocytosis. In pure cases of leukemia treatment with quinin is as useless as a combination of quinin with iron preparations. The same applies to ferruginous mineral waters.

In view of the good results obtained with *phosphorus* in the treatment of malignant lymphoma, it seemed natural to try this method in leukemia. In the former disease this drug apparently caused the swellings of the glands to disappear and the leukocytosis to decrease. English physicians in particular have accomplished some very deserving results in this direction; yet while it is true that in leukemia phosphorus seems to decrease the hardness and size of the enlarged glands, and even to decrease the number of the leukocytes considerably, still it has never positively led to a cure, so that the remedy cannot be recommended in this disease. The same applies to inhalations of *oxygen*, recommended on the supposition that the oxygenating powers of the leukemic organism were reduced.

The tincture of eucalyptus globulus alone, or in combination with piperin and quinin, as recommended by Mosler, is said to produce contraction of the spleen, and in this way act favorably on the general disease process. The writer has made a great many experiments with this remedy, and with the combination recommended by Mosler, but has never seen favorable results, and considers it to be utterly devoid of value. The same applies to iodin preparations, particularly the syrup of the iodid of iron, and to cod-liver oil with or without iodid of iron.

Organotherapy has also been tried in this disease, particularly in the myelogenous form. Glycerin extracts of the tarsal bones of a calf were administered internally or injected subcutaneously; later, tablets of spleen, lymph-gland, or bone-marrow extract were administered, depending on the form of leukemia present. The writer has frequently used this method without ever seeing the least result. Recently *thyreoiodin* has been considered of value in the treatment of leukemia; beginning with 3 tablets, as many as 29 were given in a day, equal all in all to 240, a quantity corresponding approximately to 72 gm. of thyroid substance. Following this a decrease in the number of leukocytes in leukemia has been seen. Even this therapy has never led to any particularly good results. The tablets came from English factories, particularly from Burroughs, Wellcome & Company, in London, and from the analine-dye factories of Fr. Bayer, in Elberfeld. [With such large doses of thyreoiodin one must be watchful lest thyreoidism develop, with tremor, emaciation, sweating, palpitation, diarrhea, nervousness, and slight fever. Even exophthalmos has been recorded as following the use of too much thyroid extract.—Ed.]

Local Treatment.—This is chiefly directed against the swelling of the spleen and lymph glands, and probably originated in the wrong idea that the disease of these organs was the pathogenetic starting-point of the general disease. The favorable results obtained by Mosler

from the use of arsenic induced this author to inject *Fowler's solution* directly into the parenchyma of the spleen. He had previously obtained fairly favorable results in non-leukemic tumors of the spleen. After only 10 injections he saw a considerable decrease in the size of the organ; after eight weeks it became hard, solid, and nodular; the injections were well borne. Mosler expresses himself as follows in regard to their effect: "It seems that a transient arrest of the leukemic process in the spleen, if not a cure, can be obtained by parenchymatous injection of Fowler's solution. This is manifested by an increase in the solidity of the spleen and partial obliteration of portions of spleen parenchyma as a result of hyperplasia and the subsequent contraction of the connective tissue. Very frequently the subjective symptoms caused by the tumor are ameliorated by these injections; in addition, the moral influence exercised on the patient by active treatment of this kind must not be underestimated." It is certain that this treatment should be given with certain precautions; above all, the patient should be in a fair state of strength; very severe anemia and cachexia and the hemorrhagic diathesis must not be present. In addition to arsenic, ergotin and iodin have been employed for parenchymatous injections, with fairly good results.

The application of *cold*, particularly in the form of cold douches in the region of the spleen, has also been recommended in order to bring about a decrease in the size of the organ. Botkin has recommended *faradization* of the spleen in leukemia, as in other forms of splenic tumors; other authors have recommended local galvanization. There can be no doubt that by electricity the size of the enlarged spleen can be reduced; this is readily verified. However, the writer was unable to determine a favorable influence in the general course of the disease itself. Riess and others make the same statement. Some authors have seen a considerable increase in the number of leukocytes following electrization. The same may be said of galvanopuncture, performed as follows: Several needles are introduced into the spleen through the skin and connected with the negative pole; the positive pole is placed upon the abdominal walls, or possibly connected with another needle, which is also stuck into the spleen. After each sitting a mild fever and slight signs of peritonitic irritation appeared; these symptoms in some cases, however, were absent. No permanent good was obtained; on the contrary, the spleen seemed to enlarge a little. At all events the electric treatment of the spleen in leukemia must be considered useless.

Splenectomy has been tried a number of times in these tumors, as well as in non-leukemic swellings of the spleen. It has always rapidly led to death, and is to be condemned if for no other reason than that danger is threatened from the appearance of the hemorrhagic diathesis, which makes all operative procedures in leukemia particularly dangerous. Collier has gathered 16 cases of splenectomy. Since then the number has been very much increased. A number of splenectomies in leukemia terminated fatally from hemorrhage. (Compare the Section on Splenectomy, p. 672.)

[The treatment of leukemia by the *Röntgen ray* is still *sub judice*, but enough has been done in this line to warrant further trial. Long-continued treatment of the spleen, bones, and glandular masses by the *x*-ray, each exposure being for a few minutes and not too frequently repeated, say two to three times a week, has been followed in quite a number of cases by unmistakable lessening of the size of the spleen and lymphatic glands. Of greater significance has been the change in the condition of the blood. Quantitative reduction in the number of white corpuscles frequently follows the application of the *x*-ray. The number of leukocytes may be reduced even to the normal. But in some cases there has been a qualitative improvement as well, and the mononuclear forms (myelocytes and lymphocytes) have gradually approached their normal percentage. Capps and Smith, from their study of a series of cases, find much encouragement, especially in the cases of chronic lymphatic leukemia. Pusey has had a remarkable result in a myeloid leukemia. And scattered reports are coming in from all quarters tending to show that the Röntgen ray has a remarkable effect in many cases, producing, at least, a transitory improvement that is never or only rarely seen in the natural course of the disease or under the treatment by arsenic. Too vigorous use of the ray is not advisable, both because it may cause a serious burn of the skin and because toxic symptoms, fever, etc., have been known to follow, suggesting a freeing of toxic substances—formed by breaking down of spleen tissue (?)—by the action of the ray.—Ed.]

TUMOR OF THE SPLEEN IN PSEUDOLEUKEMIA.

Pseudoleukemia is a chronic anemia leading to cachexia, in which, aside from relatively insignificant changes in the blood, nothing abnormal is found excepting a swelling of the lymph glands or the spleen, or both. The changes in the blood affect only the red blood-corpuscles and their hemoglobin, and produce a number of symptoms dependent on these lesions, particularly manifestations of the hemorrhagic diathesis.

Corresponding to leukemia we differentiate a splenic, a lymphatic, and a myelogenous form, depending on which of the blood-forming organs is particularly involved. Mixed forms between the first two are especially frequent. [See editor's note, p. 565.]

This disease has been given a great number of names, and this in itself shows how very obscure were, and still are, our conceptions in regard to its nature. Thus, it has been called Adenie of Trousseau, Hodgkin's disease, anemia splenica seu lymphatica, malignant lymphoma of Billroth, malignant lymphosarcoma (Langhans), cachexie sans leucémie, etc.

On postmortem a widespread cellular *hyperplasia* of the lymph glands and lymphatic follicles is found, usually combined with an enlargement of the spleen, numerous lymphoid nodules in the interstitial tissues of the liver, spleen, kidneys, and other organs; all changes corresponding exactly with those seen in leukemia.

Etiology.—The causes of this disease are unknown. We must consider different kinds of irritations exercising their effect for a long time in the region of the diseased glands, traumata affecting the spleen, attacks of intermittent fever, and possibly the existence of syphilis; scrofulosis, however, must be strictly excluded. Colonies of Bacterium coli have repeatedly been found in pseudoleukemic spleens, but this finding has little significance. Men are more frequently affected than women; the disease is found not infrequently in children.

Pathologic Anatomy.—The *spleen* in pseudoleukemia is characterized, from the pathologico-anatomic point of view, by a simple *hyperplasia*. The organ is always enlarged, usually to twice its normal size, and occasionally so much so that it reaches as far as the umbilicus and dips into the pelvis. On cross-section the parenchyma is of moderately solid, somewhat marrowy, consistence; the cut surface is smooth and marbled, and the follicles are usually light gray, numerous, and distinctly outlined against a uniformly red pulp. The capsule is usually somewhat thickened; the margins of the spleen rounded and smooth. On microscopic examination all the signs of a simple hyperplasia are observed.

Of the microscopic findings in the spleen of pseudo-leukemia, Langhans[1] reports as follows: "The spleen was firm and much enlarged, 17 cm. long, 14 cm. wide, 6 cm. thick; the outer surface and the cut surface uneven as a result of numerous prominent white or yellowish-white, very solid nodules that are fairly transparent; of these the smallest ones are miliary; the largest ones 5 mm. in diameter, round, drawn out, ramified here and there, occasionally confluent, and of either a flattened, wide, polyhedric-shape, or, near the periphery, more wedge-shaped. They are packed closely together and simulate in their arrangement a number of follicles; like these they are penetrated by blood-vessels that can be seen on their transverse and longitudinal sections as punctiform or linear depressions that are either simple or ramified. Between them are seen narrow or broad bands of tough, reddish-brown pulp; here and there trabeculæ are visible within this substance. Under the microscope the peculiar relation of the nodules mentioned above to the blood-vessels is still more clearly distinguishable. Within the nodules a finely granular or homogeneous, shiny matrix is seen, particularly in the larger nodules, and here, again, most distinctly in the peripheral layers. This matrix never shows a fibrous structure; lymph corpuscles are arranged in a reticular manner within it. Here and there numerous polynuclear and even giant cells can be seen. The larger vessels have very thick adventitias; small vessels are present in scanty numbers; the pulp itself looks normal, much compressed, and contains brownish-red pigment in those portions that are in immediate contact with the nodules."

On microscopic examination of the spleen nothing is found that is different from an ordinary hyperplasia. The lymphoid nodules found within the spleen, the liver, and the kidneys are characteristic for

[1] *Virchow's Archiv*, vol. liv.

pseudoleukemia as well as for leukemia; they are either in groups or diffused all through the organ, and are found chiefly in the newly formed connective tissue, within the liver around the acini, within the kidneys in the interstitial tissue, and within the spleen near the periphery of the follicles.

The follicles of the spleen are considerably enlarged, hard and stiff, and reveal under the microscope an increase of the lymph cells and a thickening of their reticulum, sometimes even true connective-tissue formation. Their surrounding tissues are not involved, although they may become slightly affected by the pressure exercised by the new tissue.

The involvement of the *lymphatic glands* also consists in a cellular hyperplasia of considerable dimensions, so that these organs may swell considerably, forming large tumors that may be either soft or hard. Their cut surface looks white, whitish gray, or grayish red; the glands are usually grouped in the form of grape-shaped masses. On microscopic examination a profuse proliferation and increase of the lymph cells is found, so that the reticulum of the glands seems to be filled by these cellular elements. In the so-called hard forms the connective-tissue development and the thickening of the reticulum are particularly conspicuous, although, of course, an increase in the number of lymph cells is also seen. The writer does not think that it is possible accurately to differentiate the hard and soft forms. Occasionally the new formation extends through the capsule of the gland and involves the surrounding tissues.

Hyperplastic processes are also seen in the *tonsils* and in the *lymphatic apparatus of the intestine*. On bacteriologic examination of a pseudoleukemic spleen numerous colonies of Bacterium coli have been found, just as in leukemia (Kelsch and Vaillard, Fermi, Gabbi, and Barbacci). Serious objections, however, have been brought forward against the assumption that these bacteria have anything whatever to do with the etiology of the disease.

Symptomatology.—No description, however detailed, can give an adequate idea of the varying symptom-complex of the course of this disease. The fundamental fact in regard to the nature of this disease is that it originates from the spleen and lymph glands, or from both; if we deviate from this point of view we must refrain altogether from characterizing this affection as a special disease.

1. In the pure forms of *splenic pseudoleukemia*, in addition to the cachexia, there is found a hard tumor of the spleen, which may extend into the pelvis and may be accompanied by perisplenitis. In comparison to this tumor of the spleen, which is most conspicuous and seems to characterize the whole picture of the disease, the swellings of the glands are relegated to the background. Some authors have described this form under the name of splenic anemia and have attempted to establish it as a special disease; this, however, is not justifiable, for it is left to the option of the observer whether he wishes to characterize the disease as an anemia with the simultaneous development of a large

tumor of the spleen, or as a severe form of essential anemia with secondary enlargement of the spleen. [See editor's note, p. 598.]

2. The purely *lymphatic form of pseudoleukemia* is distinguished by the swelling of the lymph glands without any tendency on the part of these organs to suppurate or to undergo cheesy degeneration. Wherever suppuration does occur, it is an accidental complication. According to the number of the cellular elements or the thickening of the reticulum, we distinguish a soft and a hard form of lymphoma. The swelling first appears in the glands of the neck, then in the supraclavicular and axillary glands, finally in the inguinal glands; the bronchial, mesenteric, and retroperitoneal glands are not involved until later. No distinct sequel of involvement, however, is observed, and it is not necessary that bilateral groups of glands should be involved at the same time. Occasionally a rise of temperature accompanies the swelling of the glands, but this may be absent in the later course of the disease; the enlargement of the glands causes no pain. In this form the spleen is not necessarily involved; as a rule, it is, however, although the increase in its volume is usually slight. Gowers found the spleen normal in only 17 of 97 cases of lymphatic pseudoleukemia.

We must include in this disease those gland tumors that we call *malignant lymphoma* (lymphadenoma, lymphosarcoma of Langhans). Winiwarter, Billroth, and others differentiate from the ordinary tumors of the glands those rapidly growing forms of multiple tumors primarily involving the glands of a certain region of the body, usually of the neck; then rapidly involving neighboring glands, the lymphatic glands of the axilla and the inguinal region; then those of the large body cavities, as the bronchial and abdominal glands, and, finally, forming metastases in internal organs. Their localization always follows the course of the lymph channels. Even the largest tumors show no tendency to exceed the limits of the organ itself, so that they do not by direct extension involve neighboring tissues nor the nearest lymph glands. The involvement of the whole lymph apparatus of a certain region of the body causes swellings of enormous size, within which, however, the single groups of glands can be palpated. The skin over these tumors is freely movable and shows no inflammatory changes. The swellings that these different groups of glands form do not become adherent to the surrounding tissues nor with each other; pain on pressure is not elicited.

Penzoldt and Fleischer described a case in which they saw the transition of a malignant lymphoma into lymphatic leukemia [others have described similar cases].

Lymphosarcomatosis as described by Virchow must be strictly differentiated from malignant lymphoma, and the general anemia observed in the former disease is related to it in the same manner as in the other forms of sarcoma of equal malignancy. Sarcoma of the lymph glands, which may resemble very much the lymphomata under discussion, is distinguished from them by its tendency to heteroplasia and

adhesion of the different tumors with one another; also by a variety of other inflammatory symptoms.

3. In the pure form of *myelogenous pseudoleukemia* we should expect the same involvement of the bone-marrow as in the corresponding form of leukemia. The writer has good reason to believe that such cases have been observed; furthermore, it would hardly be possible to diagnose them positively during life. In those cases of pseudoleukemia that he has been able to dissect he found the bone-marrow changed in the same manner as in pernicious anemia.

The *general symptoms* are those of anemia (vertigo, fainting spells, dyspnea, edema), the hemorrhagic diathesis, fever of no particular type, palpitation, small pulse, dyspnea, lack of appetite, dyspepsia, transient or persistent attacks of diarrhea, swelling of the liver, edema, even general anasarca, sweats, and occasionally pain in various parts of the body, the exact origin of which cannot be explained. Thus, for instance, very violent pains starting from the abdomen and radiating to the extremities are noticed; repeatedly, enlarged retroperitoneal glands have been found pressing upon the nerves leading to the legs, and have been considered the cause of these pains; occasionally the swollen glands situated in the inguinal region may produce congestive edema of the legs. The pressure of lymphatic tumors may produce compression symptoms in other parts of the body; thus, dysphagia, difficulty in breathing, certain heart symptoms from pressure on the vagus, and icterus or ascites through compression of the bile ducts or portal vein by the abdominal glands. The tonsils are also occasionally swollen, and at times the circumvallate glands on the dorsum of the tongue.

Very persistent and violent bronchial catarrhs and tuberculosis must be mentioned as complications; further, the development of lymphomata and sarcomata in the skin.

The Blood.—Anemia of high degree without marked increase in the number of white blood-corpuscles is the most significant symptom of this disease; occasionally a distinct leukocytosis—that is, an increase of the polynuclear form of leukocytes only—is seen. [The anemia of pseudoleukemia is not necessarily of high grade. Often for a long time the decrease in the red corpuscles and in the hemoglobin is only moderate. Occasionally a slight lymphocytosis is present.—Ed.] The number of red blood-corpuscles is diminished, the hemoglobin reduced considerably—more than would correspond to the decrease in the number of erythrocytes. A rapid reduction of the hemoglobin is occasionally seen; thus, in 1 case the writer saw the percentage of hemoglobin drop from 85 to 40 per cent. in one week; at the same time neither hemoglobinuria nor recognizable hemoglobinemia was present. Poikilocytes and microcytes occur regularly; macrocytes, however, are absent. Normoblasts (the small nucleated red blood-corpuscles) are rarely absent, at least in small numbers; gigantoblasts, however, are only seen if the anemia be very severe. The number of eosinophile cells is not increased very much, nor are the cells containing blood-corpuscles present in great numbers in the blood; in the spleen, however, they are found in large

quantities. The blood-plaques, according to the writer's examination, are almost constantly increased. In contradistinction to leukemia, Charcot's crystals are never found in the blood of pseudoleukemia.

Within recent years different authors (Pel and Ebstein) have described cases of pseudoleukemia with peculiar attacks of recurrent fever and have called these conditions *infectious pseudoleukemia* or *chronic recurrent fever*. Such cases are characterized by an increasing anemia and cachexia, periodic fever, swelling of the spleen, the liver, the mesenteric and retroperitoneal glands, occasionally icterus, the diazo-reaction, and a decrease in the quantity of hemoglobin. During the course of the disease the patients are seized with from 7 to 10 fever paroxysms, occasionally lasting five, seven, eleven, and even twenty-two days. Between the fever periods are intervals free from abnormal temperature that may also last seven, nine, thirteen days or more. The single fever periods, which may be ushered in by chills, are of a pronounced, remittent, regularly ascending and descending type. During the course of the fever the spleen increases in size, and decreases again during the time of apyrexia. Occasionally the glands situated near the surface of the body may become enlarged; chiefly, however, the bronchial, retroperitoneal, and mesenteric lymph glands are the ones affected. Bacteriologic examination and culture experiments on different media have always yielded negative results, both in these cases and in the ordinary cases of pseudoleukemia that run their course without fever.

Among the older authors, Canstatt, Sharlau, and Führer have described an enlargement of the *spleen in chlorosis*. These authors describe the spleen in such cases as considerably enlarged, pale red, very juicy on transverse section, containing much parenchyma, fragile, and granular. Chvostek [1] found enlargement of the spleen in 21 of 56 cases of chlorosis that he observed in the medical wards in Vienna. In one series of cases a uniform reduction in the size of the tumor could be observed running parallel with the cessation of the other symptoms of the disease, and the amelioration of the condition of the blood. If every other etiologic factor that could produce an enlargement of the spleen can be ruled out, then, possibly, we are justified in recognizing and assuming such a connection; in this case the tumor would not be an accidental finding, but be in relation to the general disease. Such cases of chlorosis with palpable tumors of the spleen, either hard or soft, form a transition to the cases of splenic pseudoleukemia (especially in children) or splenic anemia. In the anemic cases of enlargement of the spleen the red blood-corpuscles were reduced to 1,900,000 in a c.mm., the hemoglobin was reduced considerably, as low as 20 to 56 per cent. (Fleischl), the color index fluctuated between 0.44 and 0.77, and the leukocytes were frequently increased, but their number dropped to normal as soon as the tumor regained its normal dimensions (neutrophile leukocytosis).

The prognosis is not influenced by the presence of a splenic tumor. A case of Chvostek's demonstrates that occasionally very severe anemias

[1] *Wien. klin. Woch.*, 1893.

with enormous tumors of the spleen, presenting a picture of splenic anemia, can recover in a relatively short time (two months). In this patient the spleen extended 14.5 cm. below the costal arch, the glands were not much enlarged, there were only 1, 360,000 red blood-corpuscles and 4000 white; their proportion was as 340 : 1; hemoglobin 20 per cent.; no rouleau formation. Two months later the spleen was measurably decreased and the condition much better; there were 4,500,000 red blood-corpuscles, 4600 white cells; the proportion of white to red was as 1 : 944; hemoglobin 75 per cent.; of 100 leukocytes, polynuclear 75 per cent., lymphocytes 20 per cent., transition forms 4 per cent., eosinophiles 1 per cent.

Diagnosis.—In making a diagnosis of pseudoleukemia we must always consider that in adults, and still more frequently in children, chronic tumors of the spleen of considerable size may be found, even in the absence of any recognizable etiologic factors. As, accordingly, in children considerable pallor is observed, and at the same time no positive decisions can be arrived at from the examination of the blood, it is frequently difficult to differentiate pseudoleukemia from a simple anemia with swelling of the spleen. There are cases that may be further confusing because of the presence of enlarged cervical or supraclavicular glands. These are at times seen after diarrheas or vomiting that has lasted for several weeks. As in a symptom-complex of this kind leukocytosis is very likely to develop, a transition of pseudoleukemia to real leukemia has actually been occasionally observed. It is often exceedingly difficult to correctly interpret these cases and to make a prognosis. It is well to remember that pseudoleukemia is a disease of a progressive character. This is manifested very clearly in the manner in which the lymph glands become involved; if these organs have once become swollen they rarely recede; on the contrary, as a rule, they continue to enlarge, while at the same time neighboring glands, or glands that are situated at a distance, begin to participate in the disease process. They never show a tendency to amalgamate with one another, to suppurate, or to undergo cheesy degeneration; they seem to remain isolated, and can usually be palpated in all their dimensions. The skin over these glands remains intact and does not become adherent to them and abscess formation does not occur. If all these factors are considered, the lymphatic form of pseudoleukemia can usually be recognized.

It is much more difficult to arrive at a conclusion in regard to the cases described above, for here we must decide whether we are simply dealing with a very severe form of simple anemia that is capable of retrogression and cure, or with a case of splenic pseudoleukemia. In instances of this kind the diagnosis will frequently have to remain obscure, and we shall have to await further developments before rendering a decision. The constant progression of the disease and the increasing cachexia and edema will finally throw light upon the subject.

It is hardly possible to confound lymphatic pseudoleukemia with other diseases [see editor's note, p. 598]. In the tuberculous form

enlarged lymph glands are usually multiple and show a tendency to suppuration and cheesy degeneration. The same applies to scrofulous glands, which are, moreover, usually found in the region of the neck. In very difficult and important cases glands have been extirpated for purposes of diagnosis, and the microscopic examination has usually revealed the true condition. If suppuration, cheesy degeneration, and calcification are found in the center of the gland, they should be taken as evidences of tuberculosis and scrofulosis. Cellular hyperplasia, on the other hand, with or without thickening of the reticulum, speaks in favor of pseudoleukemia.

The following case may show how difficult, under certain circumstances, may be the differential diagnosis between splenic lymphatic pseudoleukemia and lymphosarcoma of the spleen. A boy of fifteen, otherwise healthy, developed a tumor of the left upper region of the neck that, on extirpation, was found to be a lymphoma. The patient recovered very well from the operation. Half a year later pain, increasing in intensity, was complained of in the left abdominal region, the general health at the same time remaining unimpaired. The spleen gradually enlarged and ultimately formed a tumor of considerable size below the left costal arch; it was very freely movable, and could be clearly diagnosed as the spleen from its position, outline, and consistence. A laparotomy was performed, and a tumor weighing 2 kg. removed. On examination it was found that this tumor had its origin in the spleen, and contained a neoplasm that was a sarcoma or lymphosarcoma. Numerous glandular metastases were found at the hilum. Changes in the blood were not present before the operation, nor were they found afterward. The patient recovered nicely from this second operation.

Prognosis.—The disease runs a chronic course and may last for half a year to a year or more, uninfluenced by treatment. Occasionally an acute and a subacute course have been described. The majority of cases terminate fatally; here and there, however, a case may recover or improve. Recurrences may make their appearance at any time. The lymphatic form probably yields the most favorable prognosis.

Treatment.—In regard to dietetic treatment, the writer must refer to the section on Treatment of Leukemia. *Arsenic* is the most recommended of all drugs, thanks to the observations published by Winiwarter, Billroth, and others. The drug may be administered internally or subcutaneously, or injected directly into the parenchyma of the glands. The action of the drug in external use is dynamic, and, if much of it be employed, inflammatory and irritating. The fact that pathologic cells can resist the irritating action of arsenic less than normal cells is of fundamental importance for therapy. We can conclude from this observation that even the internal administration of arsenic, owing to its dynamic action, will not interfere with normal cells, but will seriously affect the abnormal ones and gradually lead to their destruction; therefore, the internal administration of arsenic should have considerable therapeutic value.

Frequently internal administration has been combined, with good results, with parenchymatous injections. The symptoms of intoxication (burning of the throat, colic, diarrheas, itching, eruptions, and others) appear much sooner on internal use. Particularly in cachectic patients the appearance of these symptoms may force us to abandon the arsenic treatment.

It is immaterial for the general result where the drug is injected. The tumors of the body are affected in the same way by arsenic whether it be injected directly into them or into some other part of the body. The former plan, however, has this advantage: larger quantities of arsenic reach the affected cell, and thus produce quicker resolution and resorption.

The influence of arsenic on the tumors is evidenced by the reduction of swelling. This may be observed after a very few days. During the first weeks of the treatment the resorption of the tumors occurs with wonderful rapidity; later, the process of resorption is slower. In the course of six to eight weeks tumors as large as a hen's egg may become as small as a cherry; small ones decreasing in proportion. The glands of the neck are the first to decrease in size, sometimes in a very striking manner; this is probably due to the fact that they are intensely affected by the arsenic. Simultaneously with the decrease in the size of these glands the other lymph glands, particularly the internal—for instance, the retroperitoneal, bronchial, etc.—begin to undergo subinvolution. Finally the hypertrophied tonsils also decrease in size. No change is manifest during this process, excepting that the glands seem to grow harder; they still remain separated and independent of one another; if anything, this characteristic is more pronounced, and as this is an important differential point between this form of tumor and sarcoma, the administration of arsenic does not confuse the diagnosis. In cases where the spleen and liver are enlarged they also decrease in size.

Sometimes when arsenic is used in the treatment of lymphomata, etc., the cachexia may increase, even though at the same time subjective symptoms are ameliorated and the appetite improved. The patients look worse, grow thinner, their skin seems to wilt and to be colored an ashy, grayish yellow; they do not recover from this condition until the administration of arsenic is interrupted. In connection with this symptom-complex, and sometimes alone, a rise of the body temperature is observed; this occurs most frequently after injections of arsenic into the parenchyma, but occasionally also after its internal use, either after the first four or five days or sometimes not for two or three weeks. The fever is either of an intermittent type (quotidian) or continuous, with evening exacerbations (up to 39.5° C.) and morning remissions. It is frequently necessary to interrupt the course of arsenic if, on beginning the treatment, fever occurs. This peculiar temperature does not always recede immediately after the administration of arsenic is stopped, but may occasionally continue for a long time—two weeks and more—afterward.

It is a very important fact that sometimes even the internal admin-

istration of Fowler's solution may produce inflammatory changes in the glandular swellings. Where the remedy is acting successfully, the tumors increase in hardness and solidity in proportion to their diminution in size. Inflammation, suppuration, and abscess formation may occasionally occur.

In general, arsenic exercises a favorable influence on general health and nutrition, stimulates the appetite, and frequently improves digestion; the force of the heart is also often improved, as seen by the character of the pulse. Improvement in the mood of the patient, in his energy, and in his confidence in himself are very manifest. If diarrhea supervene and it become necessary to stop the remedy, opiates are indicated; 5 drops of the tincture act as a sedative. Arsenic may, through meteorism, pressure on the stomach and diaphragm, produce a feeling of fear, dyspnea, and collapse; occasionally also a feeling of dulness in the head, and vertigo. Here, too, opiates relieve.

We may say, therefore, that arsenic is a valuable drug in the treatment of swollen lymph glands and tumors of the spleen in pseudoleukemia, and particularly in malignant lymphomata. The remedy is essentially without danger, but it does not protect from relapses. It is, however, a sovereign remedy in keeping the disease and the relapses under control.

The action of the drug is much less favorable in the treatment of isolated tumor of the spleen (splenic anemia) and lymphosarcoma (Virchow), but we should always use it even in these conditions, as, after all, it is our most powerful remedy.

Parenchymatous injections of arsenic have been attempted into the tissue of the spleen; they were administered in the same manner as into the lymph glands. The results were occasionally good and the size of the organ seemed to decrease. Injections of quinin and of carbolic acid have also been tried with some success. It is a good plan to precede the injections by a course of remedies that decrease the quantity of blood within the spleen by action upon its contractile elements; a good method to produce this result is to place an ice-bag over the region of the spleen for several hours.

Swelling of the glands seems to decrease after the internal administration of phosphorus and antimony. The former remedy is best administered in the form of the oil of phosphorus, but not in the concentrations described in the German Pharmacopeia of the year 1872. Here it is ordered to dissolve 1 part of phosphorus in 80 parts of almond oil in a well-closed glass vessel, to use heat and frequent shaking, and ultimately to decant the supernatant fluid from the undissolved residue. However, as the phosphorus is not completely dissolved in this quantity of almond oil, and has a tendency to precipitate, Soltmann recommends to mix the phosphorus in a glass flask with 500 parts of almond oil, and to heat the mixture on a water bath until all the phosphorus be dissolved. Five parts of the oil then contain 1 cgm. of phosphorus, and when mixed with 95 gm. of cod-liver oil makes the preparation known as the oleum jecoris aselli phosphoratum (phosphorated cod-liver oil).

Neither phosphorus nor antimony has been tested for so long a time as arsenic, and it is necessary before adopting them to gain more experience in regard to their action. Wunderlich recommends *iodid of potash*, and, for an after-cure, iron preparations and iron mudbaths.

The writer shall finally, before terminating the discussion on the remedial treatment of this disease, mention one other remedy that has, at least transitorily, given very good results both in leukemia and the disease under discussion, although it did not prevent the fatal issue; he refers to berberinum vulf. According to Vehsemeyer, berberis vulgaris is a powerful stomachic; the appetite increases, and the sluggishness of the intestinal tract is improved with its administration; doses of 1 gm. produce daily free movements of normal consistence. The favorable effect of this drug on the general condition of the patient is very striking. In regard to tumors of the spleen, the arrest of its development is apparent; occasionally, even, it produces a decrease in the size of the tumor that can only be explained by the action of the drug on the muscle fibers of the blood-vessels. The drug must be administered in doses that relieve the constipation without at the same time producing diarrhea.

[From the foregoing, it would be seen that our notions concerning the nature of pseudoleukemia are extremely obscure and misty. To-day a pure lymphatic form and a pure splenic form of the disease are regarded either as not existing or as extremely rare. Most of the cases previously classed as splenic pseudoleukemias would now be regarded as splenic anemias (see p. 600). Real pseudoleukemia is rather of the mixed type or is ordinary Hodgkin's disease. This should, however, be differentiated from malignant lymphoma and lymphosarcoma, and particularly from sarcoma with metastasis in the lymph glands where a primary growth is found in some other organ. In the true neoplasm the tendency for the growth to break through the capsule of the gland is clearly seen, as well as the involvement of other structures than the glands in metastasis.

A question of great interest has recently been raised as to the *tuberculous* nature of the whole disease process that is spoken of as pseudoleukemia. The point raised is not entirely new. Cases had been reported in which tuberculosis of the glands simulated Hodgkin's disease, and some contended that the oftener cases were examined the greater the frequency with which tuberculosis was found to be present in the glands. The grounds on which Sternberg[1] and others contend for the tuberculous nature of the process are the fact that histologic evidence of tuberculosis is found in many cases; in others tubercle bacilli are seen in sections, and in still others inoculation experiments show the tuberculous nature of the process. Clinically and macroscopically these have been cases that were passed as Hodgkin's disease. The opponents of this theory contend that some cases of tuberculosis may simulate Hodgkin's disease; in other cases a true Hodgkin's disease has been secondarily infected with

[1] *Zeit. f. Heilk.*, 1898, vol. xix.; Crowder, *N. Y. Med. Jour.*, Sept. 15 and 22, 1900, gives a full bibliography with the careful study of a case.

tuberculosis. But they still contend that there is a distinct disease that should be called Hodgkin's disease or pseudoleukemia, differing in the anatomic and microscopic structure from true tuberculosis. Dorothy Reed[1] has recently gone over the entire subject, and believes that the microscopic diagnosis can be made by the detection in the glands of large numbers of eosinophile cells, of peculiar large giant cells that differ from those of tuberculosis, as well as by the proliferation of endothelial and reticular cells and of connective tissue, the latter leading to fibrosis. It is possible that during life the tuberculin reaction and the microscopic examination of a gland cut out for this purpose would help materially in establishing a diagnosis.

In some cases of pseudoleukemia there is a remarkable involvement of the lymph structures of the alimentary tract. Wells and Mayer[2] have collected several cases of this sort, and refer to the condition as pseudoleukemia gastro-enterica. They call attention to the fact that if the lymph structures of the alimentary tract are involved they are apt to be very *extensively* involved, seeming to bear the brunt of the attack. In these cases there is certainly no anatomic resemblance to tuberculosis. Clinically they cannot be differentiated from ordinary Hodgkin's disease. One of the writer's cases of this sort, Case VI. in Wells' series, was a typical case of Hodgkin's disease. The patient died from exhaustion and dyspnea, the latter due to pressure of the enormous masses in the chest. At autopsy enormous tumor-like masses were found in the neck and mediastinum. The nasopharynx was full, and the lymphatic nodules, Peyer's patches and solitary follicles of the entire alimentary tract, even of the esophagus, were markedly enlarged.

Arsenic, as Litten says, is the best drug known in the treatment of pseudoleukemia, although the writer's own personal experience has hardly been as favorable as his. It is generally sufficient to give the drug by the mouth, and not necessary to give it subcutaneously. One must dissent a little from Litten's statement that arsenic will harm only pathologic tissue, and that it is harmless to normal cells. It is clearly proved that arsenic may produce a peripheral neuritis, and in some instances changes are probably present in the spinal cord, as evidenced by increase of the knee-jerks, spastic gait, etc.

What has been said regarding the treatment of leukemia by *x*-ray can be repeated here. Senn was one of the first to report upon the favorable effects of the *x*-ray in the treatment of pseudoleukemia.

A very remarkable effect is occasionally seen when some intercurrent infection, particularly when infection with the streptococcus, occurs during the course of pseudoleukemia. In the writer's case just referred to intercurrent erysipelas caused a most remarkable diminution in the size of all the enlarged glands, yet recurrence occurred. It was this phenomenon which led Coley as well as others to advocate the injection of erysipelas toxin in sarcoma as well as in pseudoleukemia. The effect, however, is rarely beneficial.—Ed.]

[1] *Johns Hopkins Hosp. Rep.*, vol. x., 1902.
[2] "Pseudoleukemia Gastro-enterica," *Am. Jour. Med. Sci.*, Nov., 1904.

[SPLENIC ANEMIA.

A disease that bids fair to have distinct standing as a clinical entity is splenic anemia. The term was first used by Griesinger, in the fifties; but it was not until Banti, in 1884, and in several communications after this, called particular attention to the condition that it was generally recognized.

Banti,[1] in 1898, described under the head of splenomegaly with cirrhosis of the liver a condition that he believed could be divided clinically into three stages: The first was the stage of splenic enlargement with anemia; the second stage a transitional one; the third the stage of ascites with cirrhosis of the liver. The first stage, he declared, could last for many years; in some cases even for eleven years. The latter two ran a much more rapid course, the termination, unless there was early operative interference, being uniformly fatal. The cause of the condition he regarded as the production of some toxin by the enlarged spleen. This resulted in anemia. The toxic substance, whatever it was, in its passage through the splenic and portal veins to the liver induced an intimal sclerosis or atheromatosis, sometimes even with calcareous deposits. If the disease lasted a long time the toxemia finally resulted in a cirrhotic condition of the liver, resembling microscopically and macroscopically multilobular atrophic cirrhosis. The anatomic change in the spleen consisted in an increase in size, a thickening of the capsule, frequently with numerous adhesions, a hyaline degeneration with marked fibrosis of the Malpighian follicles. This was most marked in the immediate neighborhood of the artery of the follicle. In the walls of the venous sinuses were peculiar large cells with large nuclei, often multiple. Everywhere the trabecular structure was enlarged and thickened. Banti recognized the similarity of his disease to splenic anemia, but regarded the two diseases as probably distinct and separate. He was unable to determine any bacteriologic influence, though he regarded a bacteriologic etiology as highly probable. Splenectomy was advocated, as 2 of 3 cases operated upon had shown improvement; and by splenectomy he believed he had removed the original source of the trouble.

Several other communications since then have reported isolated cases more or less in detail. We would mention in particular the case in this country reported by Sippy,[2] where a full résumé of the previous literature on the subject is given, as well as the careful clinical and anatomic study of a typical case. Two contributions in particular deserve mention, because they clarify the whole subject very markedly. They were the contributions of Senator and of Osler. Senator,[3] in 1901, reviewed Banti's articles and confirmed Banti's statement as to the clinical phenomena of splenomegaly with cirrhosis. Senator, however, was inclined to believe that splenic anemia and Banti's disease were closely related. To the symptom-complex as described by Banti, Senator added two features, the one the frequent hemorrhages from the stomach and bowels,

[1] *Ziegler's Beiträge*, xxiv. [2] *Am. Jour. Med. Sci.*, Nov., 1899.
[3] *Berlin. klin. Woch.*, 1901, No. 146.

as well as in some instances a tendency to the hemorrhagic diathesis, as shown by petechiæ, retinal hemorrhages, etc. He also called particular attention to the fact that the blood-changes were those of a secondary anemia with no increase in the leukocytes, except occasionally a slight relative lymphocytosis. In many cases there was distinct leukopenia. He further called attention to the fact that ascites in splenic anemia was not necessarily due to involvement of the liver in cirrhosis. It might be due to pressure of the enlarged spleen, to obstruction of the lymph circulation, or to advanced anemia, the so-called marantic or hydremic edema.

Osler[1] still further elaborated the clinical differentiation of splenic anemia as a distinct entity. The characteristics, as determined by Osler from a study of his own cases, those already reported in the literature, and a number of cases which were detailed to him by his colleagues in the Association of American Physicians, were as follows:

First, chronicity. The disease oftentimes lasting ten or fifteen years.

Second, splenomegaly. The spleen being greatly enlarged, and in not a few instances distinctly recognized as the first clinical manifestation of anything abnormal—that is, it was apparently primary.

Third, hematemesis. This was of such frequent occurrence as to be a most valuable clinical manifestation. It was to be explained possibly by diapedesis, by ulcer of the mucous membrane, varicose esophageal veins, or by obstruction in the vasa brevia that empties into the splenic veins. In the latter there might be a kink, producing great engorgement.

Fourth, anemia of the chlorotic type. The red blood-corpuscles averaging about 3,000,000, the white blood-corpuscles 4500, hemoglobin 47 per cent. Note the leukopenia.

Fifth. In some cases a pigmentation, a melanoderma.

Sixth. Enlarged liver with ascites, sometimes icterus.

From this review it will be seen that there seems to be a distinct disease, to be separated from leukemia, on the one hand, with its great increase in the white cells, and from pernicious anemia on the other. In the latter disease the spleen is not primarily enlarged and very rarely assumes the enormous size seen in splenic anemia; also the blood-findings are different, the reduction being more in the red blood-corpuscles than in the hemoglobin, and, too, hematemesis and melena are far less frequent than in splenic anemia. Undoubtedly many cases were previously reported under the head of splenic pseudoleukemia, and if there is such a condition, the differentiation would certainly be extremely difficult.

Etiology.—Little is known regarding the etiology of the condition. Preceding malaria has been recognized in some instances. That there is a family tendency to the disease is clearly seen in several cases reported; as, for instance, the cases of Brill.[2] In New York, in 1904, Libman exhibited a spleen obtained from a patient in whose family several other

[1] *Trans. Assoc. Am. Phys.*, xvii., 1902. [2] *Am. Jour. Med. Sci.*, April, 1901.

children had the same disease. That the enlargement of the spleen is due to some toxin is generally regarded as probable. The origin of this toxin is wholly unknown. It seems to produce irritation and fibrosis of the spleen, is hemolytic in its action, and if the action is long-continued it may lead ultimately to cirrhosis of the liver, producing, therefore, Banti's symptom-complex. Dock and Warthin[1] found in 2 cases calcareous evidence of preceding portal thrombosis with resulting narrowing of the vein. They raise the question as to the causal or adjuvant action of passive congestion in the production of the enlarged spleen. In this connection Banti's observation of atheromatosis of the splenic and portal veins, at times even calcareous plaques, is interesting. The progress of the disease would seem to be, in protracted cases, through the several stages of splenomegaly, anemia, and cirrhosis.

While this is the view that is held by Osler, at least as a temporary working view, there are others who feel that under the head of splenic anemia are included, perhaps, several conditions. The French particularly have described primitive splenomegaly, and in some cases the anatomic examination of the spleen has shown an unusual number of the large cells described by Banti. These have been collected in masses, producing what is regarded by many as distinct tumor formations, so that some of the cases described as beginning splenic anemia are regarded by some as primary tumors—endotheliomata of the spleen.

Stengel has described several cases which illustrate, he thinks, the confusion that still exists in the differentiation of the different forms of anemia with enlarged spleen.

The **prognosis** is uniformly unfavorable, although the condition is not incompatible with a fair degree of health and several years of life. Death occurs from progressive emaciation and exhaustion, from the extreme degree of anemia, from acute anemia the result of repeated hemorrhages, from cirrhosis of the liver, or from intercurrent affections.

In the **treatment** of the disease ordinary rules of hygiene should be observed. Medicinally, the only remedy to be recommended, aside from symptomatic and tonic drugs, is arsenic. This can be given in the same way that it is given in pernicious anemia and in Hodgkin's disease—that is, in gradually increasing doses. Under its administration the spleen has been seen to reduce in size and the blood to improve in quality. The *x*-ray as a means of treatment is yet in the experimental stage. From the improvement that has been noted in cases of leukemia and Hodgkin's disease, it would seem as though some hope might be held out in splenic anemia. That extirpation of the spleen is followed by improvement has been seen in the reports from several observers. Harris and Herzog[2] have dealt with this subject particularly. Splenectomy should be performed in all cases where the blood is much depleted in quality or where hemorrhages have begun. It should be performed before cirrhosis sets in. The operation in itself is serious. The hemorrhage, where adhesions are numerous, is oftentimes the cause of death on the table. It is wise, therefore, for the surgeon who goes into the

[1] *Am. Jour. Med. Sci.*, Jan., 1904. [2] *Ann. of Surg.*, July, 1901.

abdominal cavity in cases of splenic anemia to go in with a distinct understanding that if the mechanical difficulties in the shape of vascular adhesions are too great the operation must be given up. Where the operation is successful, after a period of impoverishment of the blood with perhaps an increase in the white cells, the blood-condition gradually improves, and it may approach or reach the normal. Some compensatory hypertrophy of the lymph glands and hemolymph nodes generally occurs. The patients are symptomatically, at least, much improved.

While there is still very much to be learned concerning splenic anemia, and while it is possible that under this head there are now described conditions that etiologically are different, it must still be recognized that there is a disease that has the above-mentioned symptoms, and until the cause is definitely known, no better name for it can be devised than the one advocated by Senator and Osler—splenic anemia.—ED.]

[CHRONIC CYANOSIS WITH POLYCYTHEMIA AND ENLARGED SPLEEN.

This condition, characterized by cyanosis, enlargement of the spleen, and polycythemia, was first described in America by Cabot,[1] who worked in conjunction with F. C. Shattuck. Some cases of a similar character were described by French writers. Osler[2] has contributed an interesting review of the subject. Weintraud[3] has also written upon the subject.

The clinical manifestations are:

First, the *chronicity* of the disease. In many cases the symptoms have lasted for many years.

Second, the *cyanosis*. Blueness of the face, lips, the mucous membranes, and of the skin of the entire body is described as very striking. Weintraud also calls attention to an unnatural redness of the vocal cords.

Third, there is a condition of true *plethora*. Osler gives this the name polycythemia. Weintraud speaks of it as polyglobuly. The number of red blood-corpuscles to the cubic millimeter has been found to vary from 7,000,000 to 12,000,000. Rather remarkable variations in the number recorded on different days are to be noted. The condition apparently does not depend on the reduction of the amount of blood-plasma. The red blood-corpuscles are not larger than normal, as in congenital heart disease, but are said by Weintraud and Vaquez to be normal in size, or even smaller than normal. It is to be remembered that Reinert said, judging from measurements, it would be impossible for more than 8,872,000 red blood-corpuscles to be packed in 1 c.mm. The specific gravity of the blood is increased, and the hemoglobin in most cases varies between 100 and 120 per cent.

[1] *Boston Med. and Surg. Jour.*, Dec. 7, 1899, and March 15, 1900.
[2] *Trans. Assoc. Am. Phys.*, xviii., 1903; also *Am. Jour. Med. Sci.*, Aug., 1903.
[3] *Zeits. f. klin. Med.*, vol. lv., pp. 91–129.

Fourth. The *spleen* has been found enlarged, sometimes being just palpable; in other cases extending quite a distance below the costal arch.

Fifth. *Albuminuria* and a small number of casts have been an almost constant finding. Among the less constant symptoms may be mentioned the occasional occurrence of leukocytosis, a tendency to hemorrhage, a slight enlargement of the liver, with in many instances headache, vertigo, nausea, and in some cases abdominal pain.

The cause of the disease is wholly unknown, although a very striking finding is that which is dwelt upon by Lefas.[1] In 3 cases that presented during life marked cyanosis, a primary tuberculosis of the spleen was found. Lefas is inclined to look upon this as a causative factor, although he is quoted by Weintraud as saying that the disease must extend to the liver before polycythemia results.

In the **diagnosis** the diseases that have to be considered particularly are valvular disease of the heart, especially congenital disease, myocarditis, adhesive pericarditis, emphysema, and other diseases of the lung and heart that might produce cyanosis. The chronic use also of coal-tar preparations, such as acetanilid, antipyrin, phenacetin, may give rise to marked cyanosis, in some cases with enlargement of the spleen. The history of the case, the examination of the urine to show the chemical reaction of these drugs, as well as the marked improvement on stopping the drug, will lead to a correct diagnosis. In most of these cases, too, there is in reality a smaller number of red blood-corpuscles than normal, and the corpuscles are apt to show degenerate and nucleated forms.

In the **treatment** little can be done except by way of general attention to hygiene. Overeating should be avoided, and the patient should be cautioned against too severe exertion in the same way one would caution a patient who is of the apoplectic habit. Nitrites have in some cases relieved the headaches. Venesection has also been followed by temporary improvement.—Ed.]

[CONGENITAL ICTERUS WITH SPLENOMEGALY.

Before the Eighteenth Congress for Internal Medicine, in 1900, Minkowski[2] described a case with autopsy where splenomegaly was associated with congenital icterus. Similar conditions had been described by Claude Wilson[3] as early as 1890. Recently Krannhals[4] has gone over the subject again, describing additional cases. The characteristics of this disease are that it is congenital and of the family type, several children in one family, and even through several generations, being affected. The jaundice is of varying degrees, and seems to be influenced temporarily by exposure to cold, by emotions, abuse of alcohol and food. With attacks of fever that are occasionally seen in these cases, the jaun-

[1] "La Tuburculose primitive de la rate. Contribution à l'étude de l'Hyperglobulie," *Thèse de Paris*, 1903. [2] *Abhandl. des XVIII. Cong. f. inn. Med.*, Wiesbaden, 1900.
[3] *Clin. Soc. Trans.*, xxiii., 1890.
[4] *Deutsch. Arch. f. klin. Med.*, vol. lxxxi., pp. 5 and 6.

dice is liable to deepen. The ordinary accompaniments of icterus, such as pruritus, urticaria, and occasionally xanthelasma, are seen. Some of the patients have been decidedly neurotic, showing the stigmata of neurasthenia or hysteria. Joint pains and inflammations have been occasionally seen. In some cases there is no complaint whatever upon the part of the patient; in others there is more or less of gastro-intestinal disturbance. The stools are always colored, and on postmortem in the case of Minkowski no obstructive lesion was discovered in the liver to explain the icterus. The liver during life is occasionally palpable, although there may be no perceptible change in size. The spleen is enlarged and hard. The urine is usually normal or contains a trace of urobilin. There is a moderate degree of anemia with some polychromatophilia. The cause of the disease is unknown. Minkowski is inclined to think the primary trouble is in the spleen. In his case he found it enlarged and hyperplastic. The kidneys showed a brown cortex, the color being due to iron pigment that was deposited in granular form in the cells of the convoluted tubules. The French are inclined to look upon the cause as an angiocholitis.—Ed.]

TUBERCULOSIS OF THE SPLEEN.

Tuberculosis of the spleen occurs frequently, but has very little clinical significance. It never occurs as an independent condition, but is always a secondary manifestation of a general tuberculosis, following either an acute miliary tuberculosis or a chronic tuberculosis of the lungs, intestine, or glands. The tuberculous involvement of the spleen is always apparently insignificant, as compared to the tuberculous lesions present in the other organs.

A tuberculous spleen is larger, and if the formation of tubercles be very much extended, harder than normal. The increase in size is dependent on the intensity of the infection. In fresh eruptions of tubercles in the spleen occurring in the course of an acute miliary tuberculosis a number of grayish-white opaque granulations, as large as a millet or poppy seed, are seen on transverse section of the organ. These are so-called *miliary tubercles*, and are found both in the parenchyma and in the capsule. They are found most frequently in the corpuscles of Malpighi, within and outside the sheaths of the arteries, and within the pulp of the spleen. The parenchyma is usually very dark red, engorged with blood, of a solid consistence, and very fragile. The numerous white foci are particularly conspicuous, owing to the dark, contrasting color of the parenchyma. The picture in its totality resembles the spleen in "bilious typhoid," in which disease the enlarged organ is frequently seen filled with many thousands of little grayish-yellow areas that are indistinct in outline and that gradually merge into the surrounding tissues. In typhoid these foci in the corpuscles of Malpighi are filled with and surrounded by exudate. In the beginning they are tense and as large as millet or poppy seeds; in many cases they undergo suppurative changes, so that the whole tissue of the spleen

is filled with innumerable little abscesses, each of which consists of one little drop of pus.

In regard to the tubercles of the spleen, Billroth expresses himself as follows: "The tuberculous granule in this case, as in all other cases, consists of a finely granular, molecular mass. In the periphery shrivelled-up cells and rudimentary capillaries are seen; from here transition rapidly occurs into the pulp of the spleen proper, which is filled to bursting with cells. In spleens that I have examined the different tubercles were so close that cell proliferation on their periphery could not be distinguished, although such a process should be seen in the growing tubercle. It is a difficult matter to follow the development of a tubercle from the primary collection of cells in the spleen; particularly is it difficult in the spleen as it is in the lymph glands, owing to the presence of so many cells analogous to those occurring wherever a pathologic new formation is in process of development. The tubercles, always recognizable from their molecular mass, originate within the spleen tissue, very rarely within the corpuscles. Occasionally the corpuscles are seen with their artery tightly wedged in and compressed between two or three tubercles. The little white bodies, therefore, that are visible with the naked eye are not enlarged corpuscles."

On bacteriologic examination of an infected spleen, tubercle bacilli are found chiefly in the giant cells. R. Koch has called attention to the fact that in the spleen giant cells of considerable size are found in close proximity to fully developed tubercles. These giant cells may be completely isolated or surrounded by only a very few epithelioid cells, and always contain from 1 to 3 tubercle bacilli. The number of tubercle bacilli present in a tuberculous spleen in acute miliary tuberculosis varies within wide limits. The number of tubercles themselves is usually very great.

The acute course of *miliary tuberculosis* prevents retrogressive metamorphosis within the tubercules. It is different with the tubercles that develop in the course of *chronic tuberculosis*. In this condition the tuberculous spleen contains cheesy nodules as large as hemp seeds or hazelnuts. In the center these are softened, and in advanced cases may contain cavities. Such conditions, however, are not frequently seen, for the reason that in tuberculous affections of that character death usually occurs so early that these metamorphoses of the tubercle have not had time to take place. These cavities are formed in such a manner that the necrotic plug is sequestrated by the inflammation, and in this way leaves a cavernous hole of varying size.

Chronic tuberculosis of the spleen is frequently seen in *children*, particularly in children with widely disseminated chronic tuberculosis of the lymph glands. In these cases a large number of nodules are found that are not cheesy; they are about as large as hazelnuts, and resemble in their distribution the wedge-shaped splenic infarcts. The larger caseous tubercles are usually seen near the walls of the arteries. Inflammations of the capsule are not frequent, but this tissue is usually thickened and occasionally covered with fine granules. If at the same

time tuberculous deposits have occurred on the diaphragm, the capsule of the spleen is also usually involved.

Rilliet and Barthez found among 312 cases of tuberculosis in children, 264 instances of tuberculosis of the lung and 107 instances of tuberculosis of the spleen; among these 87 cases of miliary tuberculosis, 9 of tuberculous infiltration and only 2 of softening of the tuberculous foci. Berg found miliary tuberculosis 14 times in 17 tuberculous children who had died under one year of age. In later years tuberculous infection of the spleen is not so frequent. Thus, Rokitansky found tuberculosis of the spleen only 11 times among 104 cases of chronic pulmonary tuberculosis in adults.

The **diagnosis** of tuberculosis of the spleen cannot be made positively. In acute miliary tuberculosis we may be sure that deposits of miliary tubercles have occurred in the spleen, and the diagnosis will be corroborated if the spleen be considerably enlarged and sensitive to pressure. We must never forget, however, that an acute tumefaction of the spleen may occur regularly in acute miliary tuberculosis, even though tubercles are not deposited within the organ. The tumor of the spleen in acute miliary tuberculosis may assume large dimensions, so that the organ is increased three to four times. The tumor is always soft and, consequently, not easy to palpate.

It is almost impossible to make a diagnosis of chronic tuberculosis of the spleen, because this condition, as a rule, produces no local symptoms. Only when very numerous masses of tubercles are deposited does the volume of the spleen increase. If in general tuberculous infection a large hard tumor of the spleen be found, it is usually due to amyloid degeneration, although, of course, in addition tubercles may be present in the spleen.

Tuberculosis of the spleen, therefore, never can be treated as such.

SYPHILIS OF THE SPLEEN.

I. LESIONS OF THE SPLEEN IN CONGENITAL SYPHILIS.

Hereditary syphilis almost regularly produces changes in the spleen that assume the form of *diffuse* or *circumscribed* lesions. Bednar was the first to call attention to the occurrence of tumor of the spleen in newborn children afflicted with congenital syphilis. G. Sée says that he has found an enlargement of the spleen in one-fourth of all cases of hereditary syphilis. Haslund found the spleen normal in 58 and altered in 96 of 154 cases of syphilis in the newborn. These changes consisted 55 times in general hyperplasia, once in infarction, once in peritonitis, and once in thickening of the capsule with adhesions to neighboring organs. Since Wagner found that the characteristic changes in the zone of ossification of the long bones is a valuable and reliable criterion for the presence of congenital syphilis, the relations of enlargement of the spleen to this affection have been followed more closely. Birch-Hirschfeld has demonstrated in the course of his very

careful examinations that in almost all cases of hereditary syphilis enlargement of the spleen can be found. In 92 newborn children who showed signs of syphilis, 89 of whom showed characteristic changes at the epiphyseal boundary of the femur, the spleen was found to weigh, on an average, 14 gm., with an average body weight of 2027 gm. The weight of the spleens, therefore, was equal to 0.7 per cent. of the body weight. Normally, the weight of the spleen as compared to that of the body is about 0.3 per cent., so that in syphilitic children this weight is double.

In addition to enlargement, the consistence of the organ is also increased; occasionally, however, tumors of the spleen are observed that are soft and flaccid. Peritonitis, as a rule, is absent; but infrequently spleens are found in which the capsule is thickened or covered with a fibrinous exudate or loose connective-tissue proliferations. On microscopic examination a marked increase in the stroma of the spleen is found in pronounced cases; also a diffuse cellular infiltration of the arterial sheaths that frequently show in their central parts fine granular degeneration. Birch-Hirschfeld has noticed pronounced fatty degeneration in the pulp cells, and collections of a brownish granular pigment. Amyloid degeneration does not seem to occur in syphilitic children soon after they are born; it is seen only in the later stages of syphilis in children who survive for some time.

Circumscribed *gummata* are rarely found in the spleen of newborn syphilitic children; they are more frequently found in syphilitic children who die within the first year or two, and in children of older years. We must distinguish between miliary and nodular foci; the latter may be as large as hazelnuts; the former are usually widely disseminated, whereas the latter may occur as solitary nodules. In the fresh stage they look grayish red, are translucent, solid, and protrude above the cut surface of the spleen. If they are situated near the periphery they protrude over the surface of the organ. Their form is usually round, occasionally irregularly wedge-shaped; near the periphery ramifications and branches, fine and coarse, are seen. In older foci dry cheesy masses and areas of cheesy degeneration are seen in the center, while the periphery is usually colored gray. As the gummata contract the peripheral zone becomes scarred, so that indentations on the surface of the spleen may occur if the nodules are situated underneath the capsule. This is brought about, too, by the fact that the capsule of the spleen itself is usually thickened and adherent to its surroundings (Birch-Hirschfeld). E. Wagner has shown that the vessels of the spleen and the septa have almost vanished within these growths; the same applies to the capsules of Malpighi. In general, the histologic appearance of these growths corresponds to the gummata found in other organs—a small-cell proliferation with more or less atrophy, fatty degeneration, and new formation of connective tissue that gradually merges into solid cicatricial tissue. Miliary gummata, according to Birch-Hirschfeld, owe their origin to a circumscribed proliferation within the sheaths of the splenic arteries.

II. THE SPLEEN IN ACQUIRED SYPHILIS.

Tumor of the Spleen (Splenitis Acuta).—The spleen is involved less frequently in acquired syphilis than in the congenital form. It is possible to distinguish here also a diffuse and a circumscribed form of the disease; of the two, simple tumor of the spleen, or acute splenitis, is undoubtedly the more frequent. Moxon Walter first described this lesion in syphilis. Weil called attention to the frequent swelling of the spleen in fresh infections, particularly during the period of the primary induration before the eruption. This author reported 3 cases of acute tumefaction of the spleen that receded rapidly within five to ten weeks under antisyphilitic treatment. Schneller found swelling of the spleen in 6 cases out of 22 recent syphilitic infections. In 3 of these that, in addition to their specific lesions, showed symptoms of anemia, the latter complication was removed by antisyphilitic treatment. Haslund has contrasted 154 cases of syphilis in the newborn with 44 autopsies on adults during the active stage of syphilis. In these the spleen was found normal in 10 cases, hyperplastic in 27; 11 times the soft form, 16 times the hard form were seen. According to these figures the percentage relation of tumor of the spleen is seen to be 31.17 in congenital syphilis and 61.3 in the acquired form. Neumann, to whom the writer is indebted for this computation, criticizes it correctly, as follows: "This enormous difference shows that in acquired syphilis the lesions of the spleen observed cannot be attributed to the specific trouble alone."

The swelling of the spleen can attain great size, particularly if the general infection be not treated correctly; even with appropriate treatment the tumor can sometimes be felt for weeks. A swelling of the spleen in syphilis can be interpreted in the same sense as a like condition in other infectious diseases; it is the reaction of the spleen to the virus that has penetrated the organism, and it must be considered one of the symptoms of the infection of the blood caused by syphilis. As uniform autopsy findings are not recorded, we have no exact knowledge in regard to the anatomic changes found in this form of splenic tumor, but we are justified in assuming that they are not much different from those seen in the acute tumors of the spleen found in other acute infectious diseases.

The **diagnosis** is made from the demonstration of the tumor and of signs of recent syphilitic infection. In addition, of course, we must be able to exclude any other cause for the swelling of the spleen. As a rule, the increase in the volume of the organ is only insignificant. If at the same time its consistence be increased, it will usually be an easy matter to palpate the lower margin on deep inspiration. On percussion an enlarged area of dulness may be found; frequently, however, the lowest part of the semilunar space is tympanitic, and does not sound dull until the patient takes a deep breath. The tumor is not painful even on pressure. An evening riss of temperature may be present, but more frequently seems to be absent.

[The enlarged spleen in secondary syphilis may mislead one into a diagnosis of some other infectious disease, such as typhoid fever. There is often malaise, anorexia, headache, and the temperature may resemble that of a mild typhoid. If with these symptoms a palpable spleen is found, and if with these a maculopapular rash makes its appearance, the resemblance to typhoid may be striking. The examination of the blood for the Widal reaction and for typhoid bacilli, a careful study of the rash, together with a search for adenopathy and other signs of syphilis, usually enable one to make a correct diagnosis.

Occasionally in syphilis there may be chills and fever, and the spleen, if enlarged, might lend color to the diagnosis of malaria. The blood-examination, the exhibition of quinin, etc., will clear up the diagnosis. —Ed.]

The **prognosis** of acute swelling of the spleen during a recent syphilis is favorable, for the reason that it produces no marked functional disturbances and always recedes under specific treatment. It is not definitely determined whether this form of acute tumor ever becomes chronic.

Interstitial Splenitis.—This form of diffuse involvement of the spleen forms a chronic tumor of the spleen, in contradistinction to the form of swelling described above. It occurs less frequently than the latter and is usually accompanied by a syphilitic involvement of other organs. This is not alone chronic hyperplasia of the organ, as it is seen following stasis in diseases of the heart, the lungs, and the portal veins; but it is at the same time a diffuse interstitial process, leading to contractions and cicatricial-tissue formation similar in all respects to the changes observed in other organs (cirrhosis of the liver and of the kidneys).

The increase in size is inconsiderable, the consistence increased, the organ hard and fibrous, and its surface irregularly indentated as a result of cicatricial contractions and lobulation. On transverse section the tissues of the spleen appear anemic, pale, and reddish; the trabeculæ of the stroma look like grayish-white bands, running through the organ in all directions and radiating irregularly. The pulp lying between these trabeculæ looks pale and is occasionally filled with dark pigment (Neumann). The increase in the connective tissue may be very considerable, and the interstitial processes may be so marked that the follicles grow smaller and become atrophic and the pulp proper very scanty. The capsule is thickened and covered with semicartilaginous nodules; occasionally it is adherent to neighboring organs.

According to Virchow, the development of these processes is as follows: At first a hyperemia of moderate degree exists, and the different parts of the parenchyma of the spleen swell either in lobulated foci or in bands that radiate irregularly all through the organ. These foci gradually grow more solid, and look darker and more compressed on transverse section; at the same time they assume a dark-red color and can hardly be distinguished from hemorrhagic infarcts proper. Later the redness disappears, at first in the middle; the tissues grow darker

and harder and assume a pale, sometimes a reddish-gray, color. From now on an increase in the connective tissue becomes clearly marked wherever the process appears in foci, and cicatricial contraction occurs. The adventitia of the arteries is considerably thickened, and the lumen of both arteries and veins is reduced. In the case of the arteries we have the well-known form of syphilitic lesion of these vessels first described by Heubner. As a final result of this vascular lesion the lumen is gradually distorted and frequently becomes obliterated. If the involvement have progressed very far and if it be very severe, the spleen becomes thickened and converted into a hard fibrous tissue in which the lymphoid elements are atrophied. The hard yellow spots seen in the spleen show a large amount of fat on microscopic examination.

The **diagnosis** of interstitial splenitis cannot be definitely made. We may suspect that this lesion is present when in an old and inveterate case of syphilis we find a very resisting, hard tumor of the spleen. As, further, we know from our experience that this form of involvement of the spleen never occurs alone, but is always associated with syphilitic lesions of the liver, digestive organs, and kidneys, the symptoms observed can never be positively attributed to an involvement of the spleen alone. Other diseases that could be considered would be some severe disease of the blood, with enlarged spleen. Occasionally the capsule of the spleen is involved and then the organ may be painful.

The **prognosis** of interstitial syphilitic splenitis is always unfavorable, even though the disease *per se* never precipitates a fatal issue, and may even be arrested if a suitable therapy be instituted early enough. A splenitis must always be considered a serious disease, not alone because of the functional importance of the organ, but because it is usually combined with lesions of other organs that are functionally just as, or more, important. The prognosis, therefore, must not be made only from the condition of the spleen, but also from that of all the other organs that may be involved. The prognosis in this form of splenic tumor will be particularly unfavorable, as a complete re-establishment of normal function is not conceivable. Such a complication in the spleen certainly exercises a deleterious influence upon the general condition of the patient.

Amyloid Degeneration of the Spleen in Syphilis.—Amyloid degeneration must be mentioned as the last one of the possible diffuse lesions of the spleen in syphilis. This form of involvement is frequently found on autopsy of syphilitic bodies. It is seen both in acquired and in the later stages of congenital syphilis, particularly if ulcerative processes of the skin and bones be present. It is but part of a widespread amyloid degeneration; yet occasionally the spleen alone is involved. In looking through the anatomic reports of a great many cases we discover the remarkable fact that in amyloid degeneration the spleen usually is first involved, whereas the kidneys may only be in the beginning of this degeneration, although they are most frequently involved next to the spleen. Among 100 cases of amyloid degeneration

that the writer established anatomically, the spleen was found involved in 98 cases, the kidneys in 97, the liver in 63, the mucosa of the intestine in 65. Dittrich, who first described visceral syphilis, has also given us a detailed description of amyloid spleen in syphilis. This form of syphilitic involvement of the spleen is not distinguishable from the non-syphilitic form of amyloid degeneration, so that we may refer to the description of this condition given above (p. 550). Frequently amyloid spleen is combined with gummatous or interstitial splenitis.

Amyloid degeneration may appear in varying forms and in varying degrees in the spleen during syphilis. It may involve the follicles of the spleen alone, so that they resemble gray, translucent, boiled sago grains. If a diluted potassium iodid solution (so-called Lugol's solution) be poured over the cut surface, the follicles of Malpighi immediately assume a brownish-black color, and become conspicuous by contrast to the lighter color of the pulp; if dilute sulphuric acid be poured on the cut surface, the follicles assume a bluish or dirty-green color. This circumscribed form of amyloid degeneration, in which the spleen increases particularly in its transverse diameter and appears to be very hard, is called *sago spleen*. In the second form of amyloid degeneration the change is seen diffusely all through the tissues of the organ. Whereas the sago spleen, as a rule, is only slightly increased in size, higher degrees of diffuse degeneration of the spleen, or *lardaceous spleen*, lead to an enlargement of the organ, occasionally to five times its normal size. The margins of the spleen in this condition are rounded, considerably thickened; the indentations are deeper, the consistence hard but not elastic. The color is dependent on the amount of blood, and may be either light, brownish red, or anemic yellow. In the most advanced degrees of this degeneration the spleen looks like yellowish wax; the dull luster of the tissue and its transparency in thin sections are characteristic. The sections show the same color reactions as the whole organ, particularly if they be brought in contact with the specific reagents shortly after removal from the organ and after washing with water.

In sago spleen the degeneration is limited to the walls of the small arteries and to their lymphoid sheaths (Malpighi's corpuscles); the walls of the capillaries are particularly degenerated. In regard to the microscopic changes seen, we refer to the description of amyloid degeneration given above. In both forms the capsule is much distended and cloudy in spots or over a large part of its surface.

The **diagnosis** of amyloid degeneration of the spleen must be made from an increase in the volume and the resistance of the organ; provided, of course, that other etiologic factors, particularly malaria, can be excluded, and provided we are dealing with individuals who, as a result of an inveterate form of syphilis (particularly grave ulcerative skin and bone lesions), are in a condition of cachexia. As the sago spleen is chiefly increased in its transverse diameter and feels very hard and resistant, it will be an easy matter to palpate it by the bimanual method. If the spleen be examined by this method, the hardness and

bluntness of the lower margin will be so conspicuous that the pathologic change existing can be diagnosed from this finding alone. As the spleen is rarely involved alone, but is usually diseased simultaneously with other organs, as the kidneys, the intestine, and the liver, we shall find symptoms attributable to such lesions of these organs, as albuminuria, colliquative diarrheas, edema, hydrops, ascites, emaciation, a cachectic color, and a general loss of strength. Albuminuria may occasionally be absent, even though the kidneys have undergone amyloid degeneration. We may mention that if the disease of the spleen develop very rapidly, the capsule may become distended, and in this way cause considerable pain.

The **prognosis** is always very unfavorable, and it is impossible to arrest the progress of this form of degeneration by treatment. The possibility of causing a restitution to normal is very remote, especially as the general system has suffered too serious alterations as a result of the infection. In those cases where a cure of amyloid spleen has been reported a chronic tumor of the spleen of some other kind probably existed. The writer has personally seen such cases that were combined with albuminuria, and has seen the tumor disappear.

Gumma of the Spleen.—Gumma is the only form of circumscribed syphilitic involvement that we know. Both gummata and amyloid degeneration are found in the later stages of syphilis in the case of the spleen, just as in the case of other organs. Occasionally a deviation from this rule can be reported. Thus, the writer observed the case of a student of medicine who developed a gumma of the brain a few weeks after the primary infection, and died before the initial sore was completely healed.

Gummatous involvement of the spleen, contrary to the statement of Virchow, Wagner, and Beer, is a very rare occurrence, and much less frequently observed than any other syphilitic lesion of the spleen. In acquired syphilis gumma appears in two forms, just as in congenital syphilis—*i. e.*, as miliary or as large gumma. In addition, a simple interstitial splenitis may exist. The size of the gummata may vary from that of a grain of millet to that of a walnut. They are round or wedge-shaped; fine and coarse ramifications and extensions of a fibrous character are seen at their periphery. The gummata themselves are distinctly circumscribed, and are situated either near the center of the spleen or extend to its surface; in the latter instance they protrude over the level of the surface and also above that of the cut surfaces. Their appearance varies with their age; if they are recent they have a grayish-red color on transverse section and are usually harder than normal spleen tissue. The older ones are found near the periphery and have dried, cheesy masses in their centers, or the whole gumma may be in a stage of cheesy degeneration. Finally, they undergo contraction and appear as cicatricial tissue, so that they form retractions and indentations in the tissues of the spleen; if near enough to the surface, the capsule appears thickened and adherent to its surroundings. The vessels, particularly the arteries, are usually thickened and considerably

narrowed, sometimes even impermeable, owing to the well-known proliferation of their endothelium. They may also occasionally become completely obliterated and disappear in the same manner as the septa of the spleen and its follicles. In one case of syphilis the writer found a solitary gumma about as large as a hazelnut within a spleen that was affected with interstitial splenitis. This gumma had undergone cheesy degeneration in the center, and another gumma exactly like it, but degenerated on its surface, was found in the esophagus.

Baumgärtner, in *Virchow's Archiv*, has described miliary gummata of the spleen without the presence of larger nodules, as follows: The spleen was three to four times its natural size, as hard as board; through the capsule, which was slightly clouded, innumerable millet-sized foci of straw-yellow color could be seen. On transverse section a pale-red, waxy tissue was seen crowded with millet-sized, pale-yellow foci of a granular consistence. Here and there these foci had undergone degeneration in their centers, so that little plugs of a pus-like substance could be expressed from them. Histologically, these nodules were seen to be typical gummata within an amyloid spleen. The pus-like substance in the center was not really pus, but tissue that had undergone fatty mucoid degeneration. The solid marginal portions consisted of small-cell granulations. The nodules seemed to have originated from the septa and the small veins of the pulp.

It is impossible to make a **diagnosis** of gummatous involvement of the spleen during life. It may be suspected in those rare cases in which, during the later stages of syphilis, we can feel that the spleen is enlarged and has several nodules on its surface. In order to palpate such nodules they must be situated at the lower margin of the spleen, superficially, and immediately under the capsule, and be much harder than the rest of the spleen tissue. A perisplenitis existing at the same time might corroborate such a diagnosis.

The **prognosis** is absolutely unfavorable.

Treatment.—A rigorous antisyphilitic treatment is indicated in all lesions of the spleen. But in those cases in which the patients are very much reduced and cachectic, a strengthening therapy should precede the specific treatment, except when urgent symptoms force us to fight the specific trouble at once. The syphilitic lesions of the spleen need no local treatment unless we wish to relieve pain that may possibly be present. This is best done by warm moist compresses. For the treatment of the general infection the ordinary rules are valid. If the iodin and mercury treatment be successful we may expect a restitution of the spleen to its normal dimensions, a contraction of the nodules, and finally a cure of the inflammations of the capsule in the course of a few weeks or months. Other cases are seen in which the tumor of the spleen resists all treatment, even though other symptoms of syphilis disappear. In such cases a long-continued after-treatment with iodid of iron (in the form of syr. ferri iodidi) and sulphur baths are indicated.

CYSTS OF THE SPLEEN.

We can distinguish three forms of cystic new formations that develop in the spleen: First, unilocular and multilocular cysts that are not of parasitic origin (serous, blood, lymph and fibrocysts); second, echinococcus cysts; and third, dermoid and atheromatous cysts.

The latter have only been found by chance on autopsy and are curiosities; as they are always deeply embedded in the parenchyma of the spleen they have no clinical interest. The contents of these cysts are the same as in analogous cysts of other organs. Andral, in 1829, described the best-known and the first case of this kind. Among other things, this author mentions small vesicles filled with a serous fluid that were found in the spleen in large numbers, either circumscribed and isolated or grouped in masses. Their contents could best be compared with the fluid found in follicles of the cervix uteri. Bednar also called attention to the formation of cysts in the spleen. In his case a cyst as large as a hop seed was observed in a child seven days old, suffering from congenital pemphigus. He also calls attention to the fact that occasionally in children with congenital pemphigus large and small serous cysts are found within the spleen. In the collection at Würzburg a specimen is preserved of a cyst of the spleen as large as a hazelnut, having a very thick fibrous wall. Magdelain describes a cyst of the spleen with one cavity, having smooth walls, with here and there hard plates, the latter containing carbonates, phosphates, calcium, and magnesia. The contents of this cyst amounted to 3 liters, was dark yellow, and contained albumin, white and red blood-corpuscles, and cholesterin. Leudet found a cyst with four or five compartments that were separated by fibrous walls; the lining was covered with epithelial tissue. Livois describes an analogous case. Böttcher describes cysts of the spleen that seemed to have been caused by retrogressive metamorphosis of an amyloid spleen. We will recur to this later. Chiari reports several serous cysts in another case of amyloid degeneration of the spleen. Echinococcus cysts will be described at some length in the next section, so that we will limit ourselves for the present to the description of *non-parasitic cysts.*

Case Reports.—We are justified, from a developmental point of view and from a study of the contents of these cysts, to distinguish different kinds, particularly as different pathologic processes are concerned both in their etiology and in their location. Aside from small cysts distributed in the spleen, and varying in size from that of a pea to that of a hazelnut (and presenting either a unilocular or multilocular structure), we find a number of cases reported in the literature of cysts attaining to the size of a child's head. These are clinically and surgically very interesting. Filippow and Kusnezow[1] report 5 cases of this kind that were cured by total extirpation of the spleen, and 2 others in which cure followed partial resection. In later publications the writer has found 2 additional cases that were also cured by resection, so that in all

[1] *Centralbl. f. Chi.*, 1891.

we have 9 cases with 9 cures. The writer has personally observed a tenth case that was, however, only diagnosed, an operation not being performed.

He would like to report briefly on the most important of these cases. The first case was that of a large cyst of the spleen that was clinically diagnosed and operated on; later it was described by Credé.[1]

The patient, a mason, aged forty-four, had suffered injury ten years before, when a brick struck him with great violence in the region of the spleen. For five days he suffered moderate pain that gradually disappeared; occasionally he still had stitches in the side. A year before operation he noticed in the left side of the abdomen a swelling about as large as his fist that at first grew slowly, but later developed rapidly. Six months later this swelling prevented him from working, stooping down, and particularly made it impossible for him to wear a truss; it was tender only on very strong pressure.

On the day of the operation the following was recorded: The abdomen is distended; on examination a tumor is felt about the size of a large child's head, tense, fluctuating, very mobile, adherent on its left side and above, not sensitive, and, judging from percussion and palpation, undoubtedly covered with intestine and mesentery. The examination through the rectum gives no additional information; the blood is normal.

As the author did not dare to perform puncture for fear of injuring the intestine which was situated in front of the tumor, the diagnosis was left open between hydronephrosis and a cyst of the spleen, and it was decided to perform an exploratory laparotomy, to be followed by a radical operation. I will show later on that an exploratory puncture could not have decided absolutely between these two conditions.

The operation was successful and the loss of blood almost *nil*. The spleen without the cystic fluid weighed 380 gm.; with it, 1720 gm. The organ was 26 cm. long, 14 cm. wide in the middle, and 6 cm. thick. Under the microscope the tissues were seen to be normal. The inner wall of the cyst had a reticular structure and was divided by numerous thick ridges and lined with pavement epithelium. Recovery ensued without fever and without the slightest reaction. After eight days the sutures were removed, and after two weeks the patient was up.

Whereas the healing of the wound was normal, the general condition was not. The patient had an excellent appetite; all functions seemed to be performed regularly; he complained of no pain, but grew visibly anemic, so that four weeks after the operation he could hardly walk a few steps without growing dizzy. His skin assumed a peculiar leathery consistence, and it was necessary to make incisions of 0.5 cm. in order to procure even a drop of blood. Four weeks after the operation a distinctly visible, painful, doughy swelling of the whole thyroid occurred that lasted with variations for four months. It disappeared, finally, when the general strength had improved, and the patient was able to resume his work as a mason. Eight days after the operation, and from then on, a distinct increase of the lymphogenous blood-corpuscles could be determined in the blood, also of the small nucleated red microcytes that come from the red bone marrow. At the same time the splenogenic white corpuscles [the polymorphonuclear neutrophiles] and the red corpuscles were decreased. At the end of two months these changes, which were determined every week, had become so modified that a maximum of blood-degeneration had been reached, inasmuch as the proportion of the white to the red blood-corpuscles was as 1 : 3 or 4. From this time a normal condition was gradually reached at the end of four and a half months, almost simultaneously with the reduction of the thyroid swelling and the general improvement of the patient. Swellings of the glands were not noticed; the patient was completely cured; the abdomen not painful; intestinal note in place of the splenic dulness.

The fluid (1350 gm.) removed from the cyst was yellow, clear, almost free from albumin, and contained many cholesterin crystals.

Case of Bardenheuer.[2] This case is interesting because the cyst was adherent

[1] *Arch. f. klin. Chi.*, vol. xxviii.

[2] *Deutsch. med. Woch.*, 1890.

in the pelvis and had been diagnosed as an ovarian cyst. The case was that of a woman of forty-seven. The contents of the cyst were hemorrhagic. It is possible that in this case trauma was the primary cause. At the time of the operation the cyst was firmly fixed in the pelvis. In this location the spleen was severed with a knife, the hemorrhage at the hilus stopped by ligatures, and that of the parenchyma with the thermocautery. The spleen was then returned to its place. Complete recovery ensued. The symptoms produced by the cysts were pain in the abdomen, radiating from the pelvis into the left hypochondrium and accompanied by serious disturbances of digestion, violent pains in the stomach, eructations, vomiting and, notably, a feeling of violent tugging in the left hypochondrium, and, finally, obstinate constipation.

Anatomic Finding.—At the upper curvature of the cyst was seen atrophic, flattened, dense spleen tissue, occupying nearly the whole periphery of the cyst. Below this the tissue gradually merged into a connective-tissue cyst wall that was 2 mm. thick and very solid. The outer surface of the cyst was smooth, only here and there a few loose connective-tissue fibers were seen (apparently adhesions that had become separated from their surroundings). At the upper edge of the cyst, in close proximity to the atrophic parenchyma of the spleen, a plate was seen about 12 cm. in diameter, and 3 to 4 mm. thick, cartilaginous, and slightly prominent above the level of the rest of the cyst wall. On transverse section the walls of the cyst showed calcareous deposits arranged in bands. The inner surface of the cyst, as well as the posterior surface of the atrophic spleen tissue, showed numerous large and small strands of connective tissue and connective-tissue thickening; by the interlacing of all these strands a dense connective-tissue net was formed. On the other hand, the inner surface of the plate mentioned above was smooth. Here and there a few blood-vessels were seen; *microscopically*, the walls of the cyst consisted of firm connective tissue containing much blood-pigment and also some calcareous matter. In the plates the connective-tissue fibers were still firmer and more solid; they contained almost no cells—only in the innermost layers, that were somewhat less dense, were a few cells found. No epithelial lining could be demonstrated. The spleen tissue was everywhere atrophic and gradually merged into the connective parts of the cyst.

The hemorrhagic character of the fluid contents of the cyst and the bloody infiltration of its wall made it probable that it was of hemorrhagic origin. The fluid evacuated was of a dirty-chocolate color and contained much blood-pigment and cholesterin. No scolices were seen. The tumefied, almost cartilaginous character of its walls made it probable that the cyst had existed for a long time.

Report of a case of Fr. Fink's, from Gussenbauer's Clinic, in which a cure was produced by resection:[1]

The patient, a boy of fourteen, according to the statement of his mother, had always been healthy. Five months prior to his admission to the hospital he had suddenly complained of a pain in the region of the spleen. Shortly thereafter he discovered a tumor as large as an apple and freely movable in the left upper abdominal region. Later he was taken sick with an acute fever, nausea, and vomiting, so that he had to stay in bed; after five days these symptoms disappeared and the boy felt relatively well. At the same time he noticed that the tumor of the abdomen was growing rapidly, and the symptoms that had been slight in the beginning were more intense. They consisted of dyspnea, and pain in the region of the spleen, as soon as he lay on his back; even when sitting up the patient had to lean to the right side in order to be comfortable. All other functions were normal. Malaria had never existed.

Present Condition.—The patient is well developed and well nourished. In the left hypochondriac region a prominent swelling is seen extending from the left costal arch to the middle line, and about the width of the hand below the navel; in the longitudinal axis it is 25 cm. long; in the transverse axis 15 cm. Its consistence is soft, elastic, and fluctuating; percussion sound over the tumor empty; it can be moved about very freely. Examination of the blood reveals normal hemoglobin and no numeric changes in the morphotic constituents. A diagnosis of cyst of the spleen was made.

[1] *Zeits. f. Heilk.*, vol. x.

The abdomen was opened by a median incision 15 cm. long, beginning a few inches above the umbilicus and passing around to the left. On entering the peritoneal cavity a tumor was at once seen, about as large as a child's head, of a whitish appearance, and lying within the peritoneal cavity. Above and on its inner side it was in contact with the stomach, in all other directions with the intestine. It was easy to determine that the tumor was situated in the lower half of the spleen. The upper half of this organ was hidden underneath the costal arch and looked normal. A part of the gastrosplenic ligament was ligated and partially severed near the hilus. The boundary of the cystic tumor was well differentiated from the parenchyma of the spleen, and the latter was in a state of good nutrition. In view of these findings and in order to avoid damage of the organism accruing from total extirpation, resection was performed.

Four weeks after the operation the boy was dismissed free from all trouble and feeling well. No swelling of the lymph glands and no increase in the volume of the thyroid could be observed. The examination of the blood made the day before his dismissal revealed the following proportions: Red blood-corpuscles, 3,740,000; white blood-corpuscles, 15,333; proportion, 1:244. Six months later the patient presented himself for examination and was found to be in an excellent state of health; the blood was normal, no swelling of the glands, no pain in the bones, no enlargement of the thyroid could be found. The spleen could barely be palpated.

The *microscopic examination* of the resected cyst showed that the growth had developed in the lymphatic apparatus of the spleen. Within the tumor, that was as large as a child's head, 1500 gm. of a reddish-yellow fluid were found, consisting of numerous hemichromatic red blood-corpuscles, a few white ones, and cholesterin crystals in abundance. Here and there thrombi were seen on the inner surface of the cyst. As we have already mentioned, the cyst was situated in the lower half of the spleen and was surrounded by a membranous sac. Wherever pieces of spleen tissue were adherent to this membranous covering, it was found that they consisted of a system of trabeculæ, so arranged that on the concave surface of the spleen and the place of contact with the cyst they looked like cavernous tissue. The inner surface of the convexity, on the other hand, was smooth. To judge from the findings on the inner wall of the cyst, it is probable that the large cyst originated from a rarefication of the system of trabeculæ. The contents of the cyst and the endothelial lining of its inner wall are important in the understanding of its genesis. The evacuated fluid, and the coagulation products that filled the fissures and cavities of all transverse sections, corresponded exactly with the contents of lymph cysts found in other regions of the body. To this circumstance are due the conclusions that this cavity and cyst formation had originated in the lymphatic apparatus of the spleen, that this tumor was a *lymph cyst*, and, finally, that it had developed from ectasis of lymphatic vessels.

The following may be added in regard to the importance of the endothelial lining of the inner cyst wall. This membrane consisted in general of two layers; one consisting of connective tissue, the other of endothelium. The latter, forming the immediate boundary of the cavity, was preserved only in a few places in the shape of a simple, outlined membrane, with long, spindle-shaped nuclei. As a rule, it consisted of double or triple layers of endothelial cells that had developed profusely through proliferation. These cells were of various forms; the large nuclei were oval with clearly visible mitoses; the endothelial cells nearest the cavity were in a state of retrogressive metamorphosis and had loosened their connection with the row lying behind them.

As this endothelial lining of the inner wall of cysts of the spleen has not been found in other cases, the writer quotes the author, as follows: "The whole wall of the cyst was formed by a fibrous membrane containing very few cells. On the inner surface of this tissue no endothelial lining could be seen. I may mention, however, that Prof. Chiari was able to find a delicate endothelium immediately after section, so that it is possible that this endothelial layer disappeared as a result of the hardening in alcohol. In those parts of the wall that form the cavity proper of the cyst were seen lymph fissures, the endothelium of which was proliferated in isolated places. No giant cells had been formed." (Compare Chiari[1] and Piering.[2])

[1] *Zeits. f. Heilk.*, vol. vi.

[2] *Ibid.*, vol. ix.

Of the 3 cases that have been communicated, the first was a serous, the second a hemorrhagic, the third a lymphatic cyst.

The contents of a *serous cyst* consist of a clear, white to yellowish fluid of low specific gravity, 1004 to 1009; it is either clear like distilled water or opalescent. Even after long standing or centrifuging no sediment is, as a rule, formed; at best a scintillating deposit at the bottom of the centrifuging tubes, consisting of cholesterin, is observed. These characteristic crystals are found in every case of serous cysts of the spleen, occasionally in large number. The cyst fluid usually contains no albumin; occasionally traces are found. It is different from echinococcus fluid in so far as it does not contain remnants of capsule membrane, scolices or hooks, or succinic acid. In common with echinococcus fluid is the presence of granules of calcium carbonate. The morphotic constituents of the fluid are a few leukocytes, possibly some loosened epithelium, or, more rarely, endothelium, depending on the character of the lining membrane of the inner cyst wall. When they are found they show either their normal characteristic outline or pathologic changes. Serous cysts do not, as a rule, attain to such enormous dimensions as the hemorrhagic, but they, too, can grow to be the size of a large child's head, and may contain several liters of fluid.

Cysts of the spleen with *hemorrhagic contents* vary in their appearance according to the age and the consistence of the fluid they contain. Very rarely a purely hemorrhagic contents, resembling undiluted blood, is observed. More frequently the blood is diluted with serum, or is in a stage of concentration, owing to partial resorption of its liquid elements. According to the presence of one or the other condition, the color and consistence of the fluid are different; the color may vary from dark red to black red, from chocolate to yellowish red. Under all circumstances blood-pigment is found, coming, of course, from the red blood-corpuscles. In addition, well-preserved red blood-corpuscles or microcytes, or blood-corpuscle shadows are seen, and in addition remnants of red blood-corpuscles and of cells carrying blood-corpuscles. The latter may be very numerous. Amorphous and crystallized blood-pigment, particularly the former, is often seen. In addition, cholesterin in considerable quantities, shreds of fibrin, and coagula. Numerous crystals of cholesterin and possibly epithelial remnants of the lining membrane of the cystic sac are found; the former without exception. No evidence of a parasitic origin of these growths has ever been found.

In regard to the *etiology* of this form of cyst, a history of trauma can usually be elicited; frequently, however, it will be found that the injury occurred a long time before the symptoms appeared, so that the development of these cysts appears to be very slow. Whether a real injury (a blow, a fall, a contusion, or, as in a case reported by Spencer Wells, a clumsy reposition of an enlarged dislocated spleen) is the cause of the development of a blood-cyst cannot be determined, but we can usually assume that the cyst was originally serous and became converted into a hemorrhagic cyst by some accidental trauma, hemorrhage, or

inflammatory process, which at the same time caused an increase in its size. We must further remember that hemorrhage by rhexis alone can produce blood-cyst; particularly as a result of pathologic changes in the splenic vessels, chiefly the arteries, if hypertrophy of the left ventricle coexist. Hemorrhage by diapedesis, as it occurs in infarcts, is never the cause of the transition of a serous into a hemorrhagic cyst. Atheromatous degeneration of branches of the splenic artery, aneurisms, and other pathologic processes involving these vessels must also be considered. Lesions of the venous apparatus of the spleen probably never have anything to do with the etiology of hemorrhagic cysts. Aside from blood-constituents of the most varying and different forms, leukocytes are found, frequently containing fragments of erythrocytes, and finally epithelial cells.

The contents of *lymph cysts* are different from those of serous cysts, chiefly in regard to their specific gravity, which is much higher. The first form of cyst contains more albumin and both red and white blood-corpuscles, so that the fluid looks like flesh water, and has a tendency to spontaneous coagulation. A difference in the number of cholesterin crystals is not, as a rule, observed. The most important point is, of course, to prove that these cysts have developed from ectasis of lymphatic vessels, and this evidence can only be adduced after the organ, or a part of it, has been resected or extirpated. In these cases microscopic examination will reveal transitions from visible lymphatic ectases to cysts.

The contents of the so-called fibrocysts (Atlee) are also yellowish and of comparatively high specific gravity (up to 1020); they coagulate at once on coming in contact with the air, and usually contain formed elements, fiber, cells, etc.

Lastly, we must mention *cholesterin cysts* of the spleen, in which the whole contents of the cyst have undergone fatty degeneration and are thickened, finally forming a scintillating mass of cholesterin. In these cases the cholesterin originated directly from the cells. Such cysts are very rare and are always of long standing. The cysts are small and are found by chance during autopsies. Occasionally they do not contain any fluid, but are completely filled with this shiny mass.

Etiology.—No definite and conclusive observations in regard to the etiology of *serous cysts* have so far been made. The writer is not of the opinion of other authors, however exact and modern they may be, that we must rely in the explanation of these cysts on analogies with similar processes playing a rôle in the formation of cysts in other organs. These authors speak of "organs related to the spleen," and the writer confesses that he does not know what they mean by this expression; probably the blood-forming organs, as the lymphatic glands and the bone marrow. If this be what they mean, he must call attention to the fact that serous cysts are very rare in these organs; and, on the other hand, that there is hardly an organ in the human body that is so frequently affected with cyst formations (particularly in the form of numerous small cysts situated underneath the capsule) as the kidney.

This organ, it is true, is topographically related to the spleen, and this is what these authors probably mean; it is certainly not related to it physiologically. The cysts found in the kidney are, of course, retention cysts, and are caused by the impermeability of the neck of Bowman's capsule, and consequently have nothing whatever in common with the serous cysts of the spleen which are not retention cysts. A number of the smaller serous cysts of the spleen may, in the course of years, increase in size as a result of traction or adhesions with their surroundings, or from other causes. Again, traumata may produce repeated hemorrhages into the cysts, and such accidents may cause them to enlarge considerably and to be converted into hemorrhagic cysts. In addition, all sorts of tugging, pushing, and general maltreatment of the cystic growth must be considered. The writer refers particularly to an interesting case in which a dislocated spleen was converted into a hemorrhagic growth owing to repeated repositions of a hernia situated in its vicinity, and frequent, unskilled application of the truss. Further, adhesions to the surroundings of the organ, and inflammations of the inner wall of the cyst, may convert the originally clear serous contents into a cloudy purulent one, consisting chiefly of pus corpuscles. On the outer surface of the cystic tumor inflammatory products are deposited, transforming the originally thin and delicate wall into a thick, solid, connective-tissue plate that may become calcified and adherent to its surroundings; such a plate may grow to be several millimeters thick. The outer wall of the cyst in such cases contains numerous large and small strands of connective-tissue thickenings that feel cartilaginous.

Böttcher[1] reports an interesting case of multiple cysts within an amyloid spleen. There was in the first place a cyst about as large as a pea, and filled with thin, watery contents. The cavity was crossed by a fine network of trabeculæ. In addition were found numerous cysts of the size of millet or hop seeds, with a more gruelly contents; and finally numerous microscopic cystic cavities. The author attributes this multiple formation of cysts within the spleen to a softening of the tissue, and a necrotic sequestration of the spleen pulp as a result of amyloid degeneration and occlusion of the vessels.

Hemorrhagic cysts with purely bloody contents undoubtedly originate from hemorrhages directly into the tissues of the spleen. In these cases we are dealing exclusively with hemorrhages per rhexin and not by diapedesis. Hematoma resulting from the rupture of the vessel becomes encapsulated. The fluid parts of this formation are partially absorbed, partially thickened and converted into a chocolate-brown mass containing blood-pigment, both in its amorphous and crystalline shape, and numerous crystals of cholesterin. The further changes of the cystic contents correspond to those seen in other apoplectic foci; the rupture of vessels can result from atheromatous or other changes in the arteries, more rarely in the veins, or it may be the result of a trauma of the spleen. Cysts that originate in this manner may remain very small for a period of years, until some intercurrent accident causes

[1] *Dorpater med. Zeit.*, 1870.

them to enlarge rapidly and to form tumors as large as a child's head. In 1 case the trauma had occurred ten years before.

In regard to the etiology of *lymph cysts* developing in the lymphatic channels of the spleen, histologic examination furnishes us with no clue. The contents of these cysts and the character of their endothelial linings have an important bearing on their genesis. The fluid evacuated and the products of coagulation that fill the fissures and cavities on transverse section correspond exactly to the fluid contents of other lymph cysts found in other parts of the body. The cavity and cyst formation occurs in the lymph apparatus of the spleen, and originates from ectatic lymph vessels.

The inner wall of lymph cysts is formed by a fine endothelial lining of 1 or 2 layers; some of the endothelial cells are in a state of proliferation and occasionally of fatty degeneration; sometimes they form cells resembling giant cells, such as have been described in the lining membrane of so-called "gas cysts." Serous cysts, on the other hand, always have a single layer of pavement epithelium, comparable to the endothelium of serous membranes; this, too, may be in a condition of fatty degeneration. In hemorrhagic cysts this cellular lining is often absent; it is quite possible, however, that it is originally present, but is destroyed when the specimens are kept for a long time in preserving or hardening fluids. If perfectly fresh specimens be examined, this lining can sometimes be seen.

It is worthy of mention, finally, that in all the cases so far described, with the exception of one in which the cyst was situated nearer the upper half of the spleen, these growths are found in the lower half of the spleen, while the upper half of the organ is perfectly normal. All of them were circumscribed by a membranous sac, and wherever the spleen tissue was adherent to this sac it was covered on its inner surface with a system of trabeculæ that gave the cyst the appearance of a cavernous structure. The large unilocular cysts probably originate in the majority of cases from the rarefaction of the system of trabeculæ.

Symptomatology.—Cysts of the spleen usually develop without at first producing symptoms; symptoms do not become manifest until the swelling has attained a considerable size. These are apparently not dependent on the kind of tumor, but are a result simply of an increase in the volume of the spleen; and the larger the latter, the greater the disturbances. Fr. Fink mentions an interesting symptom-complex of this kind in the case of a boy of fourteen who developed a lymph cyst. This boy one day, on returning from the gymnasium, complained of pain in the region of the spleen; a short time thereafter he discovered a tumor in the region of the spleen, about as large as an apple and freely movable. Later he developed acutely a high fever, nausea, and vomiting, so that he had to remain in bed. After five days the symptoms disappeared and the boy felt relatively well. At the same time the swelling of the abdomen increased in size and the slight symptoms complained of in the beginning increased in intensity. The most prominent symptoms were pain in the region of the spleen, and dyspnea,

appearing as soon as the patient lay on his back. When the patient was standing he had to lean over to the right side in order to be comfortable. No other symptoms were complained of. It is probable that during his gymnastic exercises the spleen had been squeezed in some way, so that inflammatory processes occurred and caused a large increase in the volume of the spleen. As a result, pain, on pressure and spontaneously, and dyspnea in the dorsal position made their appearance.

In other cases of cyst of the spleen, but not always, however, pain in the region of the spleen, possibly radiating into the left hypochondriac region or even to the left axilla, with digestive disturbances, eructations, and even vomiting, have been observed. These symptoms are due to the size of the tumor and the dislocation and compression of all the neighboring organs. In a case of Bardenheuer's, in which a large hemorrhagic cyst of the spleen became dislocated and adherent in the pelvis, the following symptoms made their appearance: Pain in the abdomen, radiating from the pelvis into the left hypochondriac region, combined with serious disturbances of digestion, violent pains in the stomach, eructations, vomiting, obstinate constipation, and a feeling of tugging in the hypochondrium. This tumor was successfully resected and the symptoms disappeared completely, the relief from the obstinate constipation and the feeling of tugging in the hypochondriac region being especially noteworthy.

Large tumors will produce a feeling of weight and pressure, pain, either spontaneously or on pressure, occasionally constipation, and frequently belching. In other cases no symptoms were observed at all until the tumor was found by chance. Changes in the blood, in regard either to the numeric proportions of the red blood-corpuscles or to the percentage of hemoglobin, have so far never been observed even in the largest cysts of the spleen. If the tumor be compressing or dislocating some of the surrounding organs, functional disturbances attributable to this will appear. The most important and decisive symptom is, after all, the discovery of a tumor, with the characteristics of a cyst, in the left hypochondriac region.

Diagnosis.—The diagnosis can be positively made only when the cystic nature of the tumor is directly demonstrable by palpation. This is usually easy, as large cysts are, as a rule, found in the lower portion of the spleen, and are consequently accessible below the costal arch. Difficulties are encountered in those cases in which the cystic tumor is covered by the intestine and the mesentery (Credé).

On inspection an oblong protrusion is usually seen in the left half of the abdomen, extending from the left costal arch toward the middle line. On deep inspiration a swelling, in case the spleen is not adherent, is seen to move downward. On percussion an empty sound is heard over the protrusion, corresponding to the circumference of the tumor; above the costal arch this sound gradually merges into the normal splenic dulness. If the intestine be distended with water a dull percussion sound will be obtained on the lower and left borders of the

tumor, corresponding to the place where a tympanitic sound was elicited before. If the water be allowed to run off, this dulness disappears.

On palpation a tumor will be felt corresponding to the visible outlines of the protrusion. It is usually distinctly circumscribed and may have rounded projections in different places. In the case observed by the writer the tumor could be felt underneath the left costal arch and followed as far as the median line, where it seemed to stop underneath the umbilicus. The feeling of fluctuation can best be elicited by placing the second and third fingers of each hand, about 4 to 5 cm. apart, upon the tumor and pressing alternately with the fingers of the one hand and then of the other; the movement of the fluid will give the feeling of fluctuation. If the cyst be very full, the feeling of fluctuation may not be elicited. As soon as a portion of the fluid has been removed by aspiration, fluctuation may appear. Fluctuation can be more easily determined if an assistant press the spleen forward from the lumbar region. Occasionally, short taps in the lumbar region will give a feeling of ballottement. In order to elicit this symptom the left hand should be placed flat over the tumor, and the right should percuss as described.

Naturally, these methods of examination will demonstrate only the presence of a sac filled with fluid. Other methods are necessary in order to determine the kind of cyst and the organ in which it is situated. The nature of the cyst contents can only be positively determined through either an exploratory puncture or an exploratory laparotomy, followed immediately by the removal of the mass; the writer will not go into detail in regard to these different methods. He will recur to this subject later, for it is really a surgical problem, and this is not the place to discuss it. From the point of view of the surgeon he would certainly consider any exploratory puncture superfluous if it be desirable to open the abdomen in order to produce a surgical cure. Very frequently, however, such cases come to internists in whom they have confidence, and it is often useless to advise them to consult a surgeon; they are either obstinate or are afraid of any operation. They usually consent to a simple exploratory puncture, particularly if someone who is not a surgeon perform it. The writer wishes to put himself on record here that, according to his own experience, he has never had a disagreeable complication in the almost innumerable exploratory punctures that he has performed, many of them before antiseptic methods were known. He is in favor of an exploratory laparotomy, followed at once by a radical operation, as soon as the diagnosis is clear. He has, at the same time, never seen suppuration or any other dangerous complication following exploratory puncture. In one exceptional case one of his colleagues had an unfortunate result; even here he did not introduce pathogenic bacteria nor convert a serous into a purulent cyst, but produced rupture of a softened hemorrhagic spleen, which was followed by the death of the patient. Aside from this most deplorable accident, that could not have been predicted, he has never seen untoward results ensue from exploratory puncture, provided it was properly executed.

In the majority of cases the diagnosis was rendered more positive. Exploratory puncture is particularly indicated in those cases where a decision must be rendered between echinococcus or some other cystic lesion of the spleen. In order to arrive at reliable conclusions in regard to this question, it is best to have the patient lie on his stomach for some time prior to the puncture; this is necessary, for the reason that in the ordinary dorsal position the solid particles of the cystic contents will sink to the bottom of the cyst and will not be reached by the needle; in such cases only fluid is aspirated, and the observer may be misled in regard to the contents of the sac. In one instance that the writer remembers it was necessary to perform puncture twice; the first time only fluid was aspirated; the second time the patient was placed on his stomach for some time prior to the operation and the writer obtained a mixture of solid and fluid constituents.

Other lesions that are important from the point of view of differential diagnosis are cystic degenerations of neighboring organs, particularly of the left kidney, and especially if this organ be dislocated; further, echinococcus of the left lobe of the liver, left-sided pleuritic exudates, and, finally, the rarer cysts of the pancreas, mesentery, omentum, broad ligament, and masses of inflammatory tissue in the mesentery. A cyst that has developed in a dislocated spleen which has become adherent may offer great diagnostic difficulties and frequently lead to confusion with ovarian cysts.

In a retroperitoneal hydronephrosis the percussion note over the tumor will usually be tympanitic, because the intestine, which is distended with air, passes in front of the tumor of the kidney. This tympanitic sound should disappear as soon as the intestine is filled with water from the rectum, immediately reappearing when the fluid has passed off. In a tumor of the spleen, on the other hand, the intestine, which is situated laterally, will also give a dull sound on percussion if filled with water. In this case, however, a dulness that already existed would simply be increased in size. All this will be different if the kidney be situated congenitally within the peritoneum, and on the occurrence of hydronephrosis pushes the intestine aside and thus produces dulness. It is very important, if left-sided hydronephrosis be suspected, to examine the spleen carefully, particularly to investigate whether on deep inspiration its lower margin can be felt. In addition, it is important to demonstrate whether the splenic dulness is in direct contact with the tumor or separated from it by a zone of tympanitic sound. When hydronephrosis is suspected it is also necessary to palpate the right kidney in order to determine whether it has undergone compensatory hypertrophy. It is, of course, of paramount importance to determine the possible cause of the hydronephrosis—that is, whether a stone in the ureter or some other cause is operating by compression to cause it, or whether the uterus or vagina is prolapsed. Finally, cystoscopic examination may decide whether the left kidney is still functionating. In many cases an exploratory puncture alone can clear the diagnosis. In a case of hydronephrosis or pyonephrosis of short duration the presence

of urea, uric acid, urinary pigments, or pus would determine the diagnosis. We know, however, that if a hydronephrosis exist for a long time, every trace of these specific urinary constituents is lost, so that finally the contents of a hydronephrosis cannot be differentiated from that of a cyst of the gall bladder or from a serous cyst of the spleen.

If the fluid within the cyst contain many crystals of cholesterin, this will speak in favor of a cyst of the spleen. In the same way spontaneous coagulation is an argument in favor of this diagnosis. The differential diagnosis between a serous or a blood-cyst and an echinococcus cyst of the spleen must be made by exploratory puncture, for the reason that hydatid thrill is not constantly felt, and does not occur at all if the cyst be very tense. If such characteristic parts as scolices, membranes, and single hooklets are found, the diagnosis can be made with absolute precision. The presence of succinic acid, and occasionally of sugar, is characteristic. Traces of albumin are found both in echinococcus and in large serous cysts, and have, therefore, no significance in the diagnosis. Cysts of the pancreas are sufficiently characterized by the presence of large quantities or of traces of pancreatic fluid with its characteristic properties. If such a cyst be very old, so that the pancreas no longer secretes, no trace of the typical secretion will, of course, be found within the cyst. In case a cyst in the upper part of the spleen should push the diaphragm upward, an occurrence that has so far never been reported, it might be possible to confuse this condition with a left-sided pleurisy. In a case like this it would be necessary to determine the exact outline of the dulness, and to see whether the diaphragm phenomenon could be discovered on the left side, in front. In unilateral pleuritic exudates this is always absent on the diseased side; whereas, in a forcing upward of the diaphragm by a cyst, it would undoubtedly be present.

Course.—The danger of cysts is dependent on their size and the rapidity of their growth. Small serous cysts occasionally exist for a long time without causing any symptoms. In these cases, ultimately, the contents thicken and the wall becomes calcified. The writer was once able to feel such a large chalk nodule that had probably originated from a cyst; he could recognize its calcareous shell from the peculiar sound elicited when the needle was stuck into the spleen.

Other cysts that may have existed for years without producing any symptoms may suddenly grow from some external cause or for some unknown reason, and within a short time become as large as a child's head, or larger. This is particularly the case in blood-cysts, for new hemorrhages occur from time to time, thereby rapidly increasing the volume of the cyst. Such hemorrhages are usually accompanied by violent pain in the region of the spleen, caused by the sudden and forcible stretching of the capsule; eructation has also been observed as an accompanying symptom of such an accident. The pain, which the patient usually characterizes as "stitches," may also occur as a result of inflammatory irritation of the serous covering, a result of the stretching and tugging to which the latter is exposed. Clinically such a peri-

splenitis can easily be recognized by the appearance of a rubbing that can be felt and heard, and that occasionally may be as loud as the creaking of new leather ("Neulederknarren"). Other dangers that may accompany large cysts of the spleen are dislocation and compression of neighboring organs; perforation into the abdominal cavity, with peritonitis; perforation of the cyst into neighboring organs after adhesions have been formed, as, for instance, into the intestine. In this accident the cystic contents are emptied from the bowel in the same manner as they are occasionally observed in cysts of the ovary. Finally, the cystic contents may suppurate. No case of perforation is reported in the literature of the last ten years. In almost all cases the diagnosis could be correctly made or, at least, rendered very probable, so that operative procedures were instituted sufficiently early.

Prognosis.—The prognosis, in general, is not unfavorable, because the indications for operation are usually very clear, and all reported cases that have been operated on have recovered. The smaller cysts that were not operated on were unimportant, as they produced no symptoms. In case these should suddenly begin to grow they can easily be recognized and removed.

Treatment.—Small cysts exhibit no symptoms; consequently, they can be neither diagnosed nor treated. The only treatment for large cysts is *operative;* no permanent result can be expected from simple puncture followed, possibly, by the injection of irritating fluids, and surgeons have abandoned this procedure altogether. Three operations for removal of cysts of the spleen are possible. The first operation may be performed in two stages; in the first stage the walls of the cyst are sewed to the margin of the abdominal wound; and in the second the cyst is incised, trusting that following the incision the cyst will contract and become obliterated through suppuration. Total extirpation of the spleen is the second measure; and, finally, resection of the lower end of the spleen containing the cyst. The latter procedure is particularly recommended and has been successfully executed by Gussenbauer and Bardenheuer. The first method of operation has probably been altogether abandoned, so that total extirpation and resection are the only ones that need to be considered. The former, as we have shown, has been performed frequently with good success; at the same time there is no doubt that if the danger were no greater and the result as favorable, partial resection would be preferable to total extirpation. We know, in addition, that the latter operation exercises a considerable influence on blood-formation, in the sense that after removal of the spleen a considerable decrease in the number of the red blood-corpuscles, an increase in the number of leukocytes, and the appearance of numerous microcytes are observed. In addition to this deterioration of the blood, inflammatory swelling of the thyroid and the superficial lymph glands, occasionally also of the bronchial and mesenteric glands, has been seen. No analogous changes have so far been observed as a result of partial resection of the spleen. In addition, shock and the danger of postoperative hemorrhages from the pedicle of the adhesions (as Spencer Wells,

Billroth, Bonsra, and others experienced after total extirpation of the spleen) are less to be feared in resection. The reports so far on the two operations do not give us sufficient information in regard to this point.

Franz Bardenheuer, at the suggestion of the Cologne surgeon of the same name, has made some very exhaustive experiments on partial resection of the large abdominal glands, and has found that large parts of these organs may be removed without in any way impairing the function of the remaining part. In fact, he determined that a compensatory hypertrophy of the remnant occurred, so that on later inspection of the resected organ it was often impossible to find the spot from which the piece was removed unless adhesions had occurred at that point. Ponfick has performed a great many liver resections that were followed very shortly by a new formation of glandular tissue. Basing on these experiments and experiences with partial resection of the kidneys in man, we are justified in saying that the dangers of total extirpation of the spleen are considerably decreased by partial resection, possibly even altogether removed. On account of a leukemic tumor, Bardenheuer removed the spleen from a man who was otherwise quite strong and healthy; the patient died thirteen days after the operation. The wound was in good condition. By making use of the firm, new perisplenic capsule, the operation had been performed almost entirely extraperitoneally. The edges of the wound were stitched to the opening in the peritoneum, and in this way the cavity itself was not entered. In the beginning the patient felt very well, but grew paler, almost white, and very anemic, presenting the picture of a patient who was suffering from chronic hemorrhage, although he had lost no blood either during the operation or afterward.

In other cases of operation that ran a satisfactory course, a severe leukocytosis has been observed following total extirpation of the spleen. This leukocytosis, however, entirely disappeared afterward. However indicated, therefore, this operation may be in suitable cases, partial resection is certainly to be preferred in case the primary trouble can be removed and still a part of the spleen be retained. This is particularly so if we know that the two operations are equal in value and equally free from danger.

Bardenheuer performed the operation in his cases of hemorrhagic cyst of the spleen as follows: The assistant grasped the lower end of the spleen directly over the cyst and compressed the whole organ. At the same time the operator severed the spleen transversely over the cyst. Hemorrhage, even when the assistant no longer compressed the organ, was comparatively slight, and only a trifling parenchymatous hemorrhage of the spleen tissue was noticed. A few streams of blood spurted out of some of the connective-tissue septa. The hemorrhage in the capsule near the hilus was a little more severe. The assistant continued the compression of the whole organ for about five minutes, the operator at the same time pressing iodoform gauze against the wound surface; when pressure was stopped the hemorrhage was very slight. The operator placed a few sutures through the capsule toward the hilus

and near the lower end of the spleen, then scarified the wound surface of the spleen with a few strokes of the cautery. This stopped the bleeding. The spleen, reduced about one-third by the operation, was then pushed back into the abdominal cavity, and, following the traction of the stretched gastrosplenic and phrenosplenic ligaments, rose into the left hypochondriac region. The peritoneal incision was closed with silk and the extraperitoneal wound in the abdominal wall packed with sterilized gauze. The postoperative condition was normal and without fever; leukocytosis was completely absent, both in the week following operation and later (after seven weeks); no swelling of the thyroid could be seen.

Gussenbauer, in his case of lymph cyst of the spleen, decided on partial resection, for the reason that no changes in the constitution of the blood could be found, and because he hoped that none would occur following this operation. The operation was performed extraperitoneally with the thermocautery. The separation of the cyst from the spleen was made transversely through the spleen, corresponding to the middle of the organ; the incision by the cautery was made step by step, and all hemorrhage immediately stopped by cauterization. Only two vessels near the hilus of the spleen that bled a little freely had to be caught with the forceps. The operation progressed without accident; little blood was lost, owing to the scarification. The resected spleen was reposited in its normal place and the abdominal wound sutured by six deep and twelve superficial stitches.

Partial resection is indicated in those cases where pathologic changes are limited to a part of the spleen. In such cases everything is obtained that we desire: first, all pathologic tissue is removed; second, the functions of the organism are in no way disturbed. It is true that observation teaches us that human beings and animals may survive a long time after removal of the spleen, and this experience and other experiments have demonstrated that the spleen cannot be considered as an organ absolutely necessary for life. However, extirpation of the spleen has been followed by changes in the blood, in the thyroid, and in the lymph glands, in cases where the blood was normal before the removal. Credé, in particular, has called attention to this phenomenon in extirpation of the spleen, and Ceci has corroborated it. Zezas demonstrated by his experiments on animals that a change in the constitution of the blood and an enlargement of the bronchial and mesenteric glands occur. All these changes have not been observed in man, so far, after partial resection of the spleen.

ECHINOCOCCUS OF THE SPLEEN.

General Remarks.—Echinococcus is found comparatively rarely in the spleen. Finsen, who has collected 235 cases of echinococcus of the abdominal organs, shows that the liver was involved 176 times, the kidneys 3 times, and the spleen twice. In 54 of Finsen's cases it was impossible to determine in which abdominal organ the parasite had

settled. Neisser, after careful perusal of all the literature on the subject, found only 28 cases of echinococcus of the spleen in 900 instances of this disease. He did not decide how often the echinococcus was found in the spleen alone. Mosler collected 18 cases that were observed during life, in addition to 12 that were found by chance on autopsy. Hirschberg completed this table in 1888 by collecting 41 cases of solitary echinococcus of the spleen that were distinctly recognized clinically. In 37 other cases echinococcus of other organs, particularly the abdominal organs, was present. Therefore we may say that echinococcus of the spleen is observed in from 3 to 3½ per cent. of all cases. In the scale of frequency of all organs that are affected, the spleen occupies eighth or ninth place.

The following is the order of frequency with which the different organs are involved: the liver in 50 to 70 per cent.; then the kidneys, the lungs, and the brain and meninges approximately as often; then the pelvis, the female genitals, the mammæ, the circulatory apparatus, and finally the small genital organs, as frequently as the spleen. There is no difference in the frequency of echinococcus of the spleen in the two sexes. In regard to the age of patients with echinococcus of the spleen, we can only state that the majority were young, or in the first years of manhood. In early childhood the disease seems to be as rare as in the later years of life. The youngest case of echinococcus of the spleen that the writer himself has ever seen occurred in a boy of ten; the writer finds no younger cases reported in the literature.

Cases of echinococcus of the spleen must be divided into two large groups: first, those in which the spleen alone is involved; second, those in which other organs also are affected. Another possible differentiation of cases might be arranged according to the seat of the cyst within or on the organ proper.

Pathologic Anatomy.—It is not known positively how the echinococcus egg found in the intestinal tract of man reaches the spleen. According to the latest views, we must assume a passive movement of the echinococcus eggs through the bowel into the organism. In regard to the further distribution, we must assume that they follow the blood-channels within the organs of the greater circulation to which the spleen belongs; the germs pass the lymph channels of the mesentery, follow the well-known passages into the intestinal lymphatic trunk, and then pass, by way of the thoracic duct and the jugular vein, to the right side of the heart. From here they may pass into the branches of the pulmonary artery, where they may be retained within the capillaries of this vessel and form echinococcus of the lungs. However, if they succeed in passing through the lesser circulation and entering the left side of the heart, all the organs of the body become exposed to infection through the arteries. The splenic artery carries the germs into the spleen.

[The ovum of Tænia echinococcus, a small tapeworm, found oftenest in the intestine of the dog, if swallowed by man has its shell dissolved in the stomach or bowel. The embryo or scolex escapes, penetrates the wall of the stomach or intestine, and by way of the lymphatics or veins

enters the general circulation. That the entrance is often into the radicles of the portal vein seems highly probable, from a consideration of the frequency with which echinococcus of the liver is met.—Ed.]

The parasite is found in only one form within the spleen—*i. e.*, in that of the unilocular echinococcus cyst. Echinococcus multilocularis, rarely seen in other organs, is never present in the spleen.

Echinococcus lesions consist of round cysts of varying size, and filled with fluid. In the spleen they may become as large as an apple. Most frequently only a single cyst is found; occasionally, however, several are seen. The cyst is situated either near the center of the organ or near its surface. If it be situated close to the capsule, this tissue appears cloudy, thickened, covered with deposit, and is occasionally adherent to its surroundings; for instance, the colon, the stomach, the diaphragm, and the abdominal walls. Portal reports that echinococcus may be adherent to the surface of the spleen by a pedicle, and that it may occasionally become altogether separated from the organ. In other instances primary echinococcus has been seen in the subperitoneal tissues or in other places near the spleen, only secondarily invading that organ.

The increase in the size of the spleen is dependent on the number and size of the cysts. The parasite finds favorable conditions for its development in the soft tissue of the spleen, so that it frequently attains to a considerable size; the pulp is forced aside and atrophies. If the growth were originally near the center of the organ, the remnants of spleen tissue may be seen as nodular protuberances on the outer wall of the cyst. In multiple development of echinococcus the greater part of the spleen tissue may perish by atrophy; however, this does not always occur. The writer has seen cases of echinococcus of the spleen in which the parenchyma, aside from the part occupied by the cyst, was intact. Repeatedly, hyperplastic changes have been observed in remote parts, assuming the form of elastic nodules; these may be interpreted as compensatory hyperplasias of the spleen tissue.

The shape of the spleen will depend on the location of the echinococcus cyst. If the cyst be situated near the upper pole, the diseased organ will press upward against the diaphragm, in this manner occasionally producing considerable compression of the left lung, and even dislocation of the heart. If, on the other hand, the cyst be situated at the lower pole of the spleen, the organ will grow downward into the left side of the abdomen, in this manner producing considerable protrusion of the abdominal wall. The echinococcus cyst is surrounded by a connective-tissue capsule several millimeters thick, and containing blood-vessels. It is formed directly from the surrounding spleen parenchyma, as a result of reactive inflammation caused by the parasite; the more violent the irritation, the thicker the membrane. The echinococcus cyst proper may be enucleated from this membrane. The latter consists of a milky membrane resembling coagulated egg albumin and containing fluid. When the membrane is punctured a clear white or yellowish-white fluid appears, normally looking like distilled water or like a whitish, opalescent mass. If the cyst be incised, the free

margins of the incision roll inward and a finely granular mass, resembling fish roe, and called the germinal or parenchymatous layer, is seen on the inner surface of the membrane.

The membrane of the cyst contains chitin; treated with sulphuric acid this gives glucose. In addition to a large quantity of carbohydrate, another substance that contains much nitrogen is present, which Hoppe-Seyler considers hyalin. In younger cysts this is mixed with salts of calcium.

The cystic contents are usually neutral, occasionally alkaline or acid. The specific gravity is usually low and fluctuates between 1006 and 1015. The fluid does not coagulate on boiling. In rare cases, however, small quantities of albumin are found, even in the absence of inflammatory processes. The percentage of sodium chlorid is 0.5 to 0.75. The presence of succinic acid, or of sodium or calcium salts of this acid, is very characteristic. These substances may be found in the spleen itself. In addition, echinococcus cysts of the spleen contain glucose and inosit, just as do analogous cysts of the liver; less constantly leucin, tyrosin, and cholesterin are found. Crystals of hematoidin have so far not been found in echinococcus of the spleen. As they are found especially in echinococcus of the liver, Habran concludes that possibly they are derived from crystalline bile constituents. The writer has occasionally found small chalk granules in the echinococcus fluid.

In many cases the cyst is not constructed as simply as above described. Numerous, frequently very large, daughter cysts are found within the mother cyst; a number of daughter cysts may in their turn contain granddaughter cysts, and these again great-granddaughter cysts, sometimes amounting to many thousand. Frequently they occupy all the room within the mother cyst, so that there is hardly space for the fluid. If only very few daughter cysts be present, they are usually spheric; if very many be present, they usually assume varied shapes, owing to mutual compression. They are constituted and constructed very much like the mother cyst.

On microscopic examination echinococcus membranes are seen to be arranged in several parallel layers; even in small fragments the free margins of this membrane show a characteristic tendency to roll inward in the same manner as the echinococcus capsule proper. On microscopic examination of the so-called germinal or parenchymatous layer, it is seen that little granules resembling fish eggs are the most characteristic part of the whole group. These grains are seen floating around in large quantities in the cystic fluid; they probably become separated from the membrane during the process of maceration. These grains are the heads of the echinococci (scolices), and are characterized by their shape and the double wreath of hooks attached to the rostellum of each; they also have 4 suckers apiece. The heads are usually single and float around in the fluid contents of the cyst; in other cases they are attached to the parenchymatous layer by thin rods.

Occasionally a lesion does not develop further than the stage of an acephalocyst—that is, no proliferation of the head occurs. Even in these cases the sac may become very much distended. Helm attrib-

utes this sterility of the echinococcus in part to disease of the germs, or of the parenchymatous layer of the cyst, or possibly the surrounding connective-tissue capsule. In echinococcus with daughter cells, some or all of these may be sterile; of course, in these cases no heads are found on microscopic examination.

Occasionally cysts burst spontaneously and the contents are poured into the abdominal cavity, or, depending on the nature of the adhesions that exist and the place of perforation, into neighboring organs, either the left pleura, left lung, stomach, or intestine. However, perforation of echinococcus of the spleen into neighboring organs is comparatively very rare. Occasionally a left-sided pleurisy or a pleuropneumonia has been observed in echinococcus of the spleen. Holstein saw the latter follow an exploratory puncture of echinococcus of the spleen.

Small cysts that ultimately become obliterated and calcified develop in the spleen more frequently than in any other organ.

Symptomatology and Diagnosis.—Simple echinococcus cysts of small size situated near the center of the spleen remain unrecognized during life. In many cases symptoms of an indistinct character have been observed, particularly belching, vomiting, and digestive disturbance in general.

Definite symptoms occur only when the volume of the spleen is much increased, when the echinococcus of the spleen is situated near the surface and can be directly discovered by the methods of physical examination, when symptoms of compression make their appearance, or when echinococcus cysts perforate into neighboring organs. The *subjective symptoms* are very inconstant and may be absent for a long time. Only when the tumor increases very much in size is complaint made of a feeling of weight and tension in the left hypochondriac region; the patient is not so free in his movements, and has the feeling as if some foreign body were located in the left hypochondriac region. In addition he may complain of violent pain. Mosler emphasizes this particularly. Yet these pains may be transitory or may be completely absent. As soon as the tumor has attained a considerable size, and if the abdominal walls are rather tense, so that they hold the organs closely together, symptoms of compression make their appearance; lack of appetite, gastric disturbances, belching, constipation, nausea, vomiting of food particles and even of blood occur. In some cases, as in one described by Martineau, the echinococcus cyst has compressed the nerves of the left thigh; clinically, this was recognized through pain in the left leg and a decrease of the tactile sensation and in the power of flexion at the knee. After $1\frac{1}{2}$ liters of pus had been removed by aspiration the symptoms disappeared in great part. Other symptoms occasionally observed in this disease may be altogether independent of echinococcus of the spleen, and be caused by the presence of the parasite in other organs, particularly in the liver and in the lungs.

In regard to the *objective signs* observed, inspection usually shows a protrusion of the lower ribs on the left side and a widening of the lower intercostal spaces. This observation will usually lead to palpation of

the region of the spleen, and in this manipulation a distinct protrusion below the left costal arch will be felt if the tumor has attained any considerable size. The extent of this protrusion will depend on the size of the tumor; it may extend downward as far as the pelvis.

Besnier calculates the time that must elapse from the beginning of the disease to the formation of a distinct tumor, large enough to be palpated, as about two years. A tumor that can be felt through the abdominal wall, that can be seen to move with inspiration and expiration, and that extends as far as the pelvis, frequently creates the impression of an enlarged spleen. The tumor can be recognized from its outline, the presence of one or more indentations on the median margin, and its respiratory mobility. The latter symptom is only absent if the organ be adherent to surrounding structures. The enlargement of the spleen can be determined by percussion; palpation, however, is of much more value in the objective diagnosis. In palpating the surface of the swelling a spot is often felt which seems to fluctuate. This is not necessarily the most prominent point of the spleen; in other places on the surface we find spots that seem to be more elastic than the normal spleen tissue and that protrude over its surface. These are the remnants of spleen parenchyma that has grown atrophic from pressure. Quite frequently fluctuation is entirely absent, chiefly if the cysts are situated near the center of the organ, if the cyst walls are very thick, or if the cyst is distended very much by the fluid. In cases of the latter kind the writer has frequently been able to determine the presence of fluctuation after aspirating a part of the cystic contents.

After fluctuation the most important symptom, the one that is felt in all hydatid cysts situated near the periphery, is *hydatid thrill;* some authors characterize this sensation as a fluctuation. The symptom under discussion was first observed by Blatin and first described by Briançon. Piorry describes it as follows: "The fingers percussing the tumor, or the hand pressing upon it, experience a sensation similar to that which they would notice if they were in contact with a repeating clock that was striking, or with an arm-chair with springs that were vibrating after some concussion; it is, withal, a peculiar trembling, that gives an impression to the sense of touch similar to the sensation given to the sense of sight by the trembling of gelatin." According to Briançon, the phenomenon is caused by the thrill of the echinococcus membrane and of the hydatids when the tumor is percussed. Cruveilhier assumes that it is caused by the friction of the daughter cysts within the mother cyst. Küchenmeister is of the opinion that the symptom is only felt if several cysts of gelatinous consistence be found within one cell. Davaine tried to demonstrate by experiments that the thrill is not due to the cysts and their consistence, but to the vibrations of their fluid contents. According to Mosler, a single isolated membrane can vibrate and communicate a feeling like a thrill to the hand; the feeling is increased with the volume of the cyst and the density of the enclosed fluid. The same author emphasizes that many investigators do not consider the hydatid thrill as characteristic for echinococcus, and that this

phenomenon is observed in different cases of ascites and in cysts of the ovaries, provided that all precautions are taken that the examination be carried on in the same manner as in echinococcus cysts—*i. e.*, that the tension of the abdominal walls be the correct one and that the percussion be executed rapidly. Statements in regard to the frequency with which the hydatid thrill is felt are as varying as those in regard to its location and its nature. Frerichs claims to have found it in one-half of his cases, and Finsen did not find it at all in 235 patients.

The writer thinks we can conclude from the great diversity in these statements and descriptions that different authors are describing different phenomena. According to his own experience, the hydatid thrill is, in fact, more of a distinct fluctuation, combined, however, with a characteristic after-trembling. The latter symptom is not always felt in the same manner; the waves that produce this trembling may feel very fine or very coarse, or very long and large. According to the presence of the one or the other kind of wave a different impression will be given; these differences can only be interpreted after a great deal of practice and experience. The writer would compare the impression imparted with the sensation that is felt when a number of echinococcus cysts or a mass of coagulated meat jelly is enclosed in both hands and shaken. Sometimes the waves are so coarse that they give to the sense of touch a sensation similar to that made by humming on the sense of hearing.

The thrill is best felt on percussion with a pleximeter and a hammer. If the pleximeter be placed on the fluctuating part of the spleen or on its immediate surroundings, and the ulnar side of the left hand be placed on the abdominal walls, a distinct vibrating, trembling, or thrilling may be felt when a short percussion blow is executed. The phenomenon can also be perceived very distinctly if during percussion the pleximeter be held between the thumb and index finger of the left hand, and allowed to remain in contact with the abdominal wall some little time after the blow. The phenomenon is in this way very clearly felt in the ball of the left thumb. The writer does not believe the thrill is produced exclusively in the fluid of the sac independently of the presence of daughter cells and other membranes, so that in his opinion it cannot occur in any other pathologic condition, as ascites, ovarian tumor, hydronephrosis, and others. He considers it absolutely characteristic for echinococcus cyst, and has so far only felt the thrill in hydatid echinococcus of the endogenous form—that is, in those cysts that are characterized by the presence of numerous daughter cysts within the mother cyst. He has not found it, for instance, in a case of large, superficial, non-parasitic serous cysts situated near the surface of the lower part of the spleen. It is furthermore important to remember that in the same case the phenomenon will not be elicited at all times and in the same manner; its presence is dependent to a large degree on certain physical conditions, the most important of which are the tension of the cyst walls and of the abdominal muscles. The writer has made the same observation that he has mentioned in regard to the presence

or absence of fluctuation in the case of the hydatid thrill—*i. e.*, that with very dense cyst walls the symptom may be absent, and become manifest only when a part of the cyst contents is aspirated. In such cases the thrill may disappear again as soon as the cystic contents increase and the membrane is placed under increased pressure. In regard to the frequency of the phenomenon, the writer can state that he has found it in about one-half of the cases of spleen and liver echinococcus. The statements made in the literature in regard to this are exceedingly varying, and there probably is no physical phenomenon concerning which the knowledge is so inexact.

In addition to the fluctuation and the hydatid thrill, perisplenic rubbing or symptoms of *perisplenic inflammation* are occasionally observed in echinococcus of the spleen ; this, of course, only if the echinococcus focus reach to the periphery of the spleen. In all such cases inflammatory processes develop on the capsule of the spleen, corresponding to the process going on in the parenchyma. In this manner a loud friction sound is heard over the fluctuating area, increasing with inspiration and expiration, and occasionally developing into a loud " Neulederknarren." This may be so loud that it can be heard at a distance; frequently it can be felt as a rub, and may be as intense as a very severe and recent pericarditis, and may, like the latter condition, persist for months. If friction sounds and rubbing are heard and felt in different places on the surface of the spleen, this symptom may be interpreted to signify that several cysts are present ; such an occurrence, however, is very rare in the case of the spleen.

In many cases the result of *exploratory puncture* has determined the diagnosis of echinococcus. It is well to examine the aspirated fluid both chemically and microscopically. The fluid contents of an echinococcus cyst are colorless, clear, and slightly opalescent, usually neutral in reaction, and of a low specific gravity ; it contains much chlorid, and is colored brown on addition of diluted solution of chlorid of iron (reaction for succinic acid). Sugar has been found in echinococcus of the spleen, but is less constantly present than in cysts of the liver. The question has been much discussed whether the cystic fluid can contain albumin in the absence of inflammatory processes. According to the writer's own observations, the fluid is more frequently free from albumin ; in isolated cases, however, it may coagulate on boiling, even though no inflammation has been discovered. This same fluid gives a precipitate with nitric acid. The characteristic chemical constituent present only in echinococcus cysts of the spleen and not in other cysts of the organ is succinic acid or its salts. Occasionally crystals of cholesterin are found.

The diagnosis is cleared absolutely if *microscopic examination* yield a positive result—that is, if constituents be found within the fluid that are direct products of the echinococcus. To this class belong all remnants and shreds of membrane ; microscopically, these are arranged in parallel layers in such a manner that the layers of different thicknesses are easily distinguished from one another by fine granular lines running

between them. Further, we find single hooks or whole garlands of hooks; and, finally, the most characteristic constituents, whole hydatids (scolices). These may have either retracted or protruding rostella, and are further characterized by the presence of suckers. In addition to these solid parts the writer has occasionally found small granules of chalk at the bottom of the tube in which the fluid was sedimented. Occasionally he has succeeded in finding a number of living heads in the sediment of centrifuged echinococcus fluid; once he saw 16 in each microscopic field (with a low power and a periscopic eyepiece), which stretched their rostella forward and pulled them back again alternately. This was one of the most interesting microscopic pictures he has ever seen.

It is frequently necessary to hunt carefully and for a long time in order to find hooks. It is well worth the while, however, because the presence of a single hook determines the diagnosis. The examination may be made very difficult if the contents of the cyst have suppurated. The writer does not believe the statement made by some observers, that under such conditions the hooks are dissolved and perish. He has repeatedly found hooks, under the microscope, in the pus from suppurating echinococcus cyst. In this manner it is possible to make a differential diagnosis between suppurating echinococcus cysts and abscesses of the spleen which owe their origin to other causes. If the above-mentioned morphologic constituents are completely absent in the cyst, this may be considered as a proof that we are dealing with a sterile cyst or an acephalocyst.

It is important, finally, to have the patient lie upon his stomach for some time before puncturing the cyst, so that the solid constituents will not drop backward and the puncture yield nothing but a clear supernatant fluid. The writer could demonstrate this point very clearly in one case of echinococcus of the spleen. The patient was first placed in the dorsal position and the cyst aspirated; no characteristic constituents were found. The patient was then instructed to lie upon his stomach for some time; the spleen was then aspirated again, and a very beautiful, positive result was obtained.

The question whether or not exploratory puncture is justified has been much discussed, surgeons in particular declaring against it. A surgeon is in the happy position of being able to perform an exploratory laparotomy before the definite operation, and this, of course, makes exploratory puncture superfluous. At the same time, it cannot be denied that, despite certain dangers we shall mention below, an internist cannot do without exploratory puncture if he wish to arrive at a positive diagnosis. Moreover, it is possible to avoid these dangers, which consist chiefly in infection of the cyst, if sufficient care be taken. There are, however, several other dangerous occurrences, all of which can possibly be avoided; among these may be mentioned, aside from certain eruptions, a series of very threatening symptoms, as syncope, dyspnea, nausea, vomiting, diarrhea, chills with fever, and occasionally collapse. Martineau lost a patient from syncope during puncture. Other dangers

are the infection of the echinococcus sac and the suppuration following such an accident, together with the possibility that some of the cystic contents may enter the peritoneal cavity. It is reported that severe peritonitis has followed the latter accident. As it is impossible to determine in advance whether the cyst walls are adherent to the parietal layer of the peritoneum or not, it will frequently be difficult to prevent the pouring out of some of the cystic contents; even in those cases in which rubbing and grating have been heard for a long time over the cyst, we cannot positively assume that adhesions have occurred between the tumor and the abdominal wall. In one very marked case of this kind loud grating had been heard for a great many months over the echinococcus cyst in the spleen of a boy of ten years. From this symptom the writer had concluded that pretty firm adhesions probably existed. When a laparotomy was performed by Fehleisen, in Bergmann's Clinic, it was found, however, that adhesions were altogether absent; there were no broad strips of adhesive bands, as we had suspected, but only a few, isolated, thin threads, extending from the cyst to the abdominal wall.

R. v. Volkmann has called attention to the fact that a generation of echinococci capable of proliferation can lead to the development and formation of new cysts within the peritoneal cavity in case some of the fluid is let out of the original cyst. v. Volkmann and Hüter observed 2 cases in which this method of development seemed to obtain. Péan expresses himself similarly. A number of other cases have been reported in which multiple echinococcus appeared after spontaneous or accidental infection of the peritoneal cavity by the contents of the echinococcus cyst. In 1 case of Lihotzki and Gratia this accident followed spontaneous rupture. The case described by Krause is particularly interesting; here the group of cysts developed half a year after puncture. Lebedeff and Adrejew have attempted to demonstrate by experiment the possibility of this method of extension of multiple echinococcus; they found that daughter cysts transferred to the abdominal cavity of a rabbit would develop and proliferate.

The contents of a cyst trickling into the abdominal cavity from the puncture canal may cause damage in another way other than by the development of new cysts. Several cases have been reported in the literature in which spontaneous rupture of the cyst was followed by death under symptoms of intoxication; this fact leads us to the conclusion that, by the resorption of echinococcus fluid, certain toxic products of metabolism are absorbed, capable of producing a violent reaction and occasionally fatal symptoms of intoxication. Brieger has succeeded in finding a substance in echinococcus fluids which, when separated from the platinum of its platinum salts and injected into mice, acts fatally with great rapidity (Langenbuch). Another investigator has found ptomains in the contents of hydatids in sheep. Mosler declares that these examinations are not free from criticism.

In other cases an eruption has been observed similar to urticaria, appearing frequently immediately after puncture or spontaneous rupture

of the echinococcus cyst. Occasionally other violent symptoms appear that rapidly lead to a fatal issue. There can be no doubt that the urticaria was produced by the entrance of cystic contents into the peritoneal or pleural cavities and by its subsequent absorption; thus, Hudson could produce an itching and the eruption of an exanthema in one case whenever he performed puncture of the cyst so that a small quantity of cystic fluid entered the peritoneal cavity (quoted by Mosler). Achard and Dieulafoy saw urticaria without any history of a traumatic cause, and it is possible that here the fluid was absorbed after oozing through some slightly injured spot in the membrane. Debove could produce urticaria in human beings by the injection of small quantities of echinococcus fluid. The writer has personally observed urticaria only once without any other symptoms, and has never seen an accident happen after puncture, although he has performed a great many in echinococcus cyst of the lungs, the liver, and the spleen. In one case the patient made some very violent movements during the little operation, and the needle was broken and remained in the cyst. Several days later the radical operation was performed by Professor Israel and the needle was recovered, so that in this case this mishap had no bad consequence. [These ill effects following a procedure ordinarily as harmless and simple as exploratory puncture are referred to by many writers on echinococcus. Evidences of toxemia and of local inflammation, as from spilling out of the contents, are often seen when even a few cubic centimeters of fluid are withdrawn for diagnostic purposes. This the writer has observed in 2 cases of puncture of echinococcus of the lung. In the lung, owing to the peculiar relation of the bronchi and bronchioles to the cyst, the withdrawal of even a small amount of fluid is apt to be followed by a rupture into a bronchus, with immediate danger of suffocation and, later, pyogenic infection and suppuration. Godlee and Fowler, in their work on Diseases of the Lungs, dwell emphatically on the fact that when a cyst supposed to be echinococcus is tapped, the surgeon should be at hand to operate immediately in case the fluid is found characteristic of that disease.—Ed.]

In case no fluid is aspirated on puncture, this may be due to occlusion of the needle by small pieces of echinococcus membrane. In such cases it is necessary to withdraw the cannula and to carefully examine it.

A *differential diagnosis* will be difficult only in case a large cyst is felt in the left upper region of the abdomen, the connection of which with some definite organ cannot be definitely determined. The most important possibilities to be considered are echinococcus of the left lobe of the liver, the left pleural cavity, and subphrenic echinococcus; rarely cases of cysts of the omentum, the mesentery, and the peritoneum. The three pathologic conditions first named may cause a considerable stretching and widening of the lower third of the thorax, enlargement of the intercostal spaces, compression of the left lung, and dislocation of the heart; this is due to the fact that these cysts develop within the bony thorax. The diaphragm phenomenon must determine whether the sac is situated above or below the diaphragm. In supraphrenic echinococcus the phe-

nomenon appears lower, in subphrenic and splenic echinococcus higher, than normal. In the former instance perforation into the lung may occur and cysts may be expectorated into the bronchi. This accident is not altogether excluded in subphrenic cases; in both instances, however, the breathing will be more interfered with than in echinococcus of the spleen unless the cyst be situated altogether in the upper pole of the spleen and push the diaphragm upward to a great degree.

Great diagnostic difficulties may be experienced in cases where the echinococcus has developed in a dislocated spleen. Finally, a few cases have been reported of localization of the parasite in floating spleen, and E. v. Bergmann has cured such a case by splenectomy.

Course.—The most favorable termination of echinococcus of the spleen is obliteration and calcification; such a termination, however, has been seen only in very small cysts. Clinically, they are rarely recognized, as these cysts probably never produce symptoms in the beginning, nor later after these changes have occurred. This is particularly the case if the cysts are situated in the central portions of the spleen; if they are situated near the periphery they may be found by chance on examination of the spleen. The writer has occasionally found cysts in this manner on examining the spleen; more frequently, however, on examining the liver. In both cases he encountered a focus that could readily be palpated, that was round in outline, small and hard. On more careful examination they were found to be about as large and as smooth as a billiard ball. The focus in the liver was, at least, as large as a child's head; the one in the spleen was as large as a walnut with its green hull. On inserting a strong steel needle, which he had manufactured for the purpose, the writer encountered a place as hard as ivory, that gave a distinctive sound when tapped with the needle—a sound identical to that heard when a steel needle is tapped against ivory. We must imagine the anatomic course as follows: The connective-tissue capsule of the echinococcus is at first converted into a thickened cartilaginous scar; later, calcification occurs, so that the echinococcus becomes surrounded by a thick, almost impermeable shell of chalk, which impedes further development of the cyst. The fluid becomes condensed, is converted into a putty-like substance, in which cholesterin crystals and the morphologic constituents of the echinococcus can be found. Occasionally so large a deposit of calcareous matter occurs that the contracted sac is converted into one large chalky concrement.

If the echinococcus cyst become infected and undergo suppuration the course is less favorable. It is rarely possible to determine positively what causes this form of infection; it may occur in any one of the different developmental stages of the parasite. Occasionally it may be caused by an exploratory puncture with a non-aseptic needle. In other cases the echinococcus dies spontaneously, owing to a considerable hypertrophy of the connective-tissue capsule. Starting from the latter, a suppuration of the whole sac may occur as a result of a general aggravation of the inflammatory irritation present. Such an accident is, of course, fraught with dangerous results. An abscess focus develops in

which the membranes are dissolved, so that only the very resisting hooks remain as relics of the condition existing before suppuration occurred.

When an echinococcus dies, the first changes are usually seen in the layer of cells found between the cyst and the membrane. This layer is concerned with the nourishment of the echinococcus. It is soon converted into a grayish-white, tubercular-like mass, surrounding the cyst like a zone of pus. The mass consists of fat-globules and granules, with a few cholesterin crystals. The fluid of the cyst in the beginning is cloudy, and gradually becomes more milky and purulent until, finally, it looks like pure pus and contains innumerable microbes; the walls of the cyst collapse and become folded. The parenchymatous layer suffers next and undergoes softening and fatty degeneration; the little heads drop off, perish in part, and float about in the cystic contents. The daughter cysts are destroyed in the same manner, and perish sooner than the mother cysts; the latter, however, ultimately are destroyed, so that finally nothing is left but a few shreds that disappear in their turn. Of the whole echinococcus, therefore, nothing is seen in the whole mass of detritus but the echinococcus bladder proper (quoted from Mosler).

Suppuration of an echinococcus sac is characterized by an irregular fever, pain, depression, and lowered nutrition. The tumor of the spleen grows rapidly; the skin over the spleen appears distended and reddened. If an operation be not performed, the echinococcus sac may rupture. The most favorable termination is an external perforation of the echinococcus sac, which may be adherent to the abdominal walls. Occasionally, however, the sac may rupture and its contents be poured into the peritoneal cavity. Such an accident is always accompanied by a violent peritonitis and alarming symptoms, leading to syncope—*i. e.*, violent chills, pain, small pulse, and cyanosis. In a case reported by Skoda the echinococcus fluid, which was not purulent, was poured into the peritoneal cavity; after five days resorption had occurred and the tumor had grown much smaller and softer. Zimmermann reports a case of echinococcus of the spleen in which the tumor had completely disappeared after a long fainting spell that had begun with violent pain; gradually the abdomen became distended again until it had reached its former dimensions. On autopsy, in addition to echinococci on the lower surface of the liver, an echinococcus cyst of the spleen and several other cysts lying free in the peritoneal cavity were found. In this case, too, a perforation into the peritoneal cavity had probably occurred. A very unfavorable termination is the perforation of a suppurating echinococcus of the spleen into the surrounding organs. This occurs chiefly into the transverse colon or the left lung. In the latter case malodorous pus is frequently expectorated. Perforation of the purulent contents through the abdominal walls may terminate favorably. If putrid decomposition of the contents of the echinococcus cyst occur, air bubbles may develop, causing a distention of certain parts of the skin over the abdomen by emphysema, and producing crepitation.

In 1872 the writer saw a case of echinococcus of the spleen, in the wards of Professor Murchison, in London, that disappeared suddenly one morning, although it had formed a considerable tumor the day before. During the night the patient had had profuse diarrhea, and on examination of the stools normal echinococcus fluid with innumerable

sacs was found. The patient recovered in this case; perforation had occurred into the intestine, probably the transverse colon, and as the contents of the cyst were not purulent a favorable termination of the case ensued.

Prognosis.—Echinococcus of the spleen *per se* is not a dangerous disease; what danger exists is dependent on the location and the size of the tumor and its proximity to other organs. The prognosis of cases operated on early is generally favorable. If the tumor assume large dimensions and be not operated on in time, death may result from disturbances in the function of other dislocated and compressed abdominal organs. If the case be complicated by the presence of echinococcus in other organs, the prognosis is, of course, still worse. A spontaneous cure by perforation of the cyst and evacuation of its contents through the skin, or by obliteration and calcification of the echinococcus cyst, occurs.

Treatment.—Prophylaxis.—As echinococcus disease is exclusively produced by the entrance of eggs, or of links of Tænia echinococcus containing eggs, into the human intestine, it is possible to reduce the danger of echinococcus infection to a minimum by exercising suitable precautions. Dogs are the immediate cause of echinococcus; consequently, the frequency of the disease will depend to a large extent on the number of dogs present in a community and the opportunities for becoming infected by contact with a dog. It is seen, therefore, that the mode of life, the habits of cleanliness, a more or less intimate contact with dogs, and, lastly, the relative frequency or absence of echinococcus disease in certain regions, are all to be considered.

We cannot be explicit enough in warning against intimate contact with dogs, the real carriers of the infection. The chief prophylactic point, however, is to prevent dogs from becoming infected with Tænia echinococcus; and this is best brought about by compulsory meat inspection, thus making it possible to destroy all echinococcus cysts found in diseased meat.

The only treatment for echinococcus of the spleen, in the light of our present knowledge, is surgical. All attempts to cure a spleen affected with echinococcus by internal remedies are a loss of time. This applies principally to the plan recommended so warmly by Vital, who administers arsenious acid internally.

Among the operative procedures, puncture, possibly followed by injection, was formerly in vogue. Simple puncture is only justified as a diagnostic means—in other words, as an exploratory puncture. Employed thus it is valuable, because it enables us to examine the aspirated fluid and to reduce the tension within the echinococcus cyst, thus facilitating palpation. It is not known that echinococcus of the spleen has ever been cured, even by repeated punctures. In one case it is stated that after removal of $3\frac{1}{2}$ liters of fluid a marked improvement lasting one year occurred. Puncture followed by injections of iodin is probably superior to simple puncture, but must also be considered as obsolete.

Two operations can be considered in the treatment of echinococcus of the spleen—namely, incision and extirpation. Which of these operations should be selected is entirely dependent on the peculiarities of each individual case. A. v. Bardeleben has formulated the following rules: "Unless the size of the tumor or adhesions with the abdominal wall seem to make incision preferable, I should certainly advise extirpation—that is, splenectomy. Further, wherever the whole spleen with the tumor can easily be drawn out of the abdomen and into the abdominal incision, I also advise extirpation." If incision be decided upon, the operation can be performed in one or in two stages. The single operation is advisable if the cyst wall and the abdominal wall are adherent; if such adhesions are absent or are not sufficiently extensive, an artificial connection is produced between the two surfaces by irritating the wound with iodoform gauze or aseptic gauze. After this irritation eight to ten days should be allowed to elapse; by the end of that time we may count on the presence of extensive adhesions. In order to remove the daughter cysts from the cavity, it is best to flush it out with antiseptic solutions; occasionally it is a good idea to remove these growths with forceps or the curet. If the cyst has suppurated, it is necessary to employ stronger solutions, and it is well to irrigate the wound surface during the after-treatment. A cure of spleen echinococcus through incision was brought about in a case operated on by Fehleisen, which the writer observed.

In a boy of ten years a tumor as large as an orange was seen in the left hypochondriac region, protruding below the left costal arch, and moving up and down with respiration. On inspection 2 prominent, round nodules could be seen on the tumor, and it was found that one-half of the mass emerged below the left arch and was soft and partially smooth; on palpating the circumference of the whole tumor a sharp margin with indentations was felt, of the same character as the inner margin of a normal spleen. The visible prominent nodules rose considerably above the level of the surrounding tissue and gave very distinct fluctuation. On palpation a distinct hydatid thrill was felt, and at the same time perisplenic rubbing, and a very intense "Neulederknarren." Puncture was made after the boy had been on his back for some little time before the operation. The writer aspirated (with a Pravaz needle) 3 c.c. of a fluid looking like distilled water; its reaction was neutral and it contained almost no albumin, but much chlorid of sodium, and was colored brown on addition of a dilute solution of chlorid of iron. Microscopic examination gave an absolutely negative result, and even after some time no sediment formed. Neither hooks nor scolices nor any trace of membrane were seen. Notwithstanding this negative microscopic finding the writer diagnosed echinococcus of the spleen. Later the patient was punctured again, this time after he had been lying on his stomach some time preceding the operation, and then the writer found many hooks and garlands of hooks. The subsequent operation was performed in two stages; at the first the cyst was exposed, when it was found that, notwithstanding the marked perisplenic rubbing that had been observed, no adhesions of the cyst with the abdominal wall were present; then the cyst was sewed into the abdominal wound. Five days after the first operation the incision was made and the contents of the cyst evacuated; the fluid contained numerous hydatids. An uneventful recovery occurred.

E. v. Bergmann reports the cure by splenectomy of a case of echinococcus situated in a floating spleen.

The patient, a woman of thirty-eight, complained of violent pain underneath the left costal arch, radiating toward the lumbar region; the pain persisted for

several weeks. This was in the summer of 1883. The woman attributed it to a miscarriage that had occurred in May of the same year. Finally, in August, 1883, a tumor was discovered in the left side of the abdomen, immediately underneath the costal arch; the growth was as large as an adult fist, readily movable, and seemed to increase slowly in size without producing any serious symptoms. On examination it was found that a large, indistinctly fluctuating tumor as large as a man's head was situated in the left side of the abdomen. The growth was readily movable, and could be transferred without difficulty from the right to the left side. On exploratory puncture watery fluid containing hooks was aspirated. The examination under chloroform excluded any connection with the genital organs, the liver, or the kidneys, so that it became very probable that a floating spleen was the seat of the echinococcus. The operation (splenectomy), made very difficult by the presence of numerous adhesions between the cyst and the intestine and mesentery, corroborated the diagnosis. An examination of the extirpated spleen revealed that the tissues of the organ were not atrophied or changed in any way; on the contrary, the spleen was found completely normal and apparently capable of performing its function. During convalescence the patient suffered from a slight attack of left-sided pleurisy.

In conclusion the writer would like to mention Schönborn's résumé of the subject, as this author agrees with v. Bardeleben: "In cystic growths of the spleen an exploratory laparotomy is indicated. If the spleen be found to be only slightly adherent, and if the organ can be readily lifted out of the abdomen, extirpation should be performed; if, on the other hand, the tumors are very large and extensively adherent to their surroundings, the operation of incision in two stages should be performed."

TUMORS OF THE SPLEEN.

Few cases of tumor of the spleen are reported in the literature. Secondary neoplasms of the spleen are rare, although the conditions for the formation of metastases in this organ are probably as favorable as for other parts of the body. Primary tumors are so seldom met with that they must be considered as medical curiosities. We can best appreciate how rare are these primary growths of the spleen by reviewing, so far as that is possible with the enormous mass of medical literature, all the cases that we can find reported.

We will begin with a discussion of the connective-tissue tumors of the spleen—*the fibromata.*

Wittigk[1] reports the first case of this kind and describes his fibroid as follows: "A nodule about as large as a walnut and partially calcified was seen lying within the parenchyma of the organ, loosely connected with its trabeculæ. It was composed of dense, concentrically, in places irregularly, arranged bundles of connective-tissue fibers. On addition of 'A' there was seen between these a mass of connective-tissue cells whose processes were everywhere in contact, and a network of fine elastic fibers. A capsule was present only here and there, as parts of it had apparently been destroyed in those areas of the tumor where calcification had occurred."

Rokitansky[2] speaks in a general way of the occurrence of fibrous tumors of the spleen, and describes them as round, nodular masses or

[1] *Prager Vierteljahrsschrift*, 1856, vol. iii. [2] *Lehrb. der path. Anat.*, vol. iii.

grape-like swellings with granular surface and body. Orth[1] describes another peculiar case of fibroma of the spleen. Fr. Fink[2] reports a growth that was studied in the pathologic institute in Prag, under the direction of Professor Chiari. The case was one of typical fibrous tumor of the spleen, but was characterized, in addition, by the presence of tubercles in the peripheral parts of the neoplasm. This very interesting growth was taken from a woman, thirty-one years old, who had died of an acute exacerbation of a chronic tuberculosis. The spleen was enlarged and its surface smooth. An incision was carried from the surface to the hilus; a spheric tumor was discovered embedded in the tissues near the convex surface of the organ; the parenchyma of the spleen was pulpy, soft, and dark brown in color, and was studded throughout with an enormous mass of whitish miliary tubercles. The growth proper was about as large as a small nut, its larger diameter being about 1½ cm., the smaller several millimeters less. It was clearly differentiated on all sides from the parenchyma of the spleen, could readily be lifted from its bed, and seemed to be connected with the parenchyma only through a number of fine threads. The surface of the tumor was divided into numerous nodules, each of which also had a granular surface. The consistence was solid, on cut surface smooth, shiny, and white, here and there showing a light-gray color, otherwise uniform in character throughout, and showing no distinguishing features macroscopically.

Microscopically, the following picture was seen: Parts that were removed from the center of the tumor showed both fine and coarse bundles, running partly parallel, partly in waves, some crossing each other at different levels, so that the same fiber was frequently seen in longitudinal, transverse, and diagonal sections. The crossing fibers enclosed small spaces that showed the greatest variety in shape and size. The bundles themselves showed peculiar striations that were very clearly marked, and followed in the direction taken by the fibers. The edges of the bundles were sharply defined, and irregularly distributed over them were seen spindle-shaped cells with oval nuclei. Filling out some of the spaces mentioned above were cells of various shapes, some lymphoid, some large and round, some elliptic and flat, with well-stained nuclei and finely granular protoplasm. In its peripheral parts the tumor was clearly differentiated from the parenchyma. The connective-tissue strands did not gradually disappear nor seem to enter the tissue of the spleen, but remained within the tumor and formed concentric bands. A very pretty picture was presented by this arrangement, and the following additional marking: On section were obtained numerous longitudinal and transverse views of blood-vessels surrounded by deposits of pigment in large quantity. At varying distances from them were found large and small collections of round cells which resembled very much tubercles in process of formation. A number of these even showed a few epithelioid cells, and were surrounded by perfectly circular strands of connective tissue of varying thickness, so that

[1] *Lehrb. der speciellen path. Anat.*, 1883. [2] *Zeits. f. Heilk.*, 1885, vol. vi.

the picture was very much like that of isolated, solitary tubercles. The surrounding tissue was filled with lymphoid cells, and the clear demarcation of the tumor against the parenchyma mentioned above seemed to be obliterated in those spaces where blood-vessels were found.

When this picture was first seen the histologic appearance of the peripheral parts of the tumor and of the miliary tubercles could very well create the impression that the whole tumor, possibly, was a fibroid tubercle of the spleen. However, when it was found that the central portions contained so well-marked a network of connective-tissue fibers, that its cells were shaped and arranged in a manner characteristic for fibroid, that no evidence of cheesy degeneration was seen, and that the tubercles were clearly circumscribed and attached to the periphery of the growth, it became evident that this was a fibrous tumor. This view was strengthened by the fact that its tubercles were everywhere in direct contact by continuity with other tubercles of the spleen which did *not* show any fibrous metamorphosis. This was, then, a primary neoplasm of the spleen, distinctly fibrous in character, in which, as elsewhere in the body, peripheral tubercles had developed as a result of the general tuberculous infection with which the patient was afflicted.

The tumor probably originated from the connective-tissue structures of the spleen; possibly from the trabeculæ.

Myxomata of the spleen are not known; the case of "myxome fibro-cartilagineuse der enveloppes de la rate" reported by Prienac,[1] and which was stated completely to envelop the spleen, can, properly speaking, not be considered here, for the reason that it was not originally a tumor of the spleen, but a neoplasm of the capsule surrounding the organ.

Characteristic *lipomata*, *enchondromata*, or *osteomata* of the spleen are not recorded in the literature. All these tumors are devoid of clinical interest; the possible occurrence of tumors belonging to these groups would be interesting only in the anatomic sense. For instance, one case of lipoma of the perisplenic tissue is reported, which is worthy of mention only on account of its rarity.

Hemangiomata or *cavernous angiomata* are also rarely met with, unless we choose to include in this group those varicosities of the vessels of the spleen occasionally encountered where the splenic arteries or veins have become chronically dilated. Förster[2] reports such a hemangioma of the spleen. The specimen, containing several cavities about as large as hazelnuts, is preserved in the collection of Würzburg. Langhans[3] observed a pulsating tumor of the spleen in a living subject; autopsy later revealed a large cavernous angioma. The tumor had a fibrous stroma, inclosing cavities lined with epithelioid tissue and containing blood in various stages of decolorization. Birch-Hirschfeld[4] reports a similar case.

Tumors assuming the character and structure of so-called *adenomata* of the spleen have been variously described. It is not always possible

[1] *Gaz. des hôp.*, 1870, No. 93.
[2] *Lehrb. der path. Anat.*, 1863, vol. ii., p. 3.
[3] *Virchow's Archiv*, vol. lxxv.
[4] *Lehrb. der path. Anat.*, vol. ii.

strictly to differentiate these adenomata from ordinary hyperplasias of lymphatic vessels, and consequently we have a number of cases that can be attributed to either kind of growth. Thus, Friedreich [1] describes multiple nodular hyperplasias of the spleen, consisting of cells that were similar in form to the lymphatic elements, but also containing cells of great size that were similar to liver cells. Weichselbaum classifies these hyperplasias among the sarcomata. Griesinger [2] reports 2 similar cases that he observed in Egypt. He saw in each of these cases a tumor about as large as a pea, clearly circumscribed, surrounded by a thin capsule, and lying in the parenchyma of the spleen. Its consistence and structure were almost identical with that of the normal spleen tissue, except that it was of a much lighter color.

Rokitansky [3] reports a case in which the spleen of an adult contained within its parenchyma a tumor about as large as a cherry, round, and resembling very much an accessory spleen. The tumor was formed of spleen tissue, and separated from its surroundings by a connective-tissue envelope. This tumor was called a lymphoma, and was in reality a "spleen within a spleen."

Orth also describes the occurrence of nodular hyperplasias of the spleen, and calls them "spleen adenomata." They consist of small nodules about as large as cherries or smaller, and are not very clearly circumscribed. They can be distinguished from the normal tissue surrounding them by their lighter color and their grayish tint; occasionally they have a connective-tissue capsule. The microscope reveals an increase of the cellular elements and in part of the reticulum. Lancereaux reports similar growths. Weichselbaum,[4] in 3 cases, saw lymphomata of the spleen that were about as large as peas, soft, and forming grayish nodules; these, likewise, were distinguishable from the spleen substance proper by their lighter color. On microscopic examination each nodule was seen to consist of 2 halves that were grown together and equal in every respect. In each half a central and a peripheral zone could be distinguished. The former resembled a nucleus, about 1 mm. in thickness, spheric in outline, and composed of the same round, closely congregated cells that are seen in a corpuscle of Malpighi; the whole structure resembled an enlarged Malpighian follicle. In contradistinction to true follicles of this kind, however, it did not contain an arterial branch commensurate with its size, but only a few very small capillary arterioles. The peripheral zone consisted of the same lymphoid cells and the same reticulum as the pulp strands of the spleen; in its external portion several Malpighian follicles were found, with centrally or eccentrically situated arterial branches. While this part of the tumor very much resembled the spleen pulp, still there was this difference: that between the lymphoid cells of the tumor only very few red blood-corpuscles could be found; whereas in the adjacent pulp of the spleen so many red blood-corpuscles were seen that the pulp cells proper were relegated to the background.

[1] *Virchow's Archiv*, vol. xxxiii.
[2] *Arch. der Heilk.*, 1864.
[3] *Wien. med. Zeits.*, 1859.
[4] *Virchow's Archiv*, vol. lxxxv.

From this description we see that these tumors are essentially built up of the same elements as the pulp strands and the follicles of the spleen, and consequently are hyperplasias of these tissues. We are therefore justified in characterizing them as *lymphomata*.

From the fact that in both halves of these tumors the central portions resembled enlarged Malpighian follicles, we are justified further in assuming that this hyperplasia primarily concerned the follicle, and that the nucleus of the tumor was formed by its enlargement. We can also understand that each tumor originally consisted of two distinct nodules, which grew together as the tumor developed.

While discussing these tumors the writer would like to mention a case of lymphosarcoma of the spleen that originated from the lymph vessels of the spleen, and was especially interesting from the fact that metastases were found near the hilus. It was not, however, a primary tumor, otherwise we should have discussed it under the heading of Sarcoma; but aside from the fact that we shall have occasion to refer to this case in the discussion of splenectomy, its character as a primary tumor of the spleen is not so well established that we are justified in discussing it under the heading of Primary Tumors of the Spleen. It is possible that in this case the primary focus of the tumor was in the region of the neck, involving the chain of glands found there, so that probably the splenic involvement was secondary; therefore it should properly be counted among the secondary tumors of the spleen. Nevertheless, it can do no harm to refer to the case in this place. The case is reported by Jordan, from Czerny's Clinic in Heidelberg, and is of very recent date.

The patient was a boy of fifteen years, who, aside from the tumor, was otherwise healthy. On January, 1895, a tumor developed in the left upper region of the neck, which was found to be a lymphosarcoma. It was extirpated in June of the same year and an uneventful recovery occurred. Toward the beginning of the next year, pain, increasing in severity, was complained of in the left abdominal region, the general health remaining good. The patient entered the hospital on the 12th of August, 1896, and on examination a tumor was found below the left costal arch. It was about as large as the head of a child, somewhat movable, and could be diagnosed as a tumor of the spleen from its position, configuration, and consistence. Laparotomy was performed and a tumor of the spleen removed, which weighed 2 kg. It was seen to be a sarcoma of the spleen with glandular metastases in the hilus. Recovery was uneventful and no changes in the blood were observed. Both tumors were compared and declared to be co-ordinated (?).

Secondary lymphosarcoma of the spleen may cause enormous enlargement of the organ and changes in the blood very similar to those seen in leukemia. The same may be said of sarcomata of the bone marrow.

Two other cases of primary tumors of the spleen are related to lymphangiomata. Fr. Fink[1] reported these cases from the Institute of Professor Chiari. One of them occurred in a man, aged forty-eight, suffering from general tuberculosis, involving particularly the lungs and the peritoneum. The spleen presented a picture which was, macroscopically, very interesting. It was larger than the normal spleen, was

[1] *Zeits. f. Heilk. Prag.*, vol. vi.

13 cm. long, 8 cm. broad, and 5½ cm. at the point of greatest thickness. The capsule, which was thickened and covered in some places, especially near the convexity, with relatively thick plates of connective tissue, appeared very white. Numerous nodules of varying size and shape were seen protruding over the convex surface of the organ; the small ones were as large as peas, while others were larger and spheric; again others were as large as chestnuts, the diameter varying from 4 to 5 cm. These smaller and larger tumors seemed to protrude from the spleen, and were, moreover, separated by deep furrows. Protuberances were also seen on the two long sides of the spleen and its poles, so that the outline of the organ was very irregular and indented. The concave surface of the spleen was similar to the convex surface, except that the irregularities were much more marked. Here tumor-like formations of medium caliber—*i. e.*, about as large as peas or hazelnuts—were seen. There was but one tumor about as large as a walnut. The growths were sharply differentiated on palpation, but all were found to be very solid and hard, while the tissue lying at the bottom of the furrows (described above) was soft and readily compressible; it was easy to tell the boundary between the two by palpation.

The cut surface of the organ showed a very unusual picture. Some parts of the spleen looked like tumors, were cavernous, and protruded over the surface. They were all of varying size and shape; cystic cavities and apparently normal splenic tissue alternated. The distribution of these different constituents was such that the great majority of the tumors were situated near the two poles of the spleen, so that they were pressed as closely as possible against the capsule of the spleen in this region, leaving spaces according to their size. In some places they compressed the pulp, thus forming the nodules described above. Here and there over the whole cut surface large and small nodular structures were irregularly distributed. The cavities were arranged in a peculiar manner. Three sections carried through the organ longitudinally showed that here and there these cavities were within normal pulp, but that the majority were only found within the tumor-like formations. The tissue of these tumors was very fine and porous, and disclosed a network of coarse and fine trabeculæ, between which were seen very small holes, and in some cases cavities as large as a pea and larger. Two of these cysts were exceptionally large, over 1.7 cm. in diameter. The distribution of these larger cysts was varied; one or more of them was found in the fine cavernous tissue of each protuberance. The form of the cysts was round, oval, or slit-shaped; the larger ones, in some instances, had irregular indentations. Occasionally a passage was found that had been cut longitudinally and that established a connection between two cysts. These passages were lined by a membranous envelope that in one place could be pulled out in the shape of a completely closed sac. Most of the cavities contained a reddish-yellow mass that completely filled the lumen. It could be easily turned out and was of soft, smeary consistence. Ridges were seen on the walls of the cavities, between which indentations of varying depth were observed.

Apparently normal spleen tissue was found between these tumors. It extended between them in strands of varying thickness, and here and there assumed larger proportions. In no instance was capsule formation seen near or around the tumors. The chief difference between the latter and the apparently normal spleen pulp was the color, the consistence, and the arrangement of the cystic cavities. The tumor-like nodules looked yellow, while the normal parts of the spleen pulp were pale violet. The consistence of the former was hard and solid, while the pulp remained very soft and was easily compressible. Here and there delicate trabeculæ that started from the capsule of the spleen could be seen; also numerous blood-vessels that had been cut transversely and were very wide, with thick vessel walls. The regular coarse network of such sections of blood-vessels could be seen in longitudinal section and traced to the convex surface of the spleen. The vessels at the hilus were very wide and their walls thick.

The cystic cavities were different as to size and shape. Round, oval, and slit-shaped ones alternated with polygonal and irregularly shaped ones. Their sizes fluctuated within wide limits. They were separated from each other by a system of trabeculæ. The single members of each system were of different widths, occasionally becoming very broad, and showed a clearly fibrillated structure, with numerous spindle-shaped connective-tissue cells. In other places they corresponded to the external nodules, and where the tissues were thicker the fibrillated structure was obscured by the accumulation of lymphoid cells, and here and there by red blood-corpuscles. This binding substance resembled in structure the connective tissue of the reticulum, so that the assumption could be made that it was a remnant of spleen pulp. The cavities were lined by an endothelial membrane of simple outline, which here and there was separated from the septa and showed long, spindle-shaped nuclei on transverse section, which seemed to protrude into the lumen of the cavities.

The smaller cysts were completely, the larger ones in part, filled with a mass that in some cases was altogether homogeneous, while in others it apparently consisted of finely and coarsely granular colorless coagula; in one or two instances a network of interlacing trabeculæ was observed within the cavities. Occasional lymphoid cells were distributed among these, sometimes isolated, sometimes in little heaps. In different places red blood-corpuscles were deposited on the septa described above, and in some of the larger lacunæ the conglomerates were so large that they completely obstructed the smaller cavities, and in places nearly obliterated the lumen of the large ones. In some of the meshes of the network small masses of pigment granules and of large cells containing red blood-corpuscles in different stages of disintegration could be seen. The same microscopic picture was seen in the larger cysts situated between the smaller ones, either in the tumor-like foci or in the pulp of the spleen itself. The membranous covering of one of these large cysts, which could be enucleated in the shape of a completely

closed sac, consisted of a distinctly fibrillary mass of connective tissue containing very few cells; no endothelial layer could be seen.

In those places where a transition seemed to occur between the small cysts and the neighboring spleen pulp, the following phenomena could be observed: Large and small cystic spaces, the latter usually arranged in small groups, approached the pulp directly and were more or less clearly outlined against it. The intermediary tissues were somewhat broader than above, and it was easy to see how the fibrillæ of connective tissue spread out into brush-like structures and disappeared in the reticular structures of the pulp. The pulp assumed different appearances in different places between two such septa. Sometimes the tissue of the pulp would be in close proximity to the endothelial membrane; in other instances the margin of connective tissue would run parallel to this membrane; the transition to reticular and fibrillary tissue was imperceptible. The adjacent pulp tissues were of entirely normal structure, only a little more injected with blood. The venous sinuses of the spleen were ectatic and filled with blood.

Another interesting observation was made on the cut surface of some of the tumor-like structures conspicuous by their yellowish-white color. In the system of trabeculæ which surrounded the lacunæ (mentioned above) small areas of necrosis were noticed. The outline of the tissue elements had disappeared, and only here and there could the fibrillary arrangement of the connective tissue of the septa be distinguished. The connective-tissue cells and the lymph cells had, as a rule, no nuclei that could be stained; in short, the normal structure of the tissue elements was replaced by a mass of granular flakes and detritus that was diffusely stained.

Dilated lymph vessels were not seen in the hilus of the spleen.

The second case of lymphangioma of the spleen is preserved as a preparation in the pathologic museum of Prag. The macroscopic and microscopic examination revealed a striking similarity with the findings in the previous case, so that we need not enter into the details, especially as Fink has described both specimens together, as follows:

In the parenchyma of the spleen a system of large and small cavities is found. They represent a series of cysts more or less connected with one another, and between which the tissues of the pulp are preserved in different thicknesses and slightly modified in structure. The cavities show great variation as to size and shape, are surrounded by a reticular structure that may be wide- or narrow-meshed, and that consists of a mass of fibrous connective tissue. The meshes of this network are interlacing, and the communication of its interspaces is readily demonstrable; they are lined by a single layer of endothelial cells with large spindle-shaped nuclei. From the parenchyma the cysts are separated by membranous sacs, the inner surfaces of which are studded with numerous prominent ridges. This demonstrates that the larger cysts were formed by the confluence of several smaller ones, and we are justified in calling these cavities cavernous, as they correspond both as to shape and consistence to the cavities of cavernous hemangiomata.

The contents of these cystic cavities may be of varying kind. They are often filled with coagulation products of lymph, so that we can say positively we are dealing in these cases with ectases of the lymphatic vessels of the spleen and a series of cavities and cysts that are in intimate connection with them. This can readily be demonstrated by tracing the transition from slightly dilated microscopic lymph vessels to cysts of large size, and justifies us in designating these pathologic neoplasms as lymphangiomata.

The presence of large quantities of blood in those spaces that contain coagulated lymph can only be explained by assuming a communication of some kind between the lymph and blood-vessels; the latter probably become eroded from pressure. Some of the spaces inclosed within the network have contents demonstrating the probability of this theory, for there we often find a conglomerate mass of red blood-corpuscles surrounded by homogeneous masses of lymph and clearly outlined particles of fibrin in close proximity to tightly packed masses of blood-corpuscles.

The necrotic areas sometimes seen within the tumor-like foci probably have their origin in a rarefication of the septa or a compression of the blood-capillaries by the pressure exercised by the lymph within the cavities; in this way disturbances of nutrition occur, with retrogressive metamorphosis as a result.

No definite statements can be made in regard to the origin of these lymphangiomata. At all events, nothing can produce them but a strictly localized disease of the lymph vessels. It is probable that lymphatic ectases occur in the spleen much more frequently than we have been accustomed to believe; Fink is even inclined to the opinion that most of the serous cysts of the spleen are genetically related to these growths. In support of this hypothesis he calls attention to the endothelial linings of their walls and to their serous contents.

CARCINOMA OF THE SPLEEN.

Primary carcinoma of the spleen is very rare; secondary carcinoma comparatively more common. *Secondary carcinoma* is usually found in conjunction with cancer of the liver or the stomach; also in general carcinosis and in carcinoma of the lymph glands. The neoplasm usually appears in the form of isolated nodules within the spleen. Only rarely do we find diffuse carcinomatous infiltration or larger growths. Secondary cancer of the spleen is, of course, not curable.

Primary carcinoma of the spleen is very rare. [Rolleston regards it as doubtful if primary carcinoma of the spleen ever occurs. Some of the cases reported as primary neoplasms in this organ are probably instances of the splenomegaly of splenic anemia. (See under Splenic Anemia.)—Ed.] The cases that have been described were either medullary carcinomata or, as in one case, epithelioma. About 10 cases of primary carcinoma of the spleen are mentioned in the literature, but in the majority of cases reported the diagnosis is open to criticism. Thus,

Notta, in a child of five years, diagnosed a tumor in the left hypochondriac region as a primary carcinoma of the spleen. From the description of the course and the findings, it is much more probable that it was a sarcoma of the kidney. No autopsy was made. A primary epithelioma of the spleen described by Gaucher also leaves room for doubt. The same applies to some of the other cases that have been interpreted as primary carcinomata of the spleen. Even the microscopic examinations are not satisfactory.

On the other hand, we are not justified in absolutely denying the primary occurrence of carcinoma of the spleen. Observations by Rokitansky, Brown, Affre, Günsburg, Baccelli, and Mosler seem in part to demonstrate this. The last-named author describes a primary carcinoma of the spleen in a laboring man, aged forty-five. This patient had been treated for bronchiectasis. In addition, examination revealed a very large and very hard tumor of the spleen; no cause for this tumor could be discovered. *Intra vitam* no nodules could be discovered. Icterus and ascites obtained, and rapid loss of strength and increase of icterus led to the exitus. The patient died with symptoms of cholemia and coma. On autopsy a secondary swelling of the mesenteric glands, especially in the region of the porta hepatis, was found to explain, by pressure, the icterus and ascites. The spleen was enlarged in all diameters, and its surface showed yellowish, clearly outlined spots as large as a dollar. They corresponded to nodules that were of greater hardness than the surrounding parenchyma of the spleen. On transverse section these growths had diameters of from 2 to 2½ in., were round, and in some instances stellate in outline, and of a light-yellowish to reddish color. In the liver only a very few isolated nodules of this kind were found. It is incomprehensible that in a case of such great importance no microscopic examination was made; at least, no description of the histologic findings is given in the report. v. Bamberger reports another. He says that in a case of this kind which he observed in a patient of eighteen years, the spleen was so enlarged by several enormous carcinomatous nodules that it was a foot long and nearly half a foot wide. In this case, too, unfortunately, no further description is given.

Diagnosis and Course.—Despite the scantiness of the observations so far recorded for carcinoma of the spleen, Grasset and Notta have undertaken to delineate a clinical picture of primary carcinoma of the spleen. They are of the opinion that it may be possible in isolated cases to diagnose such a tumor. We consider such an attempt as premature. Of the various clinical phenomena observed in the case of carcinoma of the spleen, the most important is the presence of a tumor. In carcinoma the spleen is enlarged moderately, but sometimes to a great extent. Its surface is uneven, and has nodules varying in size from that of a pea or hazelnut to that of a child's fist; occasionally these nodules may be absent. Sometimes the enlargement is very slight, excepting in cases of pigmented carcinoma, where the growth in a very short time assumes enormous proportions. General nutrition rapidly

declines and marasmus frequently supervenes. In most cases profuse diarrhea is observed, and frequently hemorrhages, notably epistaxis.

If, therefore, we find an enlarged spleen on which prominences, irregularities, and nodules can be demonstrated, giving the imaginary projection figure of the spleen an irregular outline, then all these observations may be utilized toward the diagnosis of primary carcinoma of the spleen. However, we should be very careful not to confound these with growths of the left lobe of the liver, and, above all, of the left kidney, such errors being very frequent. If we feel, and possibly see, a tumor in the left hypochondrium, and if this growth move with respiration, then it is a wise rule to consider this primarily as belonging to the spleen or to the left kidney. The decision is frequently easy if, above the visible tumor, the lower margin of the spleen can be felt to protrude below the costal arch on inspiration. The writer has frequently succeeded in doing this in the case of tumors of the left kidney. If this does not succeed we can fill the colon with water, as described in another place.

After having determined that the nodules are really on the spleen, we can usually say that we are dealing with a neoplasm, without, however, being able to make any definite statements regarding the character of the growth. It is more than probable that we are dealing with a malignant neoplasm, as benignant growths are hardly ever found in the spleen unless we except adenomata and cysts; as the former are just as rare and usually much smaller than carcinomata, they need hardly be considered. It is impossible to differentiate a primary carcinoma from a primary sarcoma by palpation. Clinically they are different only in the relative rapidity of their development, a sarcoma usually growing very much faster. Pain, if present, is not caused by the tumor, but by distention of the spleen or the tension of its capsule; consequently this symptom is found with equal frequency in both forms of tumor; a greater amount of pain, however, other things being equal, would favor carcinoma. Circumscribed inflammations of the capsule of the spleen (perisplenitis) are occasionally encountered in all forms of neoplasm; this complication is, as a rule, exceedingly painful, and is recognized clinically by friction sounds felt and heard synchronously with the breathing.

In making a diagnosis our chief reliance must be placed on palpation; if a feeling of fluctuation be elicited, the diagnostic possibilities are manifold. The writer will limit his remarks on the significance of this symptom to its occurrence in malignant growths that can undergo softening—*i. e.*, melanotic and non-melanotic cancerous nodules. He will not dwell on a discussion of the fluctuation felt in cystic degenerations of the spleen and in parasitic cysts and hydatids. Carcinomatous nodules that have become softened often give a distinct feeling of fluctuation, and if an exploratory puncture be made in such cases a small amount of fluid can usually be aspirated; that in cases of non-melanotic carcinomata is white, and in melanotic sepia-colored or inky black. In the former we find so-called "cancer milk," a whitish fluid containing

a varying number of degenerated cancer cells; in the latter, an inky fluid with brown or black cells of a peculiar shape and of large size. If it be probable that a carcinoma is present, then the final, and scientifically most important, part of the diagnosis remains to be made—namely, to decide whether the neoplasm is a primary growth of the spleen or whether it constitutes a secondary deposit in this organ. As melanotic tumors of the spleen are probably always secondary, it is important to decide whether this form of tumor is present in any other organ; the ophthalmoscopic examination of the retina and an analysis of the urine will usually give us the desired information. The urine turns black on contact with the air or on the addition of oxidizing substances. (Compare the writer's dissertation on "A Case of Melanotic Sarcoma of the Liver.")[1] If, on the other hand, we are dealing with a non-melanotic medullary growth we find that some of the nodules are disintegrated and fluctuate, whereas others do not fluctuate, but retain the peculiar soft consistence so characteristic of this form of growth. Here, too, we must determine whether other organs show similar lesions; if so, presumably the spleen is secondarily involved. If other organs are involved, characteristic symptoms may make their appearance as icterus, ascites, etc.

The writer has reported an interesting case of this kind: A woman, aged sixty-eight, was brought to the hospital, suffering from a large nodular tumor of the spleen. The attending physician reported that the disease had developed rapidly. On examination a large spleen was palpated, covered with nodules of varying size; these were not painful on pressure. The only other abnormality discovered in the patient was a liver of great size. Marasmus gradually developed, and soon nodules could be clearly felt and even seen in the left lobe of the liver. The tumor of the spleen continued to increase in size. The blood remained normal, but ascites and icterus developed; the cachexia increased in severity and the patient ultimately died. In the beginning the writer had diagnosed a primary carcinoma of the spleen, but when the liver began to enlarge, when the nodules appeared on its surface, and when, finally, ascites and icterus developed he changed his diagnosis to primary carcinoma of the liver. The postmortem examination proved the correctness of his diagnosis, for a primary cylindroma of the liver, starting in the bile ducts, was found, with secondary metastases in the spleen.

In all such cases it is well to be exceedingly careful and conservative, and to cautiously weigh all the evidence that can have a bearing on the diagnosis.

Treatment.—In view of the uncertainty connected with the diagnosis of primary carcinoma of the spleen, splenectomy, partial resection of the spleen, or other surgical procedures have so far not been employed. It is possible that the future will teach us how to treat cancer of the spleen surgically; for the present, all that we can do is to treat the symptoms as they arise.

[1] *Deutsch. med. Woch.*, 1889, No. 3.

SARCOMA OF THE SPLEEN.

Primary sarcoma of the spleen has rarely been observed. Mosler, in 1875, published a treatise on diseases of the spleen, and mentions nothing of sarcoma. In the year 1881, Weichselbaum [1] reported 2 cases of primary sarcoma and gave complete pathologico-anatomic findings. One case was a primary fibrosarcoma, the other a primary multiple endothelial sarcoma. The primary fibrosarcoma was found in a soldier, who had died at the age of twenty-one, from caries of the mastoid and abscess of the brain. The sarcoma was found on the convex surface of the enlarged spleen. It appeared as a tumor about as large as a walnut, spheric, readily enucleated from the substance of the spleen, and protruded above the surface of the organ by $\frac{1}{2}$ cm. The growth was harder than the spleen itself, and contained numerous whitish stripes arranged in reticular ramifications, and containing in their meshes a peculiar substance very much resembling the pulp of the spleen. That part of the tumor which protruded above the surface of the spleen showed a glandular surface.

Microscopic examination corroborated the naked-eye appearance—namely, that the growth was divided by these white stripes into several lobules of different sizes. The stripes and septa were of different widths and of different structure. The broadest consisted of distinctly fibrillated connective tissue with a few spindle-shaped cells. As the septa became narrower the fibrillary character of the intermediary substance became less distinct, until finally it assumed the appearance of a striped band of connective tissue enclosing a large number of spindle cells and blood-vessels. The structure of the different lobules also varied. In some the matrix and the cells were about equally distributed; the former was either homogeneous or of a finely striated appearance; and the latter, either spindle-shaped, angular, or stellate in outline. In other lobules there was less of the matrix, so that the cells appeared to be closely packed and collected in groups; their shape, too, was slightly different, being more rounded or elongated. Most of the lobules were very vascular; the capillaries were usually filled almost to bursting with blood-corpuscles, and here and there formed a dense network. Owing probably to this abnormal vascularity, extravasations of blood had occurred at different times, so that old and recent hemorrhagic foci and masses of pigment were seen in many of the lobules. In some places the red blood-corpuscles were found in such numbers that the cells of the tumor itself were completely obscured. In other places extravasated red blood-corpuscles were distributed among the round cells of the tumor in such numbers that the whole looked like spleen pulp. Finally, in certain parts of the tumor, small homogeneous plates were seen, with numerous angular processes extending into the surrounding pulp; the addition of hydrochloric acid did not change their appearance, so that apparently these plates were sclerotic connective tissue which had originated from obliterated vessels and from their sheaths. This view

[1] *Virchow's Archiv*, vol. lxxxv.

was strengthened by the fact that the plates were shaped much like longitudinal and transverse sections through blood-vessels and contained yellowish pigment in their peripheral portions. The margin of the tumor was not defined as clearly under the microscope as might have been expected, from the facility with which the growth had been enucleated. In a few places the substance of the spleen adjacent to the tumor seemed to be condensed into a narrow capsule, but in others the tissues of the tumor merged directly into those of the spleen.

Weichselbaum describes as follows the primary multiple endothelial sarcoma that was found, as in the other case, in a soldier of twenty-one years: The spleen was somewhat enlarged, flaccid, dark brown in color, and contained numerous follicles visible to the naked eye. On cross-section were observed a number of reddish-gray, soft nodules, about as large as lentils or peas, and protruding slightly over the level of the cut surface. They were differentiated from the substance of the spleen by their lighter color, but were not otherwise distinctly outlined macroscopically or microscopically. On microscopic examination a network was discovered, showing no distinct alveolar arrangement and not so delicate in structure as the reticulated connective tissue of the spleen pulp; its fibers were much broader and coarser. In the spaces left within this reticulum large irregular plate-shaped cells with one or more processes were found; they resembled different forms of connective-tissue endothelium, inasmuch as they were very thin and sometimes bent and folded into various shapes. Some were much larger than the pulp cells, but more round or oval, with one or two distinct large nuclei. In the peripheral parts of these tumors cells were also found containing red blood-corpuscles or small yellowish pigment granules. The cells were not clearly distinguishable from the reticulum; on the contrary, their processes seemed to merge into its fibers in such a manner that they helped to form it.

The complete absence of red blood-corpuscles, or their presence in small numbers, among the tumor cells readily explains the lighter color of these neoplasms. It is interesting to note that this form of tumor appeared in the spleen alone, and not in any of the other organs.

Birch-Hirschfeld considers the tumor just described as a large-cell focal hyperplasia. Lancereaux, Trélat, and Clark have also described primary sarcomata of the spleen. The case reported by Clark was a congenital sarcoma of the spleen in a child. Trélat's case, according to the report of Malassez and Ranvier, showed the structure of a lymphosarcoma under the microscope. Jordan, of Heidelberg, has also described a case of lymphosarcoma of the spleen in a boy of fifteen, who was otherwise healthy.

In January, 1895, this patient developed a tumor in the upper part of the left side of the neck; the growth was extirpated in June, 1895, and proved to be a lymphosarcoma. In the beginning of 1896 violent pain, increasing in severity, was complained of in the left abdominal region, while the boy's general health remained unimpaired. The patient was received into the hospital on the 12th of August, 1896. Below the left costal arch a tumor was found which was freely movable, was about as large as a child's head, and could be diagnosed from its

position and consistence as a tumor of the spleen. Laparotomy was performed and a sarcoma of the spleen removed, weighing 2 kg., and having glandular metastasis in the region of the hilus. Changes in the blood were seen neither before nor after the operation. Complete recovery occurred. Both tumors were considered to be co-ordinate.

Our knowledge of sarcomata of the spleen has been greatly enlarged since the development of surgery and the facility with which abdominal operations can be performed, so that now we are able to supplement the knowledge gleaned from autopsies by exploratory laparotomies and other surgical inroads. Hacker,[1] Fritsch, Kocher, Flothmann, and Wagner[2] report on extirpations of sarcomatous spleens. Hacker's case was described in Billroth's Clinic, and the only information given in regard to the pathologic anatomy of the growth is that, although the tumor was very large, the remnant of normal tissue was equal to the bulk of the normal spleen. On examination the following record was made: Patient, a woman forty-three years of age; examination in the dorsal position; a tumor is felt that is flat and cake-shaped, the central region of the abdomen protruding far over the level of the rest of the belly. An oval swelling is felt, situated transversely, 71 cm. in circumference, 25 cm. long, 18 cm. in the transverse diameter, which is readily movable all over the abdomen, especially toward the left. The concave surface of the tumor, which is directed toward the abdominal wall, is smooth. On the posterior surface, which points downward and is concave, nodular protuberances can be clearly felt. It is remarkable that the tumor was outlined above and below by a fairly sharp margin. The lower margin showed two distinct indentations, so that the tumor appeared to have three lobes. The lobe on the right side was the smallest. From the history we learn that the tumor was painful on pressure, and that the very violent, almost insupportable pains radiated both toward the shoulder and the sacral region.

In the case of Fritsch, anatomic findings were as follows: Weight of the spleen over 2 kg.; the surface roughened by a number of protuberances of a light-grayish color, about as large as a one-mark (25-cent) piece. Section through these nodules showed a reddish-gray rounded surface, which could be differentiated from the normal spleen tissue, but was not clearly outlined against it. These spots began in the inner third, and usually extended as far as the surface. None was found in the vicinity of the hilus. That part of the spleen which had remained intact corresponded approximately to the bulk of the normal spleen. In the diseased tissue the structure had been obliterated, except here and there where a distinct alveolar configuration could be observed. Between the delicate strands of connective tissue were seen normal leukocytes and large round cells with pale protoplasm, and with nuclei that could be stained. In the middle of the nodules, visible macroscopically, was seen between the cells a peculiar mass that did not stain well, filling out the connective-tissue network completely.

In Flothmann's case[3] a tumor was tightly wedged in under the

[1] *Verhandl. der deutsch. Gesellschaft f. Chi.*, vol. xiii. [2] *Ibid.*, vol. xxiii.
[3] *Münch. med. Woch.*, 1890.

costal arch, and was connected with the tail of the pancreas and with the surrounding organs by a short stem (about 1 cm. long) and numerous other adhesions. The spleen weighed 4 pounds, and through its substance several hundred small tumors were disseminated, which varied in size from that of a pea to that of a hazelnut. In the upper third a tumor about the size of a hen's egg was found.

Wagner-Königshütte[1] describes a sarcoma which he extirpated, as follows: The tumor weighed 1285 gm. Its surface was bluish red and smooth; its consistence something like the liver. The general outline resembled strongly a spleen enlarged in all its diameters. An incision was made parallel to its longitudinal diameter, and revealed the lumina of many vessels cut transversely and longitudinally and filled with blood. The warm, liquid blood exuded, and thereby the consistence of the tumor was greatly changed. It became very soft, and the cut surface now presented a yellowish-white and pale-pink color, homogeneous all over. No trace of the tissue of the spleen could be discovered. Microscopic examination of the tumor revealed that it was very rich in cells. There were round cells with very large nuclei, which again contained numerous nucleoli. In most of the places these cells were massed in small or large circular groups, surrounded by coarse connective-tissue fibers that contained no nuclei, and separated from one another by these strands. Nowhere was normal connective-tissue to be found. The microscopic diagnosis of the pathologist (Marchand) was recorded as follows: "Round-cell sarcoma arranged here and there in a cylindriform manner, so that possibly it is an endothelioma."

In Kocher's case[2] the tumor was a lymphosarcoma.

All cases of sarcoma of the spleen that have so far been observed clinically were found in women of middle age, with the exception of those recorded by Flothmann and Jordan. The tumor of the spleen was the first symptom described, and, as a rule, the diagnosis was very difficult. Billroth, in his case, made a probable diagnosis of neoplasm of the spleen, and suspected sarcoma. In other cases the tumor could be recognized as malignant only when it had been lifted from the abdomen after laparotomy. Following the enlargement of the spleen, the next symptom usually observed is pain. This radiates from the region of the spleen over the whole left lower part of the abdomen, and is very persistent. It bothers the patients very much, and ultimately forces them to refrain from any movement. In exceptional cases the pain radiates forward as far as the right shoulder. The discovery of nodules on the surface of the spleen is of great diagnostic aid. Palpation of these nodules causes pain as soon as any considerable pressure is exercised. It is a peculiarity of sarcoma of the spleen that changes in the blood have, so far, never been discovered. The only other feature that could possibly be considered as characteristic is the rapid growth of the tumor. The neoplasm is usually movable, and rises and falls with respiration. Even long-lasting and widely-disseminated inflammatory processes on

[1] *Verhandl. der deutsch. Gesellschaft f. Chi.*, vol. xxiii. [2] *Centralbl. f. Chi.*, 1889.

the capsule of the spleen rarely lead to adhesions of the organ, because it is so freely movable.

The lesions of the spleen that must be considered in making a differential diagnosis are malarial spleen, abscess of the spleen (characterized by the course of the fever), and echinococcus of the spleen.

Treatment, aside from the alleviation of symptoms, can only be directed toward extirpation of the diseased organ. The prognosis of this operation is, to date, very unfavorable, because in the majority of cases that have been operated upon metastases were found, and the fatal issue so far has never been prevented by the operation. Fritsch records the best success, although he mentions that the patient whose spleen had been removed did not improve very much after the operation. One year afterward this woman presented a very remarkable hypertrophy of the liver. It is possible that extirpation of the spleen for sarcoma will give better results in the future, when more clinical experience is gained in regard to this form of tumor, and the diagnosis consequently made earlier.

Flothmann[1] reports a case of extirpation of the spleen that contained a great many sarcomatous nodules (primary or secondary nodules of the spleen?). This was the case of a man, forty-four years of age, a Hungarian by birth. The spleen was resected, and death occurred from secondary hemorrhage, due to the slipping of an arterial ligature. It was impossible in this case to tip the spleen forward, so that the ligation had to be performed underneath the organ.

Secondary sarcoma of the spleen has been described much more frequently than primary sarcoma. This form of neoplasm is usually found in the shape of single metastatic nodules of the size of a pea or a walnut, seldom larger. The consistence of these nodules is not very much different from that of the tissue of the spleen, and can only be differentiated from it by palpation during life if the surrounding parenchyma be of normal consistence. If, however, the organ be very much enlarged, and this is almost regularly the case if multiple neoplasms exist, and if, as a result of this enlargement, its consistence has been changed, it is an exceedingly difficult task to isolate these small growths by the sense of touch. In fact, this can only be done in those cases where tumors protrude over the surface of the spleen or are particularly hard. The chief diagnostic clue will be the demonstration of small tumors in other organs—*i. e.*, primary neoplasms. It is a remarkable fact that if metastatic sarcomata are found in the spleen, which is very rare, these growths have rarely reached the spleen by continuity, but usually originate from some organ that is very far removed. The writer does not wish to state that this is, without exception, a perfectly regular occurrence, but his experience, and the experience of others that has been recorded, seems to bear out this conclusion. In other cases the spleen is found completely embedded in sarcomatous masses or surrounded by them, and may still be very free from all neoplastic deposits itself. The writer can report a case of this kind which he dissected,

[1] *Centralbl. f. Chi.*, 1890.

and which he considers very instructive and conclusive. It was the case of a rare primary sarcoma of the pancreas with enormous metastases in a boy of four years.

The boy was well nourished and had a very good family history. Toward the middle of September, without any apparent reason, he began to complain of pain in the abdomen, which was spontaneous and could be aggravated by pressure. On palpating the abdomen an enormous tumor mass with various protuberances, ridges, and isolated nodules could be clearly felt. This mass extended as far as the umbilicus, and was situated transversely across the whole width of the abdomen, so that the lower thoracic aperture appeared to be enlarged. It felt very hard and offered much resistance on palpation. The lower part of the abdomen contained no tumor masses. I was absent from town about two weeks, and when I saw the child again he had become emaciated almost to a skeleton, and, despite the enormous loss of flesh, the patient had gained from 8 to 10 pounds. The abdomen was enormously distended, and great tumor masses, separated into lobules, could be seen through the skin. Hard nodes and protuberances could be felt, so that the diagnosis of neoplasm seemed apparent. Further, owing to the enormous rapidity of growth, the probability of its malignancy was great. The tumor masses were uniformly solid, as hard as stone, and very painful to the touch; they extended all over the abdomen and downward below the umbilicus. Several metastases in the form of nodules could be felt in different places through the abdominal walls. It was not possible, however, to outline any of the organs nor to show where these metastases were situated. Over the whole abdomen, even in the region of the intestine, absolute dulness was elicited. No ascites was present. The patient, who, as we have said, had become emaciated to a skeleton, would take no food, and in spite of this, diarrhea existed. The urine was normal.

The autopsy, which was made shortly after this examination, revealed the presence of an enormous cancerous neoplasm, filling the whole abdomen. The single masses of tumor were as large as two adult fists; hemorrhagic spots were disseminated all through them. They seemed to be connected by a mass of degenerated cancerous tissue. One was found in each hypochondriac region, the third and largest in the middle—that is, in the umbilical region. The intestine, which was collapsed, was adherent everywhere to the tumor masses and pushed backward, so that enormous masses of tumor were seen everywhere. On further examination I could demonstrate that the tumors extended without interruption as far as the kidneys, and in such a manner that these organs were so completely embedded in cancerous masses that I could only enucleate them with the greatest difficulty. When they were removed it was readily shown that they could not possibly have been the starting-point of the neoplasm, because the neoplasms found in these organs were readily characterized as metastases, whereas the real cancer had grown inward toward the hilus, from without. Both ureters were compressed by the tumor, so that a bilateral hydronephrosis had occurred. It was a difficult matter to discover the primary seat of origin of the neoplasm. The pancreas was converted into an enormous tumor. From here the cancerous masses extended to the mesentery, which was completely adherent to the tumor mass, especially that part belonging to the small intestine. The cancerous mass had even eroded the intestine and grown into it. From the mesentery the tumor extended to the retroperitoneal lymphatic glands, which were enormously enlarged and converted into medullary masses of neoplasm. The normal mesenteric attachments of the colon—appendices epiploici—were completely transformed into ridges of cancerous tissue that stood out from the intestine as stiff, conic masses.

I will mention that the microscopic examination of the tumor showed it to be a small-cell sarcoma which was very similar to a lymphosarcoma; and, further, that the indications pointed to the pancreas as the primary seat of the tumor. Professor Virchow corroborated this opinion. I wish, however, to particularly emphasize that the spleen was absolutely intact and showed no trace of pathologic changes. This is particularly interesting, because all the surrounding organs were embedded in tumor masses or incorporated in them, even those, like the pancreas, which belonged to the portal system.

Finally, I wish to call attention to the fact that in any form of tumor that particularly involves the liver, secondary metastases in the spleen are not quite

so rare. This is particularly the case in melanotic sarcomata of the liver. These, of course, are metastases of pigmented tumors of the choroid. As they develop we frequently find a great increase in the size of the spleen, which could possibly be due to chronic venous stasis. In some instances, however, this enlargement is due to the presence of metastases of melanotic sarcoma. Sometimes these sarcomatous nodules are found to be disintegrated, so that they fluctuate, and here an exploratory puncture is necessary to differentiate them from genuine cysts. They are usually solitary and characterized by their inky contents. The blood in these cases shows no abnormalities.

RUPTURE OF THE SPLEEN.

Etiology.—Rupture of a normal spleen is a rare occurrence; as a rule, it is a result of violence, and the liver as well as the spleen is torn. Dieffenbach[1] reports a case of rupture of the spleen in a moderately corpulent man of thirty-nine years, who fell from the third story into a baluster and struck on his abdomen. He was unconscious for half an hour before he was found and removed to the hospital. The skin of the forehead was cut over the eyebrows, but the bones of the head were not broken; the skin over the abdomen was ecchymosed. The patient soon regained consciousness, and seemed to be trying to relieve the pain that he felt in the region of the spleen by lying on the left side and by pressing his hands against the left hypochondrium. His face was pale and distorted with pain, his breathing free, the apex beat weak, and the pulse small and empty. Applications of ice were made, counter-irritation applied to the skin over the spleen, and restoratives and tincture of opium administered. In spite of all treatment the patient died in a very short time. On autopsy no other external injuries were found than the wound on the forehead; the hilus of the spleen was torn in several places, and several of the splenic vessels had been ruptured. The spleen was covered with coagulated blood, and the abdomen was filled with from 3 to 4 quarts of a reddish watery fluid that seemed to consist chiefly of blood. In this case rupture of the spleen was caused by the impact, so to say, of the patient's own body.

Zuehlin[2] reports a case of rupture of the spleen that occurred in a different way, although again through violence. A piece of wood, weighing 10 pounds, falling from a height of 80 feet, struck a laborer, sixteen years old. He immediately collapsed, but seemed to recover at once and walked some 20 steps, only to collapse again; he was powerless to rise and was transported to a hospital, where he died, with the symptoms of internal hemorrhage, seven and a half hours after the accident. On autopsy it was found that the spleen was torn in two places, and that a small piece of the organ had been completely torn off.

Rupture of a diseased spleen occurs in a different manner from rupture of a normal organ. In the former case a very slight injury frequently suffices to produce this lesion; occasionally the movements of the patient's body have been known to cause rupture of the spleen, so that the external cause is usually altogether out of proportion to the serious effect that it produces. For this reason rupture of the spleen

[1] *Med. Zeits.*, Berlin, 1833, vol. vi. [2] *Schweizer Correspondenzbl.*, 1874.

has a certain medicolegal significance. Most of the reports come from regions in which diseases of the spleen are indigenous—notably from swampy and tropic districts. We know most about rupture of the spleen in malaria. Playfair observed 20 cases in the East Indies in a period of two and a half years. Stadkowsky, in Volhynia, performed autopsy on 7 people during ten years who had died of rupture of the spleen. The French naval physician Barallier[1] has given us very exhaustive accounts of cases of rupture of the spleen in malaria. Most of his observations were made in young people who had passed through several attacks of intermittent fever, had apparently recovered, and were going about their business with a feeling of complete health. Several of these suddenly died in syncope. Skerit,[2] Bowie,[3] and Stone[4] also report a number of cases of rupture of the spleen from the island of Mauritius. Bowie particularly mentions a case in which the patient, who died of rupture of the spleen, had suffered only from two very mild attacks of malaria. Corre also reports numerous observations of this kind made in the tropic colonies of Guadeloupe. This author especially describes the direct cause in each case. Thus, he observed rupture of the spleen during vomiting, or as a result of a very slight push or blow, and even from a simple fall. Cimbali[5] observed rupture of the spleen in a man of sixty-five, who had been a sufferer from malaria for many years. A large tumor of the spleen was found extending as far as the spine of the ilium. One morning, as the patient was getting out of bed, he suddenly felt a severe pain in his left side, and soon turned pale and cyanotic. The pulse became small and thready, coma resulted, and the patient died in a short time. An autopsy was performed, and a tear from 3 to 4 cm. long was found in the upper third of the enormously enlarged spleen. This tear led into a large cavity filled with broken-down tissue and blood. Palmer reports a case of exceptional interest. He saw sudden death follow rupture of the spleen in stokers who were performing their ordinary labors. In view of the fact that so many seafaring men have been exposed at one time or another to malaria, it is probable that a great many cases of otherwise unexplained sudden death occurring in stokers and coal heavers are attributable to rupture of the spleen. This point should be considered in medicolegal questions pertaining to deaths occurring at sea.

How does rupture of the spleen occur? In discussing this question we must remember that, aside from direct violence which may occur in the normal organ, rupture is seen only in spleens that are enormously enlarged and the parenchyma of which, in consequence of long-lasting morbid processes, has lost its natural resistance. In other words, we are dealing with very fragile tissue; in addition, this tissue is hyperemic and distended, so that the whole organ is under considerable pressure. The capsule, as a rule, is very tense. If under these circumstances some external violence—as a push, a blow, a sudden turning of

[1] *Gaz. de Med.*, 1878.
[2] *Brit. Med. Jour.*, 1878.
[3] *Lancet*, 1892.
[4] *Brit. Med. Jour.*, 1878.
[5] *Bull. degli osped. di Roma*, 1890, vol. iii.

the body—act upon the spleen, the movement communicated to the organ is not distributed to it in all directions, at least not as uniformly as it would be in a normal organ. In other words, the impulse exercised its whole effect almost exclusively at the direct point of contact. The tissue being fragile, it is readily split asunder and, as a result, rupture of the spleen occurs. It will depend on the force of the impulse and the resisting power of the capsule whether this tissue be also torn. In many diseases that lead to large swelling of the spleen—and it is the swollen spleen that ruptures most frequently—the capsule participates in the diseased process. The capsule, in addition to being under strong pressure, is degenerated and inflamed, and consequently has less resisting power than under normal circumstances. On autopsy the diseased condition of the capsule is usually apparent, and deposits will frequently be discovered that may be the cause of adhesions between the capsule and adjacent parts of the abdominal parietes. Such adhesions are important for the mechanical understanding of rupture of the spleen, because they are often the cause of a complicated form of rupture. If, for instance, a blow strikes a spleen that is anchored by its capsule in this way, that part of the parenchyma of the spleen nearest the adhesion will be subjected both to the impulse of the blow and to the tugging of the adhesion upon the spleen itself; this conjunction of traction and pressure can readily cause the tearing off of a piece of the organ.

Rupture of the spleen is very rare in the newborn and in infants. Coutange[1] has described such a case in an infant who was dropped from a great height by its mother and sustained a fracture of the skull. The rupture of the spleen here occurred by contrecoup. The spleen was enlarged and weighed 17 gm. This probably favored the occurrence of the rupture. During the discussion which occurred in the Paris Society, where this case was reported, another case of rupture of the spleen during labor was described, and a third in which a threefold rupture of the spleen had occurred, which afterward healed. Unfortunately, no details of the diagnosis in this latter case were given.

Symptomatology and Course.—The clinical picture of rupture of the spleen is almost identical with that of severe internal hemorrhage. The first symptom the patient describes is a violent pain, which usually renders him unconscious; this corresponds to the tearing of the spleen. The pain is found in the region of the spleen, but radiates from there into the surrounding parts. The patient often presses his hands against his side, as if he wished to compress the spleen. Very soon after the first excitement following the accident, symptoms of great loss of blood are observed. The patient grows pale and dizzy and usually faints. Vomiting and spasms are frequent, the skin grows cold, the pulse small and very rapid; gradually unconsciousness supervenes. On inspection the abdomen is usually seen to be distended; on percussion dulness can usually be elicited in some of the deeper-lying portions of the abdomen, the size and outline of which will vary with the quantity of blood shed.

[1] "Note sur un cas de déchirures traumatiques de la rate chez un enfant de 10 jours," *Ann. d'hyg. publ.*, xxv., 1890.

This dulness, of course, is due to the blood that has been poured into the peritoneal cavity after rupture of the spleen. Sometimes the result of percussion is different than that described above if the spleen be adherent and wholly or partly torn loose from its anchorage. In these cases a percussion outline that is not at all regular is found in the region of the spleen. The blood pouring out of the ruptured spleen cannot gush as readily into the abdominal cavity, and consequently accumulates near the place of rupture and fills out the whole space between the capsule of the spleen and the peritoneal covering of neighboring organs. It is very desirable in diagnosing rupture of the spleen, at least so far as percussion is concerned, that the examining physician should know the size of the spleen prior to the accident.

In case an enlarged non-adherent spleen rupture, its volume, owing to the loss of blood, will decrease. Under certain circumstances, however, when many adhesions exist between the covering of the spleen and that of neighboring organs, the dulness in the region of the spleen may become more extended after rupture, and quite frequently assumes a very irregular outline.

Symptoms only occasionally observed in rupture of the spleen are bloody stools and vomiting of blood. These occur when some connection existed between the ruptured spleen and the stomach or intestine, so that the accident established a communication between the spleen and the digestive tract, through which the blood of the spleen could pour into the stomach or intestine. In a few of the cases where this occurred, the bloody dejecta have been examined for spleen parenchyma.

Pathologic Anatomy.—The condition of the spleen itself is the most interesting pathologico-anatomic finding. It may be found torn in almost any place, and no point of predilection can be discovered on examination of a large number of autopsy reports. The general impression is conveyed that tears occur relatively more frequently on the outer surface than at the hilus of the spleen. This can possibly be explained from the position of the spleen, the outer surface offering a much wider field for the action of external violence. No regularity exists in regard to the direction of the tear. Sometimes it is longitudinal, sometimes transverse to the long axis of the spleen; sometimes it extends from above below, from without within, and *vice versâ*. A few figures have been given in the paragraph on Etiology in regard to the usual length and depth of single tears. Frequently not only 1, but 2 or 3 tears, may be found in the same organ. In addition to simple tears, complete separation of single parts of the organ or tearing loose of the whole organ may be seen. The capsule and the parenchyma are usually both ruptured. Certain cases, however, have been reported that show a peculiarity in this: the capsule of the spleen was uninjured, whereas the parenchyma was torn so that the blood had accumulated underneath the capsule and distended it. In spleens that have become ruptured we usually find in addition to the tears general changes in the organ, which have their origin in the primary disease that led to

the enlargement of the spleen and predisposed it to rupture. Occasionally, in autopsies made on cases of rupture of the spleen, evidence of infarction has been observed.

The position that the blood assumes within the peritoneal cavity after the rupture is most important. Two types can be distinguished, depending exclusively on the presence or absence of adhesions with neighboring organs prior to rupture. If adhesions existed the blood will be found in the space made by the bands of adhesion between the two organs that happen to be connected; provided, of course, that a pocket-shaped space was formed. If such adhesions do not exist the blood will pour directly into the peritoneal cavity; it is often possible in these cases to follow the course taken by the blood after the accident. The torn spleen is usually covered with coagulated blood, and, starting from it, strands of coagula and of fluid blood are seen to run downward, sidewise, and backward. In a case reported by Jowers-Lloyd a blood-coagulum completely filled the tear.

Diagnosis.—The diagnosis of rupture of the spleen is very difficult, for the reason that the clinical picture of this lesion resembles exactly that of any other internal hemorrhage, so that in most cases we have to be satisfied with a probable diagnosis. That some abdominal organ has ruptured can be assumed from the sudden collapse, the pallor, the smallness and rapidity of the pulse, the colicky spasms, the distended abdomen, and the very violent pain. We are aided somewhat in the diagnosis if we know that the patient had a tumor of the spleen as a result of malaria, typhoid, or anemia, or that he was a bleeder. In these cases rupture of the spleen will produce a diminution in the volume of the organ and will usually give it an irregular shape. If in addition to all this we can elicit percussion dulness in some part of the abdomen which might signify the outpouring of blood we are much advanced toward the diagnosis of rupture of the spleen. This dulness may be quite characteristic, as in certain cases reported by Kernig. In one of his cases the rupture of the spleen occurred subacutely, and he could follow by percussion the gradual movement of the blood from the region of the spleen into the left, and later into the right, iliac fossa, all within the first twenty-four hours after the rupture.

As the disease progresses—if the patient survive the accident—the occurrence or absence of peritonitis is frequently of value in the differential diagnosis, for the reason that peritonitis rarely follows a rupture of the spleen. In ruptures of the liver, bile ducts, kidneys, pelvis of the kidney, ureters, bladder and, above all, of the stomach and intestine, peritonitis always results. In ruptures of the stomach and intestine, in addition, the diagnosis is corroborated by the presence of air in the abdominal cavity; this can be discovered by percussion. Rupture of cysts of the spleen, especially echinococcus cysts, can be differentiated from rupture of the spleen proper by the absence of grave symptoms of anemia; they have in common the pain in the region of the spleen. The location of the pain here is characteristic of rupture of the spleen, as against rupture of some other abdominal organ. If the spleen be

adherent to the stomach or intestine, rupture sometimes causes hematemesis or melena.

Prognosis.—The prognosis of spontaneous rupture of the spleen is very unfavorable. With very few exceptions the issue has been fatal, death occurring, as a rule, immediately after the rupture. Sometimes death was delayed for several hours; rarely a day or longer. However, isolated cases of recovery after rupture of the spleen have been reported. Müller-Kalman[1] and W. Kernig, in Warsaw, each report such a case. In view of the great difficulty of making a positive diagnosis of rupture of the spleen, such communications in regard to spontaneous cure must be accepted with some reserve. Whether the future will give us a surgical treatment for spontaneous rupture of a diseased spleen is uncertain. If an operation could be elaborated, of course the prognosis would be better. We must never forget, however, that we are dealing with patients who are usually afflicted with some severe general affection, as malaria or typhoid, and who cannot well stand a surgical operation of any magnitude. So far, only extirpation of a spleen ruptured by external violence has been attempted.

Vincent publishes some statistics about rupture of the spleen. He has collected 100 cases. In 76 of these very copious hemorrhages occurred into the peritoneal cavity. In 52 of these cases death was caused by peritonitis; in 13 by pneumonia, and in the remaining cases by internal injuries that occurred simultaneously with the rupture of the spleen. Of 77 cases that died with the symptoms of rupture of the spleen, 58 died within from two to twenty-four hours; 41 surviving the injury only two hours. The remaining 19 survived several days, so that very few cases would remain in which surgical interference, assuming that a correct diagnosis had been made, would have been possible, and of these a certain proportion would have been inoperable on account of the malarial cachexia from which they were suffering.

Treatment.—Slight external violence, as a blow, a push, or even the movements of the patient, may cause rupture of a chronically enlarged spleen or of a rapidly developing acute tumor; the reason for this is that the tissues of the spleen, under the above conditions, are very tense and are under considerable pressure. Knowing this, we should caution every patient with a large splenic growth to beware of all sudden and violent motions, and to be exceptionally careful not to expose himself to the slightest injury.

[Puncture of an acute splenic tumor, as in malaria or typhoid, has been followed by rupture with serious hemorrhage. It is rarely necessary, now that the technic of the bacteriologic examination of blood drawn from the peripheral veins has been perfected, and should, as a rule, be avoided.—Ed.]

Such caution should be especially exercised in the case of malaria, because it seems that here the most insignificant causes have sometimes produced rupture in a most unexpected and unforeseen manner. For instance, the simple stretching of a limb in bed, or rapid change of

[1] *Orvosi hetilap*, Pest, 1876.

position from one side to another, in one case simply rising in order to take some food, has been known to cause rupture. As such patients are usually in bed, it is the duty of the attending physician to warn the nurse, in a hospital, or the family, at home, of this particular danger; and the physician himself should consider it in making physical examinations of the spleen. Both percussion and palpation should be executed as gently as possible, and not undertaken any more frequently than seems absolutely necessary in order to arrive at a complete understanding of the patient's condition. In case of rupture an ice-bag should immediately be placed over the region of the spleen, followed, according to Mosler, by injections of ice water into the rectum. Several liters of ice water should be poured into the colon with an ordinary irrigation tube, the patient lying on his back. Mosler's idea was to compress the spleen from below in this manner. The injection of ergotin subcutaneously can be considered in the treatment of the hemorrhage, and in the treatment of pain the subcutaneous exhibition of morphin or the administration of opium in doses not too small. We can also attempt to treat the collapse by the administration of excitants and reviving remedies, as, for instance, wine, ether, camphor, and musk, or we may bandage the extremities and elevate them. Ledderhose has also suggested transfusion, Riegner reporting success with it in his case.

[In the treatment of the hemorrhage attendant upon rupture, calcium chlorid may be used, or adrenalin solution or gelatin may be injected subcutaneously. This latter should, of course, be properly sterilized, in order to avoid the danger of infection with tetanus bacilli, for this accident has occurred in not a few cases where gelatin has been employed as a hemostatic.—Ed.]

Nussbaum was the first to advise the surgical treatment of rupture of the spleen—namely, extirpation of the organ. In his monograph on injuries of the abdomen he expresses himself as follows: "If the condition be so desperate and hemorrhage so violent that compression is excluded, then the question can arise whether we are not justified in adopting radical means, and whether or not, if the surroundings are at all favorable, we should perform a laparotomy (the dangers of which have been reduced so much nowadays), wash out the clots, ligate the vessels of the spleen, and remove the organ. It will rarely happen that a surgeon is present at the time of the accident, with everything needed for antiseptic methods, but in so violent an accident as rupture of the spleen with hemorrhage that threatens life we must seriously consider whether it is better to watch the patient's progress toward certain death or whether we should attempt an extirpation of the spleen. If we make up our minds that the patient must certainly die unless the spleen be extirpated, then I honestly believe that the attempt should be made."

O. Riegner[1] acted on this suggestion of Nussbaum. His case was that of an apprentice, aged fourteen, who suffered an injury causing the spleen to rupture. The organ, so far as was known, had been perfectly normal up to then. The diagnosis of rupture of the spleen was made. O. Riegner describes the

[1] *Berlin. klin. Woch.*, 1893, No. 8.

course of the operation and his findings as follows: "The operation was performed on the morning after the accident, the patient having fallen from a scaffolding the evening before. Under aseptic precautions the abdomen was opened in the median line by a very large incision. Immediately on entering the peritoneal cavity 1½ liters of thin, pinkish blood gushed out. This made inspection of the abdominal cavity very difficult, although the assistant sponged as rapidly as possible. It looked, however, as though the blood were pouring from the right hypochondriac region and was oozing out from under the liver. This determined me to make a transverse incision toward the right, underneath the costal arch. Behind the liver a large number of clots was found, and a considerable quantity of fluid blood. The liver, however, was found to be uninjured. The intestine was now lifted out of the peritoneal cavity, wrapped in compresses wet with warm sterilized salt solution, and placed to the right side. In the left side of the abdomen large masses of spongy coagula now became visible, and among them several particles of what could be easily recognized as spleen tissue. In order to expose the spleen more rapidly for the purpose of extirpation, an incision was carried to the left. The spleen was found to be completely severed transversely. The lower half was found lying loose in the abdomen, unconnected with its blood-vessels or its upper half, and was at once removed. The upper half was still in connection with the phrenosplenic ligament and the vessels of the hilus that were intact. The latter were ligated and the piece of spleen removed. No additional hemorrhage seemed to occur from the wound in the spleen nor from the blood-vessels. All bleeding vessels that could be found and all that were simply contused were ligated. The other abdominal organs were rapidly inspected and found to be intact. The parietal peritoneum was smooth and shiny all over. The clots were removed as quickly as possible, the intestine replaced, and all the incisions through the abdomen closed with simple sutures, and a pressure bandage applied. In the meantime 300 gm. of a 0.6 per cent. salt solution had been injected subcutaneously into both arms and thighs. On the fifth day after the operation the first signs of gangrene appeared in the left lower extremity, and the expectant plan was adopted. About four weeks after the operation the left thigh was amputated by Gritti's method. After three weeks the patient was dismissed, completely restored to health."

In this case of O. Riegner's the conditions for operation were especially favorable, as the spleen was perfectly normal when the rupture occurred. It would be very much more difficult to perform an operation if a spleen should be ruptured that was very soft or chronically diseased and already loosened from its surroundings. When we consider what Ledderhose says—that we are dealing in a great many cases with patients suffering from typhoid or recurrent fever, in whom all abdominal operations are exceptionally dangerous (as we know from our experience in operations for perforations and peritonitis)—we can understand why the prognosis of laparotomy for extirpation of the spleen must be very bad. The same applies to patients suffering from severe forms of malaria, in whom the spleen is very much enlarged and frequently adherent and the blood changed in its consistence. Operations for ruptured spleen in these cases do not offer as much hope of recovery. At the same time it is possible, or at least imaginable, that in those cases where the changes in the spleen are only slight and the general strength of the patient is not too much reduced, such an operation might occasionally be successful.

Schönborn formulates his views in regard to the general question of splenectomy in malaria as follows: "In large tumors of the spleen caused by malaria that do not yield to any internal medication and cause a great deal of distress, splenectomy should be attempted only if the

general condition of the patient be relatively good—that is, if no malarial cachexia or anemia and no melanemia exist."

From this statement the writer feels justified in concluding that he is not opposed in principle to splenectomy in ruptures of the spleen in malaria. Ledderhose's expectation, which we have quoted above, that in cases of this kind splenectomy might occasionally lead to a favorable result has since been verified. Vincent has performed an operation in rupture of a large spleen in malaria and was successful. He reports as follows:

A man of thirty-seven, suffering from enlargement of the spleen due to malaria, fell on the trunk of a tree and ruptured his spleen. The signs of internal hemorrhage appeared, with violent pain in the region of the spleen. Very soon symptoms of large extravasations of blood into the abdomen and left pleural cavity, causing compression of the lung on the same side, became manifest. Laparotomy was performed, and from 2 to 3 liters of fluid and coagulated blood removed from a large cavity situated on the left side, underneath the diaphragm. The peritoneal cavity was washed out and drained. The patient recovered.

The same author reports another similar case that is not quite so clear.

A woman of twenty-eight, with a malarial spleen so enormous that it extended into the pelvis and Douglas' pouch, was operated upon. The tumor appeared at first to be a cyst of the ovary. An attempt was made to loosen the adhesions which had formed, and in this manipulation the tumor was torn. Extirpation was not performed, but sponging was done for a long time, and finally the abdominal wound closed. Recovery took place, and the tumor gradually became smaller until it was no larger than an egg.

Appendix.—Besides malaria, typhus, typhoid, hemophilia and anemia are important in the causation of rupture of the spleen. Rokitansky has reported rupture of the spleen in typhoid in cases where the swelling had occurred very rapidly. Chrostowski,[1] in Warsaw, reports findings in rupture of the spleen in typhoid. In one of his cases rupture was caused when the patient fell out of bed. Considerable hemorrhage was found in the parenchyma of the spleen and a rupture of the capsule. In another case of Chrostowski's, rupture of the spleen occurred without any apparent cause. This case rapidly terminated fatally. Wittmann[2] reports an interesting case where rupture of the spleen was seen in typhoid fever in a boy of ten years. Clinically the case was characterized by hemorrhages from the mouth and the anus, subsequent rapid sinking of the body temperature, thready pulse, and sudden, fatal collapse. On autopsy the following was found: In the stomach a considerable quantity of "coffee-ground" fluid, which colored the whole fundus bloody. The mucous lining of the stomach showed small abrasions about as large as pinheads. In the intestine a tarry fluid was found in large amounts. The Peyer's patches were infiltrated, and some of them ulcerated at the apex. In place of some of the plaques, ulcerations as large as hazelnuts were found. The mesenteric glands were infiltrated and as large as peas, some of them as large as walnuts. The liver was pale; the spleen four times its

[1] *Denkschr. f. Hoyer*, 1885.

[2] *Jahrb. f. Kinderheilk.*, vol. ix.

natural size, pale, soft, and on its outer margin was found a tear 2½ in. long, and extending for an inch into the tissue of the organ. The rupture began at the hilus, extended toward the outer margin, and ended on the upper surface of the spleen, about ½ in. from the margin. Another tear was seen about 1 in. away from the first and connected with it. It was directed toward the point of the spleen, beginning at the hilus and ending ¼ in. from the outer margin, the course of which it followed to the lower surface of the spleen.

[Spontaneous rupture of the spleen in typhoid seems to be extremely rare. No case has come under the writer's notice, nor has he to the best of his recollection heard of one in Chicago, although for some years there was a great deal of typhoid fever there. Osler has seen no case of spontaneous rupture in typhoid at Johns Hopkins.—Ed.]

Russ[1] describes rupture of a spleen, that was twice as large as normal, in the case of a bleeder. The spleen was found lying on the iliac muscle, in the iliac fossa. It was soft, dark in color, and showed several ruptured places on its inner margin. Rupture of the spleen has also been observed in anemic cases. In one case the patient had only been sick for fourteen days, and aside from the general loss of strength had developed no symptoms excepting epistaxis.

Aufrecht[2] observed rupture of the spleen in a case of miliary tuberculosis of the abdominal organs.

If infarcts are present in a spleen, the organ seems particularly predisposed to rupture.

Simpson, Wilson, and Sidey report several cases of rupture of the spleen during pregnancy and the lying-in period. Simpson attributes the rupture to a peculiar condition of the spleen due to pregnancy. He states that during pregnancy the leukocytes in the spleen are greatly increased, causing the organ to become voluminous and less resistant. In other cases observed during labor rupture of the spleen occurred, but these cases had been complicated with malaria. It was stated that the movements of the body before and during labor produced a tear in the spleen, which was already predisposed to rupture. The involuntary movements and stretching of the upper part of the body are said to be particularly dangerous in this respect.

Cohnheim[3] reports a particularly interesting case in which death occurred following rupture of varicose veins of the spleen. The diagnosis of internal hemorrhage had been made during life, and the following was found on autopsy: "Nearly 1 liter of a bloody fluid and large masses of soft clots were found in the abdominal cavity, particularly in the left hypochondrium, so that the source of the hemorrhage could not be doubtful. The spleen was found embedded completely in this coagulum and was considerably enlarged, being 6 in. long, 5 in. wide, and at the place of its greatest diameter 2 in. thick. Its surface was uneven, the capsule protruding here and there, owing to the presence of numerous round ridges that were colored black-blue and were soft

[1] *Med. Times*, 1868.

[2] *Virchow's Archiv.*

[3] *Ibid.*, vol. xxxvii.

and almost fluctuating. In the middle of one of these ridges near the upper end of the spleen a tear was seen, irregular in outline, about ¾ in. long, and filled with loose coagulated masses. On section the organ was found to be riddled with irregularly shaped cavities that were also filled with coagulated blood. The largest of these cavities (of the size of a goose egg) was situated in the central portion of the spleen. From it channels extended to the upper part of the posterior margin, where the tear opened into one of the channels. After removal of the coagulated contents the character of this cavity was shown very clearly, and it was seen that it consisted of a number of indentations separated by ridges; further, that its walls were everywhere smooth and shiny, reddish white in color, and resembled the wall of veins. The only place in which the smooth lining of this cavity seemed to be interrupted was toward the upper end of the spleen, where, on the removal of loose clots, torn and macerated spleen pulp was seen. The whole parenchyma of the spleen was riddled by these holes. Most of them were small, about as big as a pea or a walnut, but analogous in structure to the large central cavity. They all communicated with each other, and some of them with the large central cavity."

SPLENECTOMY.

Splenectomy means total extirpation of a healthy or a diseased spleen. Resection means the partial extirpation. These operations have, so far, been performed for two conditions: First, for pathologic changes in the spleen; second, for injuries to the spleen. In the following the writer will refrain from discussing the latter contingency, limiting his remarks exclusively to the former.

It will depend upon our views as to the significance of the spleen in the human economy whether we are justified under any circumstances in advising the operation of splenectomy. The question is, Can a human being live after the spleen is removed? The first clues to the solution of this problem were given by a series of animal experiments originally undertaken for another purpose. A. Bardeleben, in 1841, published the first experiments directed toward elucidating the mysterious function of the spleen. These publications are classic. The changes which followed removal of the spleen were studied, and one of the first discoveries made was that animals could live without the spleen. Following extirpation, however, certain changes in the blood and lymphatic glands were observed. Thus, Zesas noticed enlargement of the mesenteric glands, and Winogradoff an increase in the volume of all glands, especially the glands of the neck and of the mesentery. The changes in the blood were an increase of the white blood-corpuscles, often accompanied by a decrease in the number of red ones. The disturbance in the blood, however, is only a transitory one. Vulpius first made this phenomenon the subject of experimental study. He extir-

pated the spleen and paid especial attention to the clinical phenomena observed. He summarizes his observations as follows:

First. Extirpation of the spleen produces a transitory decrease in the number of red, and an increase in the number of white, blood-corpuscles.

Second. The thyroid cannot vicariously assume the function of the spleen.

Third. The lymphatic glands and the bone marrow show an increased blood-forming activity after the removal of the spleen.

Fourth. The regeneration of the blood after loss of blood is probably less rapid in individuals in whom splenectomy has been performed.

Certain changes in the quantity of hemoglobin have also been noticed in animal experiments. The hemoglobin has usually decreased. There can be no doubt that animals can survive extirpation of the spleen without permanent injury. The question arises, "Can the experience we have gained from animal experiments be applied without further comment to similar phenomena in man?" Certainly not without a number of reservations. A man reacts, to judge from our clinical experience, much more vigorously to removal of the spleen than do animals. Notably, one thing must be emphasized—we are comparing the extirpation of the normal organ in man with the extirpation of the normal organ in an animal, and under these conditions it is true that the changes observed in man are very similar to those seen in animals. We note the increase in the leukocytes, the reduction in the number of red blood-corpuscles, and the decrease in the hemoglobin of the blood; and clinically, as an expression of these disorders, leukocytosis, great pallor, and loss of flesh. In addition to these, however, it seems that still other morbid phenomena can be observed in human beings. Thus, Credé reports that in a case in which the spleen had been removed for a large cyst, myxedematous symptoms appeared in addition to the blood-changes four months after the operation. A peculiar leathery consistence of the skin also was noticed, so that it was necessary to make incisions of $\frac{1}{2}$ cm. before blood would flow. The thyroid was doughy and enlarged and remained so for over four months. It did not regain its normal dimensions until the general condition of the patient's health had improved very much. Ceci reports that after extirpation of the spleen he observed enlargement of the thyroid, with fever, emaciation, and great hypertrophy of the tonsils.

Lennander has made very careful studies of the changes in the blood of human beings after extirpation of the spleen. In one of his cases, a woman of twenty-eight years, the spleen was considerably enlarged, and he reports as follows: "The anterior percussion line extended to the parasternal line, the lower margin to the level of the iliac crests. The spleen could be palpated, and its anterior median margin could be felt beyond the middle line toward the right. The organ could also be tipped upward, so that the median anterior surface could be felt." The cause of the enlargement of the spleen could not

be discovered. Possibly the patient had at one time suffered from intermittent fever. Anatomically the tumor was a "spleen adenoma."

Before the extirpation of the spleen the blood-examination gave the following result: The blood-corpuscles were normal; there were no poikilocytes nor microcytes. The number of red blood-corpuscles was 4,600,000 in the c.mm., of the white, 14,000 in the c.mm. (1 : 319); hemoglobin, with Fleischl's hemometer, 50 per cent.

Extirpation of the spleen was undertaken on the 26th of September. The examination of the blood performed later gave the following figures: In 1 c.mm. of blood there were:

Date.	White blood-corpuscles.	Red blood-corpuscles.	Proportion of white to red blood-corpuscles
October 5, 1895	13,000	3,200,000	1 : 246
October 7, 1895	15,000	4,800,000	1 : 320
October 17, 1895	14,000	4,900,000	1 : 350
October 21, 1895	14,000	4,700,000	1 : 336
October 24, 1895	13,000	4,100,000	1 : 315
October 28, 1895	14,000	5,100,000	1 : 364
November 16, 1895	14,000	4,500,000	1 : 322
February 3, 1896	. . .	4,200,000	normal
March 9, 1896	no count	4,700,000	

According to this table the proportion of the white blood-corpuscles to the red showed nothing remarkable. The appearance of the red blood-corpuscles seemed normal. The hemoglobin determinations with Fleischl's hemometer gave the following results on different days:

October 20, 1895, 70 per cent.
October 29, 1895, 65 per cent. (On the same day a large (syphilitic?) wound on the leg of the patient had divided into squares of from ½ to 1 sq. cm. in size, as a result of deep scarifications.)
November 4, 1895, 65 per cent. (Patient had diarrhea for several days.)
November 11, 1895, 67 per cent.
November 16, 1895, 66 per cent. (After correction according to Dehio's and Tomberg's tables, 68.8 per cent.)
November 24, 1895, about the same.
February 3, 1896, 65 per cent.
March 8, 1896, about 80 per cent.
March 10, 1896, 80 per cent. Day of discharge.

In a case reported by Burckhardt, operated on for splenic leukemia, the following blood-picture was found before operation: Determinations were made with Thoma's apparatus, and the proportion of white to red blood-corpuscles was found to be as 1 : 105. There were 4,500,000 red blood-corpuscles in the cubic millimeter; the large leukocytes were predominant. The number of white blood-corpuscles increased after extirpation of the spleen. Eight weeks after the operation the proportion of white to red blood-corpuscles was as 1 : 80; eight months after the operation, as 1 : 50.

In another case of the same author, in which the diagnosis of splenic pseudoleukemia was made, the proportion of white and red

blood-corpuscles was as 1 : 200, and remained unchanged after extirpation of the spleen. Tizzoni performed splenectomy for a large tumor (splenitis interstitialis). Before the operation the proportion of leukocytes to the erythrocytes was as 1 : 50 ; hemoglobin 82 per cent. After operation the former proportion was changed to 1 : 583 ; hemoglobin 83 per cent. An examination made later showed that the proportion of white to red blood-corpuscles was as 1 : 455 ; hemoglobin 94 per cent.

Montenovesi performed splenectomy for a large malarial spleen. After operation, leukocytosis, which had existed, disappeared.

In 2 cases of Tricomi's, in which the operation was performed for a movable malarial tumor—that is, a simple hyperplasia of the spleen—the proportion of red and white blood-corpuscles after the operation was found to be 1 : 350, then 1 : 436, and later 1 : 520 ; in both cases recovery occurred.

Vulpius gives us detailed information of 2 other cases. The first was of a man, twenty-four years old, in whom laparotomy had been performed for idiopathic hypertrophy of the spleen.

Date.	Number of red blood-corpuscles.	Number of white blood-corpuscles.	Proportion.	Hemoglobin, per cent.
July 22, 1889.	4,470,000	8,000–10,000	1 : 447–559	56
July 26, 1889.	4,570,000	8,000	1 : 572	63
July 27, 1889 (day of operation).				
July 28, 1889.	4,970,000	30,000	1 : 166	64
July 29, 1889.	4,320,000	70,000	1 : 62	67
August 1, 1889	5,180,000	60,000–70,000	1 : 74–86	77
September 10, 1889 . .	4,800,000	15,000–20,000	1 : 240–320	66
December 16, 1889 . .	4,353,000	11,700	1 : 372	85
June 25, 1893	3,300,000	11,000	1 : 300	85

The second case was that of a laboring woman of forty-two, in whom the spleen had become necrosed following suppuration ; it was removed on March 3, 1893.

After operation the blood-picture was as follows :

Date.	Number of red blood-corpuscles.	Number of leukocytes.	Proportion.	Hemoglobin, per cent.
March 4, 1893	4,000,000	40,000	1 : 100	
March 20, 1893. . . .	3,200,000	53,300	1 : 60	65
April 11, 1893	3,200,000	53,000	1 : 60	65
May 5, 1893	4,000,000	32,000	1 : 125	85
July 11, 1893	4,000,000	12,200	1 : 328	83
October 22, 1893 . . .	4,500,000	13,800	1 : 326	80

To judge from these and other reports, we must consider removal of the spleen a justifiable operation. The question arises, however: Under what conditions is the operation permissible? In other words, within what boundaries is it worth while to extirpate, and when have we a

guarantee of amelioration of the symptoms large enough to counterbalance the dangers naturally connected with this surgical inroad?

Hemorrhage is the most serious danger of this operation. Chronic tumors of the spleen are often adherent to their surroundings, and the separation of these adhesions frequently causes surface bleeding. In addition, there is always danger of hemorrhage from the vessels of the spleen and from the gastrosplenic ligament which encloses them. Post-operative hemorrhage must also be guarded against. If the spleen be pulled far into the abdominal incision, this pedicle is always stretched. During manipulation the vessels are elongated, their lumen narrowed, and occasionally occluded. When the pedicle is ligated, severed, and replaced, the lumen of these vessels will enlarge again as soon as traction stops. In this way they become distended, and the ligature may not be strong enough to hold the increased amount of blood, and can be torn in this way; or, another possibility, small vessels may be overlooked and not ligated. This latter can readily occur in operations upon the spleen, because so much traction is being exerted; besides, these smaller vessels are contracted and do not bleed during the operation. As soon as the pedicle is replaced the lumina of these little vessels become enlarged, and unsuspected hemorrhage into the abdominal cavity may be the result. Knechler, Spencer Wells, and Bonora report fatal hemorrhage following extirpation of the spleen, owing to defective ligation of the vessels.

Changes in other vessels aside from those of the spleen may also occur in extirpation of the spleen, and when this operation is performed special attention must be given to such a possibility.

When a large tumor of the spleen develops in the abdominal cavity, radical changes in the normal position of all the abdominal organs take place. Those organs that are movable are displaced and wedged in against other organs that are immovable. Two things can happen: first, different blood-vessels can be greatly stretched by traction; and, second, a tumor of the spleen, owing to its bulk and weight, may compress blood-vessels. Further, the intestine may be displaced, and abnormal bends and kinks produced in blood-vessels in this way. These torsions or tractions and the pressure combine to change the structure of the blood-vessels, particularly in the case of chronic tumors, where these abnormal conditions exist for a long time. The vessels may become fragile in different places, and softened. When the tumor of the spleen is removed, changes in the blood-pressure naturally occur within the abdomen, so that those parts of the vessel wall that have undergone degenerative changes and are suddenly exposed to greatly increased pressure may easily rupture, and in this way produce hemorrhage.

Another point must be considered in estimating the probable loss of blood following extirpation of the spleen—namely, the amount of blood contained in the spleen itself. In a spleen tumor weighing from 7 to 8 kg., Péan estimates the volume of blood found as about 2 kg. To judge from other estimates scattered through the literature, this figure is much too low. Different investigators have weighed the spleen when

it was still filled with blood and after the blood had been removed, and agree that the loss of blood from extirpation is much greater than 2 kg. Naturally, the amount of blood in the spleen will depend a great deal on the character of the pathologic change. Thus, for instance, a leukemic tumor contains comparatively little blood, while a simple hyperplastic spleen is so engorged that after removal of the blood nothing remains but a spongy tissue. This applies in a much greater degree to a congested spleen. The sudden loss of so considerable a quantity of blood must naturally be detrimental to the organism.

Finally, another factor must be considered—namely, shock (Adelmann), which may follow extirpation of the spleen as a direct result of the change in the static equilibrium that existed in the abdominal cavity. This occurrence is analogous to the cases of sudden death directly following the removal of large quantities of ascitic fluid.

In discussing the several indications that may obtain for splenectomy we must distinguish those tumors of the spleen that are a symptom of some general disease from those that are purely local in character; and we must carefully consider whether an extirpation of the spleen promises better results than possibly some other less radical operation. In extirpation of a leukemic spleen it is comparatively easy to decide this question, because a large number of reports exist, a study of which enables us readily to predict the probable result of such an operation. The extirpation of the spleen in leukemia removes only one of the organs that are pathologic in this disease, for we know of no case of leukemia in which the spleen alone was involved. As a rule, to judge from the pathologico-anatomic findings, the bone marrow and lymphatic glands are also diseased together with the spleen. Clinically, it is true, we cannot always determine during life to what proportion these different tissues are involved. If we are sure, therefore, that leukemia always involves two or more different organs, then we will certainly not advise extirpation of the spleen, for the reason that it would seem impossible that the removal of one of the diseased foci could in any way benefit the organism. In addition, we know that in leukemia the changes in the organism are so manifold and involve so many of the tissues and organs that extirpation of the spleen could not possibly be of benefit, and could neither prevent the progress of the disease nor limit it in its ravages. Further, extirpation of the spleen in leukemia is particularly dangerous, because such patients usually bleed very freely. Particularly, the loosening of adhesions may be followed by violent hemorrhages, both primary and secondary. We have already called attention to the fact that in extirpation of the spleen there is always danger of fatal hemorrhage, and in leukemia this danger is probably greater than in any other disease.

Practical experience in extirpation of the spleen in leukemia has demonstrated that such an operation exercises no influence upon the course of the disease. A patient of Bardenheuer died on the thirteenth day, and a patient of H. v. Burckhardt, eight months after the operation. In both cases the number of leukocytes increased consider-

ably after the operation. In the former case the blood was examined repeatedly after the operation, and the proportion of white to red blood-corpuscles found to be as 1 : 7, then as 1 : 5, and later as 1 : 3.

Vulpius has collected a number of reports on extirpation of the spleen, and has drawn the following conclusions from his cases. (These statistics were published in 1894.) In 28 cases of laparotomy with splenectomy performed in leukemia, 25 died immediately after the operation; 22 of these in consequence of hemorrhage, 1 from collapse, 2 from septic peritonitis. One of the cases (Bardenheuer's) survived the operation thirteen days; another (v. Burckhardt's) eight months. The last case, which was said to have recovered, belonged to Franzolini; however, this case is doubtful. It was said to be one of moderate leukemia with a small tumor of the spleen.

From these results we must distinctly deny the utility of extirpation of splenic tumors in leukemia.

Lindfors performed the first splenectomy in Scandinavia in the year 1892. His case recovered. He has formulated the following rules for this operation in leukemia: "If the leukemic blood show a proportion of 1 : 10 or below, it may be predicted with certainty that the patient will die of hemorrhage after the operation. In incipient leukemia extirpation is justifiable if the operator be positive that he is dealing with a case of splenic leukemia and if the tumor be causing much distress. We are unable to state whether extirpation of the spleen is able to arrest the progress of an incipient leukemia; when the tumor is very large the prognosis is correspondingly bad."

In the case of malarial spleen the question of extirpation cannot be readily decided. Here, too, the general condition of the patient must be primarily considered. As in leukemia, the tumor of the spleen is only one of a multitude of symptoms. The operation, besides, is not fraught with such serious consequences for the rest of the organism. Very frequently, however, the invasion of the body by the plasmodium of malaria produces serious changes in the composition of the blood, especially in the malarial form of blackwater fever. These considerations will necessarily lead us to be very careful in making a prognosis in regard to the benefits to be derived from extirpation of the spleen. Where serious blood-changes are found, general loss of strength may be expected, followed by cachexia. Wherever we find such a condition, even though the symptoms of cachexia may be very slight, the prognosis in extirpation of the spleen is very bad. It is always to be feared in these cases that the operation will kill the patient, either by producing violent hemorrhage or because of the lowered vitality of the patient. Further, tumors of the spleen of such size and weight that they cause unbearable distress are only found in very old recurring cases of malaria; and as it is only this class of patients that will decide to undergo all the dangers of an operation for the sake of relief, and as these cases, in addition, are always cachectic, the prognosis is particularly bad.

Vulpius' statistics, on the other hand, seem to favor the extirpation

of the spleen in malaria. Twenty-six cases of splenectomy are reported in which malaria was the cause of the swelling, and of these only 11 died—that is, a mortality of 42.2 per cent. However, these figures are not convincing, for the reason that probably all the cases were published that ended favorably, but only a part of those that died some time after the operation. We are therefore not justified in comparing these two series of statistics. We may sum up the consensus of opinions by saying that it is impossible to absolutely deny the advisability of an occasional extirpation of the spleen in malaria. The success of the operation, however, will depend upon the presence or absence of cachexia, and the operator should be determined in his course by the result of the blood-examination. Schönborn expresses himself as follows in regard to this point: "In those cases of malaria with tumor of the spleen, where the tumor refuses to yield to internal medication and causes much distress, splenectomy should be attempted only if the general condition of the patient be relatively good and if no malarial cachexia, malarial anemia, or melanemia exist; splenectomy for large tumors and passively congested spleen is to be condemned."

The same applies to amyloid degeneration. This form of degeneration is never limited to the spleen, but usually includes the liver, the kidneys, and the intestine. Furthermore, amyloid degeneration in the majority of cases is the result of some serious organic trouble involving the whole system, so that extirpation of the spleen for amyloid degeneration offers no guarantee of relief or cure. Chronic congested spleen following insufficiency of the heart muscle, portal stasis, or cirrhosis of the liver is a symptom only of some general disease, and the condition of the patient is not ameliorated by removal of the spleen. In addition, the operation promises very little, because patients of this kind are very much reduced, owing to the chronic character of their trouble, before symptoms attributable to a tumor of the spleen have become so severe that they will consent to so grave an operation as extirpation of the spleen. Furthermore, the loss of blood will certainly be considerable, for the reason that no tumor of the spleen is more filled with blood than the congested spleen. That this operation is utterly useless and very dangerous is demonstrated by the fatal issue that occurred in 3 splenectomies reported by Quittenbaum, H. Fischer, and LeBec.

Very little can be said in regard to splenectomy for carcinoma of the spleen. We have no authentic reports on isolated carcinomatous involvement of the spleen, so that this really settles the question. Carcinoma of the spleen is really found only in patients suffering from carcinoma of other abdominal organs, particularly the stomach and intestine, and an operation for a secondary carcinoma of the spleen is, of course, contra-indicated.

The same applies to secondary sarcoma of the spleen, which, moreover, is very rare. We have already quoted Weichselbaum's report. Billroth and Fritsch have recorded several cases of extirpation of the spleen for lymphosarcoma that for a time seemed to promise a favorable

result; in the end, however, the operation was useless, because, as was to be expected, the sarcoma recurred and the patients succumbed.

In cysts of the spleen, echinococcus of the spleen, and abscess of the spleen extirpation of the organ may be a useful procedure. When it becomes necessary, A. v. Bardeleben has formulated the following rules as to whether simple incision of the spleen or extirpation of the organ should be performed: "I would always prefer extirpation—that is, splenectomy—to simple incision unless the organ is too large or is adherent to the abdominal walls, or unless the tumor cannot be easily brought into the abdominal incision."

Splenectomy is chiefly indicated in floating spleen, particularly if the organ be only idiopathically enlarged. If the floating spleen has become enlarged as a result of some general disease, and has moved from its position as a result of this increase in size and weight, as, for instance, in malaria, those considerations must be thought of that have been discussed above in regard to the interrelationship of extirpation of the spleen to the general condition of the organism. Extirpation should be undertaken only in floating spleen of a very large size that produces distressing subjective symptoms. Vulpius has collected 40 cases of splenectomy performed for floating and idiopathically enlarged spleens; 13 of these cases died. Nearly all of them had very large tumors. Vulpius states that in arriving at a decision in regard to this operation a certain maximum size of the tumor should be our limit, and advises not to undertake the extirpation if the growth weigh more than 3000 gm.

Schönborn expresses himself similarly: "Splenopexy, after the method of Rydygier, is indicated in cases of small floating spleens that are not adherent to their surroundings and that cannot be retained in place by suitable bandages. In cases of large floating spleen and in cases of idiopathic hypertrophy of the spleen, splenectomy may be performed if the distress caused by the presence of the tumor be very considerable and if the growth does not weigh more than 3000 gm."

Ledderhose summarizes the indications for splenectomy as follows: "The operation is justifiable in cases of prolapse of the spleen into some external wound, of floating spleen, of abscess of the spleen, of cysts of the spleen, notably echinococcus, if subjective symptoms or other dangerous phenomena are complained of that cannot be relieved in any other way."

Splenectomy, in the light of our present experience, is contra-indicated in leukemia, in pseudoleukemia, in malarial hypertrophy, in cases where grave changes of the blood obtain (anemia, cachexia, melanemia), in chronic congested spleen, and in amyloid degeneration. It is justified in cases of so-called simple hypertrophy in which no changes have occurred in the blood, the general condition of the patient is good, and the state of the other abdominal organs does not seem to be the primary cause of the enlargement of the spleen. Finally, it is justifiable in the spleen of intermittent fever if the general health is good and the composition of the blood has not been seriously changed. [Extirpation

of the spleen in splenic anemia has already been referred to. (See Splenic Anemia, p. 602.) It is probable that if done early it may be the means of prolonging life by avoiding the serious hemorrhages or the development of hepatic cirrhosis.—Ed.]

Before entering upon the discussion of the physiologic considerations relative to extirpation of the spleen, the writer appends a table of statistics quoted from Vulpius' work, which summarizes everything given in the literature on the subject up to 1893.

Disease.	Number.	Cures.	Deaths.
1. Leukemia	28	3 = 10.7 per ct. (1 permanent.)	25 = 89.3 per ct.
2. Hypertrophy (simple), malarial, and floating spleen	66	42 = 63.6 per ct.	24 = 36.4 "
Malarial spleen alone	26	15 = 57.7 "	11 = 42.2 "
3. Echinococcus	5	3 = 60 "	2 = 40 "
4. Simple cysts	4	4 = 100 "	
5. Sarcoma	4	3 = 75 "	1 = 25 "
6. Suppuration	3	3 = 100 "	
7. Congestion	3	. . . . .	3 = 100 "
8. Amyloid spleen	1	. . . . .	1 = 100 "
9. Syphilis	1	1 = 100 per ct.	
10. Rupture of the spleen	2	. . . . .	2 = 100 "
Total	117	59 = 50.4 per ct.	58 = 49.6 "

Within the last few years some surgeons, where localized lesions of the organ existed, have performed resections of parts of the spleen in preference to total extirpation. Gussenbauer and Bardenheuer were the first to advocate this procedure. The latter expresses himself as follows: "Total extirpation may occasionally be indicated; however, if a cure of the primary disease seem more probable, provided a part of the spleen can be retained, then the operation of partial resection is certainly to be preferred. This would especially apply to cysts of all kinds, abscesses, and circumscribed tumors." Bardenheuer draws his conclusions chiefly from a series of experiments performed under his direction. He made partial resections of the large abdominal glands, and demonstrated that large parts of these organs can be removed without causing serious interference with the function of the remaining piece. In fact, he could determine that a sort of compensatory hypertrophy of the remnant occurred. In some of the cases the place where part of the organ had been removed could not be discovered later on unless adhesions had occurred at this point with neighboring organs. Ponfick also performed a number of resections of the liver which were followed in every instance by an enormous new formation of normal liver tissue. Basing on these experiments and the experience that has been gained so far from partial resection of the kidney in the human being, Bardenheuer draws the conclusion that possibly the dangers of total extirpation of the spleen might be considerably mitigated, if not completely removed, by partial resection.

These experiments of Bardenheuer are not corroborated by the results

obtained by Peyrani. This investigator positively denies that the spleen of mammals can regenerate spleen tissue. He made an incomplete extirpation of the organ in guinea-pigs, and saw no regeneration. Vulpius arrived at analogous conclusions in the case of rabbits. Eliasberg, on the other hand, states that in such remnants of the spleen a great number of nucleated red blood-corpuscles are found, and he considers this phenomenon as evidence that the crippled organ is making attempts to regenerate.

In conclusion, we must briefly discuss the important physiologic results and discoveries that have been made in cases of extirpation of the spleen. Those findings which were made after extirpation of perfectly healthy organs will be the most interesting, and we are fortunate in having detailed reports of a number of cases in which, following trauma, the spleen was either torn or divided into two pieces, one of which had to be removed by resection. Again, in other cases a cyst had formed in either the lower or upper part of the organ, which was removed, while the healthy part of the spleen was retained. These cases almost have the value of physiologic experiments, so that by chance we have come into possession of a series of facts that are of fundamental importance in the elucidation of the physiology of the spleen; particularly the cases of Credé and Riegner have given good results in this respect. O. Riegner's case was a unique one in so far that a series of complications occurred in it which furnish particularly interesting information. O. Vulpius, who has done the most deserving work on the surgery and physiology of the spleen, has studied the literature on the subject exhaustively, and drawn all the conclusions therefrom that could be. We refer to his work, which is a classic on the physiology of this organ.

As we know, numerous animal experiments and the observation of cases of extirpation of the spleen in human beings have demonstrated positively that *this organ is not necessary for the maintenance of life.* Different observers, however, do not agree as to the function of the spleen in the manufacture of the blood, nor upon the vicarious function of other organs after removal of the spleen. It has never been positively demonstrated that new formation of spleen tissue can occur after extirpation of large portions of the organ, although, to judge from analogies in the case of the liver and the kidneys, we can hardly deny the possibility of such an occurrence; at the same time positive proof of this compensatory growth must be adduced, as experimental observations so far lead to opposite results. Observations by Neumann and by Mosler seem to prove that the bone marrow can perform the functions of the spleen, and after the removal of the latter acquire increased hematogenic properties. It must be considered, therefore, a very happy circumstance, at least from the point of view of physiologic investigation, that in Riegner's case the bone marrow of a patient whose spleen had been in part removed could be examined four weeks after the operation; this was an opportunity that may not recur in many years. Ponfick made a microscopic examination of the bone marrow of the amputated

leg, and in addition to slight hyperemia of the fatty marrow found no notable changes. A month later the examination of the hardened and partly decalcified bone showed no abnormalities in the marrow; at the same time the trabeculæ of the bony structures of the spongy tissue revealed that an active proliferation of these tissues, particularly of the vessels of the marrow, had occurred. This was so marked that a narrowing and loosening of these trabeculæ had occurred, thus making the Haversian canals wider; particularly at the margins of the epiphyseal cartilage the young marrow was seen to be advancing into the matrix, even into the cavities of the cartilage. This process was visible over wide areas. Here, too, the otherwise straight boundaries were wave-like and uneven, so that the morbid process could be clearly distinguished. There could be no doubt from these findings that the processes observed were active new formations in the marrow; these were more active than they would have been under normal circumstances, even though the youthful age of the patient was considered, for, undoubtedly, a considerable disappearance of bone tissue had been caused by them. In a case of this kind, therefore, the striking changes that have been described by Neumann and Mosler in leukemic animals whose spleens have been removed were not found, even four weeks after operation. From these observations, however, it is learned that the marrow participates in the repair of the loss of blood, inasmuch as it takes an active part in the reparatory processes. At the same time we must remember that Riegner's patient was not purely in the physiologic state, for the reason that he had lost an enormous quantity of blood after the accident.

After Neumann had discovered that the bone marrow is an important organ for the formation of erythrocytes, experiments were made on animals whose spleens had been removed, in order to definitely determine the real function of the spleen. The theory was that both organs participate in hematogenesis, and if the spleen be removed, the bone marrow must show increased activity. Pouchet demonstrated that both organs can be removed without disturbing blood-formation. He experimented on fishes, which have no bone marrow, by removing their spleens.

Mosler, in the case of a dog, found red, smeary marrow ten months after splenectomy. Six weeks after the operation the animals had normal marrow. This finding is similar to conditions found in leukemia. Similar findings have been reported by Tizzoni, Winogradoff, Kostjurin, and Freiberg—that is, functional hyperemia of the marrow and increased activity in the direction of new formation of erythrocytes by mitoses of nucleated red blood-corpuscles.

A second hypothesis postulates that the thyroid acts vicariously after extirpation of the spleen. This assumption was first made by Tiedemann, in 1833, and seems to be strengthened by Bardeleben's experiments. This investigator observed that dogs and rabbits died very soon if both the spleen and the thyroid were removed; that a dog, on the other hand, in whom these organs were removed at different times recovered. Three other dogs in whom the spleen alone was removed also recovered. Simon saw the same unfavorable result occur in the

case of cats, and Zesas in that of a dog, in which the spleen and thyroid were removed. Zesas drew the conclusion from his experiments that the thyroid is the most important organ acting vicariously on removal of the spleen, and assumes that possibly the white blood-corpuscles are converted into the red within the thyroid. Tauber's experiments, however, contradict such an assumption, for he succeeded in keeping animals, from whom both these organs had been removed, alive a long time, it being immaterial whether the removals were performed in one or in two sittings. He adduced as another argument against the importance of the thyroid gland and its physiologic connection with the spleen that it is frequently absent in domestic animals, or present only in a rudimentary shape. He determined this from his examination of from 10 to 15 animals. Ughetti and Mattei showed, in addition, that excision of the thyroid alone is always fatal for dogs, and that the removal of the spleen at the same time makes no difference in the disease. Rabbits even can very well survive the removal of both organs without apparent damage.

We know that the removal of the thyroid is followed by serious disturbances in man, but we have not observed that the spleen can act vicariously for the removed thyroid; Kocher has devoted particular attention to this question after strumectomy.

Hyperplasia of the thyroid following splenectomy has only been observed in 3 cases, although particular attention has been devoted to this point. Credé's case is the most conspicuous. Here the patient, four weeks after extirpation of the spleen, developed a distinctly visible, painful, doughy swelling of the whole thyroid; a considerable quantity of healthy spleen tissue had been retained at this operation. Notwithstanding this the tumor of the thyroid persisted for four months, and did not disappear until the general strength of the patient had improved so much that he could resume his occupation. The struma receded at the same time that a leukocytosis had developed, and Vulpius considers this a positive indication that the thyroid has no permanent vicarious function.

Löhlein reports another case in a woman, where, twelve days after removal of an enormous floating spleen, a slightly painful swelling of the thyroid occurred, which was about as large as a hen's egg; changes in the blood were seen only on *one* day. Finally, Ceci has reported a swelling of the thyroid, accompanied by enlargement of the tonsils, following extirpation of the spleen (for hypertrophic floating spleen). The swelling of the spleen in this case was accompanied by fever and emaciation, but it gradually disappeared. Other authors (Czerny, Billroth, Albert, Trendelenburg) have unsuccessfully looked for enlargement of the thyroid in a great many cases.

The rare occurrence of thyroid enlargement after splenectomy, the time at which it does develop, as compared with the blood-findings, make it very improbable that this gland has a vicarious action in the case of man; animal experiments do not make this assumption more probable. Vulpius probably assumes correctly that we are dealing in

this case with disturbances of circulation, congestions, etc., that are present in different organs, but are most apparent in an organ like the thyroid, which is very vascular, and, owing to its superficial position, can easily be seen.

In regard, finally, to the vicarious rôle of lymph glands, animal experiments have been as unable to establish such a function as in the case of the thyroid and bone marrow. It is true that Tiedemann and Gmelin, Mayer, Hyrtl, Domrich, Führer and Ludwig, Eberhard, and Gerlach have observed considerable swelling of the mesenteric and retroperitoneal lymph glands in dogs, Simon in cats, following extirpation of the spleen; but Schiff considers these as unimportant sequelæ of peritonitis. Mosler expresses himself in a similar way, and could not discover swelling of the glands as a constant result of loss of the spleen; and Pouchet finally refuted the theory that the lymph glands can act as a substitute for the spleen, by removing the spleen without damage from animals which have no lymph glands; for instance, tritons.

Zesas, in autopsies on rabbits whose spleens had been removed, found a swelling and a hyperemia of the bronchial and the mesenteric glands. These swellings were very inconsiderable in the beginning, and reached their maximum four to seventeen weeks after the operation, disappearing at the end of six months. Winogradoff, and after him Tizzoni and Gibson, examined the swollen, cheesy, and reddish lymph glands of animals whose spleens had been removed, and found red blood-corpuscles to be as numerous in the dilated lymph channels of these glands as in the bone marrow. The lymph channels containing nucleated red blood-corpuscles extended between the follicles and the follicular strands and into the peripheral sinus. Kurloff and Grünberg also arrived at the conclusion that as soon as a deficit occurs in the number of red blood-corpuscles the lymph glands become swollen and red, and that this occurs particularly after removal of the spleen. The active formation of colorless blood-corpuscles is made manifest by the presence of numerous mitoses, and Grünberg attempts by this theory to explain the frequently observed increase of these elements in the circulating blood following leukemia. [For the effects of splenectomy and a study of the hemolymph glands after this operation one may consult Warthin's articles, to which reference has already been made (see p. 467). —Ed.]

In animals operated upon by Vulpius, chiefly rabbits and goats, no swelling of the peripheral glands could at any time be discovered, nor could any enlargement of the mesenteric glands be seen immediately after removal of the spleen, nor in rabbits which were not dissected for five months. Ponfick also failed to find vicarious hyperplasia of the lymph glands in animals whose spleens had been removed.

In man diffuse swellings of the glands have frequently been observed during convalescence from splenectomy; thus, Czerny reports the case of a woman in whom a splenectomy was performed for hypertrophic floating spleen. Two weeks afterward the inguinal and cervical glands

began to swell, and did not regain their normal size for three months. In this case no changes in the blood could be determined. Kocher, on the other hand, observed a considerable leukocytosis in combination with universal enlargement of lymph glands in a case in which the spleen had been removed for sarcoma. Lennander, who extirpated the spleen for an adenoma, reports the following in regard to the blood-forming organs: "A number of lymph glands were found to be enlarged in different parts of the body. The thyroid was normal. There was no pain over the sternum and the long bones." Riegner reports that in one case, four weeks after resection of a healthy ruptured spleen, all the external lymph glands (cervical, axillary, cubital, and inguinal) were enlarged, in addition to the mesenteric glands, resembling in their distribution and their size the condition found in lues. These tumors had disappeared at the end of seven months. As against these positive findings, Péan, Löhlein, Credé, and Czerny emphasize expressly that they looked for changes in the lymph glands following the operation of splenectomy and did not find them.

Vulpius draws attention to the possible enlargement of glands, situated in the internal parts of the body, found in animals, and thinks that possibly in these cases a recognition of the lymph-gland changes would not occur. In animals the loss of the spleen seems always to produce a reactive or reparative swelling of lymph glands, which cannot be attributed to stasis as a result of disturbed circulation. The writer is of the opinion, however, that in animals a swelling of the mesenteric and retroperitoneal glands after extirpation of the spleen is a result of the operation itself.

In conclusion we must briefly consider the changes of the blood itself that have been observed after splenectomy. Winogradoff observed 3 dogs, whose spleens had been removed, for a long period of time, and could demonstrate a decrease in the colored elements of the blood and of the hemoglobin, and an increase of the leukocytes of from 82 to 88 per cent. He made these findings in 2 of his cases; in a third he found a decrease in the leukocytes of 38 per cent. Tauber found similar conditions in regard to the red, and a constant, both relative and absolute, increase of the white cells in the experiments he made on different animals. Zesas succeeded in keeping rabbits alive for a long time after removal of the spleen, and could examine their blood; four weeks after the operation the red blood-corpuscles were present in small numbers, only darker than the normal corpuscles; the white, on the other hand, were more numerous and larger than normal. The increase of the latter continued until the tenth week; at this time the blood contained very few red blood-corpuscles, but an enormous number of leukocytes. A decrease of leukocytes began from now on, but progressed more slowly than the increase, so that the blood was not normal for six months. From these results Zesas draws the conclusion that a conversion of white blood-corpuscles into red ones occurs within the spleen, but he does not say that under normal conditions such a process occurs only in this

organ. Gregorescu arrives at the same conclusions in regard to the conversion of white into red cells in dogs.

Vulpius, in his experiments, arrives at the following conclusions: "Rabbits and goats cannot survive the extirpation of the spleen without demonstrable disturbances of their general health. In these animals, removal of the spleen produces a transitory absolute leukocytosis that disappears at the expiration of nine weeks or thereabouts. The leukocytes may increase to double their normal number, the red blood-corpuscles decrease slightly, at most 20 per cent., and reach their normal state by the end of a month.

"In animals, therefore, whose spleens have been removed the statement seems to be universally accepted that an increase of leukocytes, and occasionally a decrease in the number of erythrocytes, occur. In the case of man, observations are not yet sufficiently numerous to allow us to draw any definite conclusions in regard to the changes of the blood produced by extirpation of the spleen."

The most valuable cases for such examinations are partial cystic degeneration of the spleen. Péan reports such a case in which a few weeks after the operation a distinct leukocytosis, 1 : 200, was present. The case of Credé which has been mentioned, and in which splenectomy was performed for the removal of a cyst, also showed an increase in the white and a decrease in the red blood-corpuscles one week after the operation. At the end of two months the maximum blood-change was present, the proportion being as 1 : 3 or 4; at the end of four months normal conditions were re-established with this exception, that the white blood-corpuscles were all lymphogenous and the lienogenous ones were absent. At the same time an increase was found in the "small erythrocytes (microcytes)—some of them nucleated (microblasts)—that are derived from the bone marrow." Witzel-Trendelenburg saw no changes in the blood; Billroth-Hacker found a slight increase in the leukocytes three weeks after the operation, and Horach-Albert an increase in the red and a decrease in the white elements.

The cases of Czerny, who operated for necrosis of the spleen, and of Riegner, who operated for rupture, presented complicated blood-pictures on account of the traumatic anemia coexisting; but even if this be considered, we find a leukocytosis in these cases.

An examination in Riegner's case revealed the following: The hemoglobin, determined with Fleischl's hemometer, was down to 20 per cent. on the first few days after the operation, probably as a result of the enormous loss of blood; on the fourth day it was 35 per cent.; on the twenty-first day 40 per cent., and gradully rose to 80 per cent. Countings with Thoma-Zeiss' apparatus gave 2,500,000 red and 25,000 white cells in the cubic millimeter; a decrease of the red blood-corpuscles of one-half had therefore occurred (normal, 5,000,000), and an increase of the white of 3 to 5 times the normal number. The proportion of the white to the red was as 1 : 100, as against 1 : 400 in the normal state. The absolute number of the red elements increased rather rapidly, so that at the expiration of eight weeks they were present in normal numbers. The

absolute number of the leukocytes, on the other hand, did not decrease; at the last count there were still 25,000 in each cubic millimeter. On staining it was found that all forms of leukocytes were uniformly increased; polynuclear neutrophile cells were present in greatest number; the eosinophiles were not increased. At the expiration of a month the proportion of leukocytes had become somewhat changed, so that the lymphocytes were by far the most numerous; nucleated red blood-corpuscles were never found.

From all these observations we are forced to the conclusion that the spleen and the bone marrow convert leukocytes (that are probably preformed in the lymph glands) into red blood-corpuscles.

HEMORRHAGIC DISEASES.

INTRODUCTION.

THERE is a group of diseases in which the most conspicuous symptom is a tendency to hemorrhage, frequently so severe that it may endanger life. We call this tendency to hemorrhage, probably due to changes in the blood and the blood-vessels, the hemorrhagic diathesis. The different diseases that belong to this group are so similar to each other that for a long time they were considered one disease; they form, so to say, a natural group, which was formerly designated as "scurvy." Even to-day authorities disagree as to how far a separation of the different forms is permissible. In the light of our present knowledge the writer shall treat this class of diseases in the following three subdivisions: First, *scurvy;* second, *hemophilia;* third, *morbus maculosus Werlhofii.* He wishes to call attention to the fact, however, that our real knowledge of these conditions does not permit so sharp a distinction; the differences are in a great measure arbitrary and not based on strict etiologic or pathologico-anatomic data.

SCURVY.

Definition.—Scurvy is a general disease that seldom occurs sporadically, but usually epidemically or endemically. It is usually found where unhygienic conditions exist, particularly as a result of unsuitable diet. The disease usually begins insidiously, runs a slow course, and may have a variety of terminations (complete recovery, partial recovery with certain lasting anatomic or organic changes, or finally death). It is characterized by a severe general cachexia, and by a series of local disturbances due to what may be called a transitory hemorrhagic diathesis. It produces many of the same symptoms as the *morbus maculosus Werlhofii,* but is distinguished from hemophilia by the fact that it is always an acquired constitutional change and transitory in character; whereas the lesions of hemophilia are inherited and permanent.

History of the Disease.—With the discovery of America navigation extended farther than before, and sea trips that up to that time were made coastwise, were now taken by way of the open sea. As a result of this, sailors were exposed to altogether new and peculiar conditions of life. They would be away from land for many months, at the mercy of the wind and the waves; they lived in large

numbers in small spaces on board their ships, and were dependent for their food on articles that could be preserved for a long time after they had left their native shore. Frequently they were forced to eat spoiled food or suffer from starvation. It is apparent that such conditions of life must produce disease, and, however great and noble were the discoveries of that period, the diseases that followed as a result of these expeditions were appalling, and scurvy was frequently the cause of a most unfortunate termination of such an adventure.

Thus, in 1498, Vasco da Gama made his celebrated trip around the Cape of Good Hope; his crew becoming afflicted with scurvy, in a short time he lost one-third of his 160 companions. The following expeditions are notorious for the horrible ravages of this disease: That of Cartier in 1535; the Canadian expeditions of v. Monts, Pontgrave and Poutrincourt toward the end of the sixteenth century; Dellon's French expedition to India and Lord Anson's trip around the world with the English fleet (1740–44). The latter is particularly conspicuous from the fact that of 510 men, 380 succumbed to the disease, and that it occurred in repeated attacks in all latitudes. Notable also were the North Pole expedition of Ellis (1746–47), made with the purpose of discovering a northwest passage to Hudson's Bay; that of the English fleet under Admiral Gleary, which returned in 1780 with 2400 cases of scurvy; and many others.

The accounts of these epidemics are so clear that there can be no doubt as to the identity of the disease. Our knowledge, on the other hand, of the occurrence of scurvy on shore is not so reliable. The first reports of such a disease begin about a century after this time, and it is here that we first encounter the name of scurvy or Scharbock. Our knowledge of the occurrence of the disease in antiquity is obscure, although we are justified in assuming that wherever conditions favoring the occurrence of this scourge existed, scurvy must have occurred in earlier periods of our history and have exercised its deleterious effect.

August Hirsch has given us the best historic review of scurvy, and to a large extent we have followed his description. This investigator succeeded in finding a single description of a disease in some of the older medical writings that corresponds so closely to the picture of scurvy that we can at least assume it to be identical with this condition; the writer refers to the disease called *εἰλεὸς αἱματίτης* in the collection of Hippocrates. Hirsch calls attention to the fact that this disease *Επλῆνες μεγάλαι* (Magni lienes) may have been malaria. It is described by the following medical writers of antiquity: Hippocrates, Aretaeus, Celsus, Caelius, Aurelianus, Paulus Aegineta, Avicenna, and others. Plinius describes two diseases, Stomakake and Skalotyrbe, the former of which particularly resembles scurvy; both seem to have been affections of the mouth, but it is just as probable that this was the so-called "stomatite ulcéreuse," a disease found in armies. As Herba Britannica was used at this time in the treatment of Stomakake and Skalotyrbe, many authors have stated that the disease described was Oscedo, a disease that has only been described by Marcellus, and that

the latter was scurvy; this in the face of our complete ignorance of the nature of this latter disease and of our ignorance of the plant "Herba Britannica."

The occurrence of scurvy in the middle ages is fairly well established; there are a number of descriptions of devastating diseases that occurred in large bodies of troops during sieges, etc. Jacques de Vitry gives an account of a disease that occurred in 1218–19, in the army of the Crusaders, during the siege of Damiette; the symptoms were sudden pain in the arms and legs, gangrene of the gums, loss of appetite, and a black coloration of the tibia that was horrible to see. The patients suffered untold agony for a long time, and the majority of them died. A few of the afflicted ones fortunate enough to survive until spring recovered under the influence of the warm weather. Joinville describes the disease very clearly. His description is that of an epidemic that occurred in the army of Louis IX., in 1250, during the siege of Cairo. If we are justified in deciding that these descriptions refer to scurvy, then we are also justified in drawing the conclusion that this disease must have existed in earlier epochs of history.

Cordus was the first to designate the disease as Scharbock, but Hirsch thinks it is doubtful whether he ever saw the disease himself. On the other hand, very careful observations are preserved by Olaus Magnus, Echthius, Ronsseus, Wierus, Dodonaeus, and Brucaeus; most of these descriptions refer to epidemics in northern coast countries, North Germany, Scandinavia, and the Netherlands. Further, it seems that the epidemics occurred only when exceptional conditions existed; as, for instance, famine, war, sieges, and other socially unfavorable conditions. Whether the disease was very frequent is doubtful. Foreest speaks of it as a *morbus rarus*.

The descriptions of epidemics of scurvy are not at all reliable, and a good many fail if they are carefully scrutinized. This is due to ignorance of its peculiarities and to confusion with other diseases that may have had a certain resemblance to scurvy. To this class belongs, for instance, an epidemic that is said to have occurred in 1486 in Saxony, Thuringia, and some of the neighboring countries. Fabricius, rector of the Fürstenschule in Meissen, described the first occurrence of this disease in the beginning of the eighteenth century. Hirsch calls attention to the fact that the epidemic behaved in many respects like one of ergotism, the nature of which was unfamiliar to the physicians of that day. In reading accounts from the seventeenth, and particularly the eighteenth, century, the impression is almost created that Europe was affected by epidemics of scurvy during all this time, and that all other diseases were insignificant as compared to this scourge. To begin with, it is doubtful whether any one disease could have existed for so long a time almost to the exclusion of other epidemics, and careful investigation has demonstrated that the reverse was the case, and that people who had never seen a case of scurvy called all sorts of diseases by that name, thus bringing confusion into the subject and doing damage to medical science.

The chief blame attaches to the work of Eugalenus, *De Morbo Scorbuto Liber*, of the year 1720, of which Hirsch says that it is a literary concoction, that it occupies an exceptional position in medical literature for two reasons: first, because its author was so utterly ignorant; second, because it enjoyed so phenomenal a success that for more than a century it remained the canon of the doctrine of scurvy. It became so authoritative that even the best physicians of that day could not emancipate themselves from its influence. Eugalenus, who probably never saw the disease, simply copied some descriptions from Wier, and then attributed to this disease all kinds of symptoms, drawing entirely upon his own imagination. He particularly described, arbitrarily, a number of peculiar phenomena that he claimed to have observed in regard to the pulse and the urine, and declares these symptoms as diagnostic for scurvy. The book soon had many disciples, and for a long period of years a variety of authors simply repeated what their teacher had told them, or even expanded his doctrines still further, so that Drawitz, for instance, claims that all children come into the world with a tendency to scurvy. But, according to Bontekoe, scurvy is the root and cause of every disease. Not even Boerhave could emancipate himself completely from these views; fortunately, however, he was enough of a critic to confess that in his day, at least, the disease seemed to be less frequent in the Netherlands.

A few serious, precise criticisms were, of course, brought forward against this scurvy swindle; many of these, however, shot far beyond the mark and attempted to deny the very existence of scurvy. Hoffmann warned against so radical a position, although he agreed with Sydenham, Mead, and Willis in considering scurvy a very rare disease. Kramer gives a careful description of all the cases that he observed, and emphasizes, at the same time, that the disease is least known to those who speak of it the most. In the year 1752 a monograph by Lind appeared that is to-day considered a classic on scurvy; it is undoubtedly the best description of the disease. The author calls attention to the colossal confusion that existed between the conceptions in regard to the disease of his day and of the earliest descriptions. He re-established the outline of the disease picture so clearly that it has been changed very little since his time.

Whereas Lind has shown that scurvy was a very rare disease in the last century, the fact remains that it was much more frequent at that time than nowadays. Hirsch again has studied all the epidemics with a great deal of zeal, and has formulated a table of all land epidemics that occurred from 1556 to 1877, excluding only those that did not stand the light of scientific illumination. A table of this kind must necessarily be imperfect and give us only an incomplete idea of the occurrence of scurvy. It is manifestly impossible to find a description of every pandemic or of every smaller epidemic that occurred in this or that small circumscribed district; at the same time the table enables us to draw a series of conclusions in regard to the frequency of the disease, its geographic distribution, and the presumptive cause of its origin.

All in all, 143 epidemics are mentioned, 2 of these in the sixteenth, 4 in the seventeenth, 33 in the eighteenth, and 104 in the nineteenth century. Those figures alone demonstrate conclusively how exaggerated were the views of Eugalenus and his disciples. In his time an enormous epidemiologic literature was extant, notwithstanding the fact that in the last century only 33 epidemics of undoubted scurvy can be found. The table teaches us with certainty that the disease essentially occurs only where large masses of people live together in a small space under bad social and hygienic conditions. Of the 143 epidemics, as many as 48 occurred in bodies of troops during sieges, in isolated positions where nourishment was scarce, or among the inhabitants of besieged cities who were suffering from the same disadvantages. In prisons, workhouses, and the like, 27 epidemics occurred; in hospitals, orphan asylums, insane institutions, etc., 22 epidemics. The number of epidemics that have occurred under conditions where no large congregation of people in a narrow space existed, and where no unhygienic conditions obtained is small; only 46 are reported in the table. Of these a large proportion was limited to single cities or small districts; only 29 seemed to extend over a wider territory, and even in these exceptional conditions existed, as, for instance, a famine or other social disadvantages.

Among the epidemics that have occurred in this century, that of Paris merits particular attention. This occurred in 1870–71, during the siege, when food was exceedingly scarce. In 1871 an epidemic occurred among the French prisoners who had been brought to Germany after the war and imprisoned in Ingolstadt. This epidemic did not assume large proportions, and, according to Döring, only 159 of 10,000 prisoners were afflicted. Epidemics occurred in the London Milbank Penitentiary in 1824 and 1840; in the penitentiary of Prag in 1831, 1836, and 1842; in the workhouse at Ludwigsburg in Würtemberg in 4 consecutive years, 1850–53, and in 1857 in the prison of the same city. The last slight epidemic that occurred in Germany was in 1875–76, in the penitentiary and the city proper of Moringen; the last in France, in the spring of 1877, in the prison of Mazas. Nowadays epidemics still occur with considerable frequency in Russia.

According to Hirsch's tables, most of the epidemics were found in Russia. Other important and interesting information in regard to the geographic distribution of the disease is gleaned from these tables. After Russia, with 35 epidemics, follows Germany with 19, France with 15, Sweden, Norway, and Denmark with 14, England with 11. Of transatlantic countries, India takes the lead with 14 epidemics; then comes North America with 7; Algiers with 7, etc. The disease is probably endemic even nowadays all through Russia, and occasionally spreads over large districts. This is particularly demonstrated by the reports from the Obuchow Hospital in St. Petersburg.

In the great epidemic of 1849, that extended over a wide area of the Russian empire, 260,444 people were affected, according to Krebel, of which number 60,958 died. In Asiatic Russia, particularly along the coast of the Arctic Ocean, in the country adjoining the Siberian and

the Chinese border and the Peninsula of Kamschatka, scurvy is prevalent to-day. In the northwestern part of Europe it has never been an important disease, although in Iceland, for instance, in 1836–37, an epidemic occurred as the result of a famine; the disease, however, is certainly not endemic in this region. The same conditions exist in other cities of Europe, and epidemics occur here and there locally in prisons, etc.

The epidemics in Algiers usually extended over a large territory, but the disease is certainly not endemic there. In 1801 scurvy appeared among the French troops in Egypt. In Abyssinia the disease has only been seen in foreigners, the natives not being afflicted, although they live in great part under conditions much less hygienic than those under which the foreigners live. In the eastern Soudan and in the whole eastern rainy zone of Africa, the disease is said to occur quite frequently, both among foreigners and natives. In South Africa the disease is said to be unknown among the negroes.

Among the Asiatic countries, India is conspicuous by the large number of epidemics that have been reported, affecting particularly great numbers of the poorer population. The disease is endemic on the coast of Dschemen (Arabia). In 1839 the English troops in Aden were affected. In China, particularly in the northern provinces, where the people live in incomparable misery, epidemics are not rare; and in Japan scurvy is quite frequently found among the poorer classes.

In Australia the disease has broken out disastrously in numerous expeditions undertaken for the exploration of the interior. In later years its occurrence has been reported among the shepherds of the plains.

In America the disease seems to be entirely unknown among the inhabitants of the South; the people of the North also seem to be non-susceptible. The only epidemics that have been reported occurred among the troops of the United States who were subjected to great hardships and privations in frontier districts [occasionally it has been seen in institutions and in districts closely populated by foreign immigrants—Ed.]; further, among lumbermen in the interior of Canada, and particularly among the gold seekers of California, who had come from all parts of the world and lived under the most miserable conditions. These latter cases are particularly interesting nowadays, when great numbers of people are rushing to the new gold country (Alaska) where will be found all conditions necessary for the occurrence of an epidemic. These Arctic regions, like Greenland, are particularly notorious for scurvy.

[Since the publication of the original edition of this work, the course of events in Alaska has verified the author's prediction in a striking manner. The Russo-Japanese war in Manchuria also has added a chapter to the history of the disease. Scurvy was a potent factor in compelling the surrender of Port Arthur, while current reports indicate that there is much of it in the armies of the interior.

Quite a number of cases were seen in the Chicago hospitals during

the building of the Chicago drainage canal. Large numbers of workmen, mostly foreigners, were rather poorly housed and poorly fed along the canal, and scurvy and malaria were not uncommon among them. McGrew made an interesting study of a large number of these drainage canal cases.—Ed.]

Etiology.—So far no single definite cause has been found; two views on the etiology of scurvy exist: the one, that it is a miasmatic infectious disease; the other, that it is a constitutional anomaly. The former conception has been advocated for a long time, particularly by writers of the seventeenth and eighteenth centuries. The arguments of these authors is devoid of all value, for the reason, chiefly, that the definition of scurvy was very uncertain at that time. The attempt has been repeatedly made to show that scurvy is malarial in character; Scoutetteu and Dévé even postulated that malaria could appear in ships; in later years Krügkula has advanced the hypothesis that scurvy is an infectious disease, in which the infectious material gains entrance into the organism through the mucous membranes of the respiratory or the digestive tract. As the disease is said to occur chiefly from the action of substances that are derived from the putrefaction more of animal than of vegetable matter, he sees a similarity between this disease and typhus, and, on the other hand, says that it is related to malaria, for the reason that it is not contagious. Villemin occupies the stand that scurvy is a typhoid disease and positively contagious; further, that it is imported in ships from the coast of the East and North Sea and the Black Sea. Kühn occupies a similar position; he describes a series of cases that he saw in individuals who had been in contact with cases of scurvy. He generalized, however, to the extent of saying that he is not sure his were cases of real scurvy in our sense. He also makes a distinction etiologically between scurvy from inanition and scurvy from infection.

The authors of the last two decades merit more serious consideration, as they have expressed themselves more definitely in regard to the nature of the infectious agent, and have attempted to fortify their views by animal experiments. Petrone says tentatively that small vegetable organisms are the cause of the disease, but is also of the opinion that scurvy, like malaria, is not contagious. Seeland, who was stationed as army physician in the Amur country, states from his experience that the disease is miasmatic, and that above all the diet could certainly exercise no influence, as the soldiers received a variety of non-scorbutic food (according to his description of the diet this is not so positive). He states that the country is moist and swampy, that fungous growth is found in all the wooden houses during the whole year, and that in the dwellings of cases of scurvy there is always a considerable smell of mold. He attributes the fact that the natives are rarely afflicted with scurvy to the presence of clay floors in their houses, and to the fact that they are well ventilated by constantly burning fires.

Murri made the first experimental investigations. He injected blood from cases of scurvy subcutaneously into 4 rabbits; a rise of temperature occurred, and in all the animals small hemorrhagic spots appeared

in the ears, but no other distinct symptoms of sickness. Three of the animals were killed, and on autopsy small hemorrhages were found in the dura mater, the base of the brain, and the pleura; in 1 of the rabbits also hemorrhages in the liver, the spleen, and the peritoneum. Murri refrains from drawing any conclusions from these observations. Contù, and later Mari, repeated these experiments and injected scurvy blood into 2 rabbits; these rabbits also remained in fairly good health, except that those of Contù had a few insignificant spots on their ears. After eleven and twelve days the rabbits were killed, and on autopsy a large subpleural hemorrhagic focus and a number of smaller hemorrhages in the pleura, dura mater, and some other places were seen. Mari's animals had small hemorrhages in the meninges and the muscles of the body.

Wieruszskij attempted to discover the infectious agent by culture methods instituted with the blood of scurvy cases. In 2 series of experiments he inoculated different culture media with 111 specimens of scurvy blood. Among the first 56 inoculations he obtained cultures in 11 cases, but all the bacteria found were of known character and could not be connected in any way with the typical symptoms of scurvy. The second series of 55 inoculations gave only 3 cultures, none of which showed anything new. After injecting blood subcutaneously into 4 rabbits without obtaining any reaction, he arrived at the conclusion that scurvy is not an infectious disease due to a micro-organism discoverable in the blood.

Babes was more fortunate in his results. Starting with the supposition that scurvy is an infectious disease that gains entrance into the organism through the mucous membrane of the alveolar processes, he examined small pieces of the gum that he removed from 2 soldiers affected with scurvy in common with 14 of their comrades at the military hospital in Jassy. The examination of the blood was negative. In fresh sections and in sections hardened in alcohol a definite bacillus was found. Of a series of rabbits which were inoculated artificially in different manners, all became affected characteristically. A small part of the gum tissue was sterilized, the surface macerated, suspended in bouillon, and injected into the blood. After six or eight days both animals died with a slight fever. In one of the animals, a pregnant female, hemorrhages had appeared on the fifth day, extending all along the left side of the belly. After death ecchymoses were found in the muscles, on the serous membranes, and in the liver; the duodenum and large parts of the other intestinal divisions were hemorrhagic in their whole extent. In the fetus punctiform hemorrhages of the skin and serous membranes could be found. In the second rabbit small disseminated hemorrhages of the subcutaneous tissue and the serous membranes were seen. All the animals that were injected with the blood remained healthy. Babes also succeeded in finding the above-mentioned bacillus in combination with the bacillus of rabbit septicemia in the hemorrhagic foci of different organs. Culture experiments were successful, and animals injected with pure cultures died, but it was impossible to transmit the disease through an animal body.

Babes describes the bacillus as a long, coarse organism, pointed at its ends, about 0.3 μ wide and 3 μ long, sometimes twice as long, and occasionally even forming wave-like threads of different lengths. It is thinner and longer than the cholera bacillus. The youngest specimens are double individuals, and show a tendency to form so-called metachromatic bodies, first mentioned by Babes. These are stained dark violet by methylene-blue, and are thicker than the little rods. The latter are stained weakly with rubin, and cannot be colored by Gram's method. The bacilli resemble the Bacillus ε of Müller, and are probably always present in the mouth.

Rosenell also describes a bacillus similar to that of Babes, which he found and cultivated from the spleen and kidneys of a girl of ten years, who was said to have died of scurvy. Culture experiments in rabbits were unsuccessful; Rosenell thinks that the reason for this was that he used the fifteenth to the twentieth generation for the inoculation, and that their virulence was too much reduced. The history of this case creates some doubt as to whether the girl really was suffering from scurvy. Bornträger found cocci in one case, but refrains from declaring them to be the cause of scurvy. He does not doubt, however, that scurvy is a bacterial disease; and as he believes that the germs enter the blood-current from the intestine, he considers the dejecta of a patient dangerous and a factor in the dissemination of the disease.

All in all, evidence of the infectious nature of scurvy is very scanty. The only investigations that are at all important are those of Babes, and these will have to be corroborated. Babes himself does not expressly state that he has found the cause of scurvy, but only speaks of a "bacillus causing gingivitis and hemorrhages in scurvy." It may be well, therefore, to examine what other factors play a rôle in the causation of this disease.

Age and sex certainly have no influence, although here and there epidemics have been reported in which subjects of a certain age or of one or the other sex were principally affected. (In 1847, in the Salpétrière in Paris, for instance, according to Fauvel, only old women were affected.) Individual disposition and constitution play a certain rôle in most epidemics; a strong constitution, however, is no prevention. There can be no doubt that individuals who have recently recovered from other diseases, or are still afflicted with some disease, are particularly prone to scurvy. Of the most important predisposing factors we must mention malaria (Duchek, Wolfram, Debord), dysentery, tuberculosis, trauma, and syphilis, particularly if mercury treatment has been given (Krebel). It would lead us too far to enumerate all other favoring diseases, but the writer would like to mention that quite recently he has observed 2 sporadic cases of scurvy immediately following influenza.

Our discussion of the widespread geographic distribution of the disease shows that climate bears no etiologic influence. Moist and cold weather seems to be important, for we see from numerous reports that such weather conditions prevailed at the times of the epidemics.

On the other hand, according to the statistics of Amberger and

Duchek, and of Hermann, who records 2680 cases occurring within eighteen years at Obuchow Hospital in St. Petersburg, the disease has assumed great proportions in summer and in winter, in dry as well as in moist atmospheres.

Navigation in high or low latitudes, again, seems to be without any influence one way or the other on the occurrence of scurvy.

That the condition of the soil apparently has nothing to do with the occurrence of scurvy is demonstrated, of course, by the overwhelming frequency with which the disease occurs on board ship. It is true that numerous investigators report epidemics and endemics in moist and swampy regions; but against these observations we have the fact that numerous other conditions of the soil obtain in other epidemics, so that we are hardly justified in declaring one form of soil particularly favorable to the development of this disease.

In all epidemics, however, whatever may be the external conditions, the disease seems to follow bad hygiene, and particularly bad alimentation. It is hardly necessary to enumerate the different possible conditions under which this disease may occur; they are sufficiently plain from the fact that the great majority of all epidemics related in its history occurred during long sea voyages, in camp, in besieged fortresses, barracks, prisons, poorhouses, orphan asylums, etc. Under all these conditions a variety of hygienic defects are observable, and the question arises as to which one of these may be most potent in causing the disease. Long life in the open in bad weather, insufficient clothing, or, on the other hand, life in narrow quarters with contaminated air are certainly important. Yet numerous reports exist, according to which none of these conditions was present. On one point all observers of all times and all countries agree—namely, that in the etiology of this disease *defective nutrition* is the most important agent.

It is true that for a long time the views of different investigators varied widely as to which constituent of the food is the most important, or rather as to which class of articles by its absence would be most likely to produce the disease. Scurvy can hardly be called a famine disease, although it frequently follows ruined crops. The exclusive use of salt meat has frequently been declared to be the cause, particularly at a time before our modern methods of preserving food enabled sailors to enjoy better nourishment, and at a time when sea voyages lasted much longer than at present. Under these conditions the crews were dependent on salt meats for periods of many months. As against this supposition we know that many tribes in the far north live exclusively upon salt meat and fish all the year round, notwithstanding which scurvy is unknown among them. Further observations are on record of epidemics in which fresh meat was abundantly supplied. The lack of fresh water has also been accused of playing a rôle in the causation of scurvy, only, however, in isolated instances. (Account of Beckler on the expedition of Burke into the interior of Australia, 1861.)

The number of observers who attribute the origin of scurvy to a lack of fresh vegetable food is overwhelmingly large. We must refrain

from going into the details of this question, and refer to the work of Hirsch, who, in a "short" review, devotes many pages to this question. We shall only mention that Bachstrom first called attention to the influence of the absence of fresh vegetable food. Lee reports that the severe epidemics in southern Russia of the year 1823 began after large swarms of grasshoppers had devastated the fields. Nearly all observers seem to agree that the epidemics of scurvy which occurred in Paris during the siege of 1870–71 did not begin until the supply of fresh vegetables, particularly of potatoes, was exhausted; this despite the fact that numerous hygienic and social defects in the mode of life had existed for a long time previously.

Delpech reports the case of a wine merchant, aged forty-five, who became affected with scurvy, notwithstanding the fact that he ate plenty of fresh meat, and lived in the best possible circumstances, in a healthy, dry, and well-heated house; however, he was eating no fresh vegetables of any kind, and as soon as he was induced to do so his disease disappeared. Seldom can one employ the *post hoc, propter hoc* so safely as here, where fresh vegetables of a certain class afford the best prophylactic method, and if scurvy exist, the best remedy.

The fact that certain classes of vegetables, above all potatoes, have so sure an action in scurvy caused Garrod to notice that potatoes in particular contained proportionately a large quantity of potassium carbonate. He examined a number of other articles of diet for their percentage of potassium carbonate (potash). According to him there are contained in 1 oz. of

Large potatoes (boiled)	1.875 gr.	Peas	0.529 gr.
Small potatoes (raw)	1.310 "	Beef (salted)	0.394 "
Lime juice	0.852 "	Onions	0.333 "
Lemon juice	0.846 "	Wheat bread	0.258 "
Unripe oranges	0.675 "	Cheese (Dutch)	0.230 "
Mutton (boiled)	0.673 "	Wheat flour (best)	0.100 "
Beef (raw)	0.599 "	Oatmeal	0.054 "
Corned beef (slightly salted)	0.572 "	Rice	0.010 "

From these examinations Garrod evolved the theory that a deficiency in organic potassium salts is the primary cause of scurvy, and a number of other authors, above all, J. V. Liebig and Hirsch, endorsed his view.

The important rôle of potatoes in the prevention of scurvy is clearly shown by the observation that the extent of the disease decreased with the general introduction of the potato. From Hirsch's book we learn how little time was given to the cultivation of vegetables in past centuries; he tells us that Catharine of Aragon, the wife of Henry VIII., had to send her gardener to the Netherlands in order to procure the material for a salad.

Scurvy has not developed in the past exclusively under conditions where a lack of vegetable or potash-containing food was noticeable; Hirsch adduces a number of examples to elucidate this point. Nobody goes so far probably as to maintain that all other noxious influences need not be considered; on the contrary, the exceptions to the above

rule prove that these other factors have, at least, a great predisposing significance. We can also imagine that in the exceptions mentioned a sufficient amount of potash was ingested, but that the body was incapable of assimilating it, owing perhaps to the operation of a number of other factors. Bunge formulates the theory that a direct factor in the causation of the disease may be sought in salt meat, for the reason that in the process of salting all the salts of the meat proper, and therewith its potash, are removed.

However seductive the potassium theory may be, it is not absolutely established, nor does it absolutely exclude the possibility that scurvy is an infectious disease. It is possible that scurvy is an infectious disease that is not contagious, produced by a micro-organism which finds its best medium in an organism containing little potash.

Pathologic Anatomy.—The most striking characteristics of the body of one dead of scurvy are numerous petechiæ and ecchymoses on a dirty grayish-yellow ground that are distributed all over the skin, with the usual exception of the face. In addition, numerous post-mortem spots appear early. Typical for this disease is the fact that rigor mortis occurs early, as does also decomposition. The lower extremities particularly are edematous. On microscopic examination of the hemorrhagic areas it will be found that in the smaller spots the blood has oozed out of the capillary network surrounding the hair follicles. In the larger ones its origin may vary, and blood may have been poured into the superficial or the deep layers of the skin. The extravasated red blood-corpuscles are in all stages of degeneration, and the surrounding tissues are impregnated with blood-pigments of different color.

In the subcutaneous tissues and in the muscles hemorrhagic infiltrations of different kinds are seen; they may be diffuse, partially circumscribed, and, according to their age, of different colors and consistence. These are the cause of the hardening. In old foci that have not undergone retrogressive changes solid masses of connective tissue are found in place of the fibrinous coagula. The muscular tissue surrounding these masses is partially contracted, partially atrophied, and the tendons are adherent to the muscles over long areas, or may be so hardened that their motion is rendered impossible. In this manner stiff joints and deformities—for instance, club-foot—occur. In the cavity of the joints a serous or bloody exudate is occasionally found; the tissues around the joints are not necessarily changed. If hemorrhages have occurred at the same time, the capsule of the joint will be seen to be hardened, blood will be found between the bone and the cartilage, and a mushy softening of the epiphysis will be discovered. In the bones subperiosteal hemorrhagic exudates are found, explaining many of the clinical symptoms; this blood may be seen in all stages of coagulation or destruction; further, there are ulcerations of the periosteum and necrotic changes in the bones themselves. Occasionally the insertions of the muscles are loosened by these processes. Sometimes hemorrhage occurs into the interior of the bones, particularly into the cancellous tissue. Lymphoid changes have been observed in the bone marrow.

Except upon the gums the mucous membrane of the mouth is very little changed. Here and there a few isolated hemorrhagic or ulcerative spots are seen; the gums are moderately swollen, reddened, and completely permeated by red blood-corpuscles. In older cases a solid thickening is seen as a result of connective-tissue proliferation. As a rule, the surface of the gums is ulcerated and sloughed. Microscopically, Babes could distinguish five layers that he describes as follows:

"Beginning from without, first the upper layer, largely denuded of its epithelium, moderately thick, pale, resembling a diphtheria membrane, containing very few fragments of nuclei and some bacteria, particularly streptococci; second, a structureless mass about 0.1 mm. thick. On coloration with Löffler's blue it is seen to be a mesh-work of crooked, frequently wavy bacilli of great length, and very thin; these extend in the form of bundles or strands into the deeper tissues and along the superficial layer described above. In the latter they sometimes undergo granular degeneration. Third, mononuclear and polynuclear round cells; fourth, mucosal tissue swollen by edema and granular exudates and containing numerous bacilli of the kind described under second; within the vessel walls and in their neighborhood enlarged spindle cells with a reticulated protoplasm that is readily stained by methylene-blue. Fifth, dilated larger vessels, containing in their vessel walls large spindle cells; in the vessels that are engorged with blood numerous masses of cells, different kinds of granular leukocytes, endothelial and mast cells are found, but no bacteria."

The pleura and pericardium are frequently hemorrhagic, so that the pleural space and pericardial cavity may contain large amounts of a hemorrhagic fluid or of pure blood, and occasionally also fibrinous deposits. The heart muscle is pale, flabby, frequently hemorrhagic, sometimes in different stages of fatty degeneration; the valves are usually intact, but occasionally show evidence of an acute verrucous or ulcerative endocarditis. In the lungs bloody edema or hypostatic consolidation in the lower posterior portions is often seen; occasionally croupous pneumonia, the result of secondary infection; in some instances hemorrhagic infarcts, rarely gangrene, are observed. The mucous membrane of the air passages is frequently covered with petechiæ and a bloody slime; edema of the pharynx may be present.

In the peritoneal cavity similar conditions to those seen in the pleural sac are found. Such changes, however, are less frequently observed nor are they so intense.

The mucosa of the whole digestive tract is also covered with small areas of hemorrhagic exudate; occasionally ulceration is discovered. The most striking changes are found in the colon, particularly in those cases that had bloody stools during life; its mucosa is swollen, fragile, and covered with bloody masses that can be readily removed. The underlying tissues are softened or in a state of disintegration. Occasionally conditions are seen in which the changes are limited to the follicles; here these structures are ulcerated and surrounded by dense

bloody infiltrations. In all these cases the contents of the stomach and intestine are mixed with blood. Usually no changes are found in the glandular organs of the abdomen, the liver, and the pancreas, with the exception of occasional hemorrhages or fatty degeneration. The spleen alone is occasionally enlarged; owing to its engorgement with blood it may be soft, even liquefied, and occasionally infarcted. The kidneys are usually the least affected organs, but if much albumin has been present in the urine, some degree of parenchymatous nephritis can usually be seen. Slight degrees of albuminuria frequently leave no trace whatever in the kidneys. Infarcts are rarely found in these organs; hemorrhages in the capsule and the mucous membranes of the urinary passages are occasionally observed.

Symptomatology.—The chief symptoms of scurvy are: (*a*) the marked *alterations in the gums*, which in their spongy, bleeding, often ulcerated or necrotic state produce an insupportable fetor *ex ore;* (*b*) the widely scattered *hemorrhages* into skin and mucosa, into joint and body cavities, into the muscles under the periosteum, into the bones and in many other places; (*c*) the grave *disturbance of the general health* which accompanies the foregoing—whether as cause or effect we do not know—and culminates in a profound cachexia.

As a rule, beginning cachexia is the first symptom noticed, and for a long time may be the only disturbance complained of, as the disease begins and develops very slowly. In the beginning the patients feel tired and without energy, but are not incapacitated from work; the fatigue increases constantly, slight exertion becomes very difficult and causes dyspnea and palpitation. To these general symptoms are added pains in the limbs, later pains in the joints, which appear to be rheumatoid in character; they are principally localized in the lower extremities, although they may affect any part of the body. With increasing weakness and discomfort on exertion an increased feeling of chilliness and of somnolence appears. The latter symptom is not relieved, although an unusual amount of sleep be taken. The appetite is frequently lost, or, as in other cases of anemia, a craving exists for acid foods. In other instances an enormously increased appetite is found, just as in cases convalescent from typhoid; this may be so exaggerated that all judgment in regard to the good and bad quality of the food is lost. This bulimia need not necessarily be accompanied by a feeling of great thirst.

As the feeling of illness increases, external signs of the disease begin to appear; the facial expression becomes melancholic and denotes suffering; the freshness of the color yields to a cyanotic pallor; the visible mucous membranes become livid; the eyes recede within their cavities, look tired, and are surrounded by rings. The skin of the body loses its sheen and electricity, becomes dry and rough, and usually desquamates as in the pityriasis of old people; occasionally it assumes a goose-skin appearance, particularly on the extensor surfaces of the arms and legs. Opitz has observed bronze spots on the skin at the very beginning of the disease, which were of different size and shape; these

rarely disappeared until the disease was cured. Fever is not present, as a rule; at least, not in the beginning.

In proportion to the loss of strength a loss of flesh occurs, so that the patient steadily emaciates.

The tension and volume of the pulse decrease and the heart beat is slow; as soon, however, as the patient indulges in moderate bodily exercise the volume of the pulse and its rapidity increase, and the patient experiences the subjective sensation of palpitation. At the same time nothing abnormal can be found about the heart, either when the patient is at rest or when he is moving about. Similar conditions obtain in regard to the breathing and the physical examination of the lungs. On violent exercise breathing becomes very rapid and puffing.

Occasionally these premonitory symptoms are completely absent and the disease begins with its characteristic lesions. As a rule, however, the latter are preceded by prodromata that may make their appearance several days (usually from eight to fourteen), or in exceptional cases several weeks, before the disease breaks out. As we have mentioned above, the place of predilection for the appearance of the first characteristic signs is the *gums;* it seems that the part of the gums bordering the teeth are particularly affected, so that in the case of children in whom no teeth have appeared, and in the case of old people whose teeth have already fallen out, the gums remain free. Wherever carious processes exist and the teeth are partially destroyed, or where the crown is lost but the roots are still present in the alveolar process, the disease is found very frequently. It is also worthy of mention that, as a rule, particularly in the beginning, the anterior portions of the gums are chiefly affected, and the remaining portions of the membrane of the mouth are not involved to any great degree.

The process, as a rule, develops as follows: At first the outer margin of the gums begins to swell, particularly at the protrusions between the teeth; at the same time this piece of tissue seems to separate from its base and to assume a dark bluish-red color. This color is not only an expression of an edematous hyperemia, but usually also indicates hemorrhagic infiltration, and is clearly distinguishable from other forms of stomatitis. The zone of involvement soon extends over other portions of the gums, the swollen parts become very painful, and light pressure or even simple touching will produce hemorrhages. The longer the duration of the disease and the more violent its character, the more the affection of the gum will extend. The swelling will continue to increase, sometimes to such a degree that almost nothing can be seen of the teeth; at the same time a most disagreeable odor develops from the mouth, that in the later stages is insupportable. The inflammatory swelling of the gums frequently develops still further, so that diphtheric membranes of a dirty-grayish color develop on the mucous membranes, to which they are firmly attached. When they are removed a considerable part of the mucous tissue is torn away, leaving a bleeding and very sensitive surface. Occasionally the mucous membranes may become gangrenous, so that they form a malodorous, smeary, purulent

mass, the upper layers of which may become loosened and be ejected with the saliva. If this process continue for a long time, such destruction of the gums may occur that the alveoli are exposed and the teeth become loosened and drop out. It can be imagined what a torture such a condition must be to an unfortunate patient, especially as an exaggeration of all the other symptoms usually follows an aggravation of the local symptoms in the gums; this is particularly true of the cachexia, which increases steadily and becomes very severe. Yet, as Immermann has emphasized, this cachexia is not a result of the various local lesions, but is, on the contrary, a chief symptom of the disease, responsible to an extent for the intensity of the individual localized symptoms.

The second point of localization for the specific lesions of scurvy is the skin. At a very early stage of the disease, and increasing with the development of the general involvement, small petechiæ are seen, that usually have a diameter of from 1 to 5 mm.; they are so numerous that the skin appears as though it had been spattered with blood. These petechiæ are found principally in the lower extremities, but gradually extend over the whole body, and are found in all stages of discoloration and retrogressive metamorphosis of the blood-pigments. These smallest hemorrhages are not elevated above the level of the skin, but other more prominent ones are seen which form small nodular protuberances; according to their size these are occasionally designated as acne scorbutica or lichen scorbuticus. Rarely the epidermis is raised into little vesicles by a slightly bloody fluid, so that herpes scorbuticus is occasionally spoken of. Sometimes these forms assume larger dimensions (pemphigus scorbuticus); or large surface hemorrhages, ecchymoses of irregular shape, occur; finally hard, streaked, band-shaped hemorrhagic infiltrations may appear. These symptoms appear spontaneously; the slightest mechanical irritation, sometimes even simply touching the skin, will increase them greatly. In particular, contusions of the limbs following a bump, or the pressure of the back, the glutei, and the calves against uneven parts of the bed, folds in the bedding, etc., can produce them. As new eruptions continually occur before the old ones disappear, all colors are seen, so that the appearance of a case of scurvy is very characteristic and peculiar.

Frequently, however, this picture is still further modified; little vascular eruptions may burst and a rupia scorbutica result. The adjoining parts of the skin ulcerate and dirty, bloody, blackish crusts form, underneath which the cutis separates. Even simple ecchymoses can produce sores, especially if their rupture be favored by some other slight lesion. Old and cicatrized sores are likely to break open again when scurvy develops, or sores that already exist are likely to become aggravated. It is a general characteristic of this form of disease that almost all pathologic symptoms present in the organism are aggravated when scurvy supervenes (so that these symptoms may grow very much worse). Further, as we have already seen above, those individuals who are in a marantic condition or are afflicted with some other disease are particularly prone to scurvy. In the latter instance it is frequently difficult to

determine whether certain symptoms are to be attributed to the one or the other disease.

The small hemorrhagic extravasations into the skin are frequently found close to the hair follicles, and look as if the hairs had bored through them; the hair soon breaks off and perishes. The tissues around the nails are also a favorite place for these hemorrhages. If these tissues begin to suppurate, the process frequently extends to the root of the nail, so that paronychia or an onychia develops, followed by the death of the nail. The sores that develop in other parts of the skin, particularly the lower extremities and the glutei, may assume large proportions. They are partially covered by dark, solid crusts or show dirty-looking bases covered by hemorrhagic, purulent shreds of tissue; or finally a number of squamous granulations are seen, which bleed on the slightest touch. The ulcers usually continuously excrete a thin hemorrhagic, purulent or sanious, very malodorous fluid. Aside from the fact that these ulcers rarely heal before the general condition is improved, they have a tendency to extend either laterally or downward into the tissues, so that occasionally large blood-vessels are eroded and violent hemorrhages may occur, which sometimes bring about the death of the patient. Aside from the possibility of such an accident, the ulcerations of the skin are dangerous because they weaken the organism by the great quantity of albuminous matter that is lost in their secretions.

In addition to the ulcerations that begin at the surface and progress into the tissues, there are other kinds that present the same picture, but originate within the tissues and break through to the surface. These ulcers have their beginning in lesions of the *subcutaneous tissues* and the *muscles*, and are found chiefly in the lower extremities, particularly in the region of the tendo Achillis and of the popliteal space. In the beginning a soft growth is noticed, which gradually grows harder; the skin over it is not movable, and the growth is not strictly circumscribed nor defined from its surroundings; the skin is red, edematous, shiny, hot, and painful. At the expiration of several days these phenomena decrease in severity and a brownish color appears. The inflammatory focus underneath either disappears very soon or may persist for some time; in the latter case it can be felt through the skin, which desquamates and finally remains pigmented. If the swelling does not recede, but, on the contrary, continues to increase, the skin over it becomes thinner and its reddish coloration turns to blue, until finally the swelling breaks through the skin and a large quantity of blood mixed with disintegrated or gangrenous tissue is evacuated. The result of such an occurrence is a deep ulcer. Occasionally the course of this ulcer is not so acute; swelling and hardening progress much more slowly, pain and fever are absent, and the lesions of the skin are correspondingly slight. The latter tissue simply assumes varying colors, that may become more intense or less vivid according as the lesion is situated near the surface or deep down. Naturally the presence of such a focus seriously interferes with the function of the muscles, whether it be situated within the

muscle itself or within neighboring connective tissue. If lesions of the muscles occur simultaneously with lesions of the connective tissue, it is not possible to differentiate them. Here and there isolated foci are found in the muscles, which are distinguished by the fact that they are not accompanied by corresponding changes in the skin over them. These, too, produce varying symptoms, may be circumscribed or diffuse, painful or painless, running an acute course with fever or developing slowly without a rise of temperature.

All manifestations of scurvy which are found in other organs and other parts of the body are fundamentally dependent on the chief characteristic of this disease—that is, hemorrhages. We find in nearly all organs hemorrhages that may be internal or external, according to the situation of the tissues involved. *Epistaxis* is one of the most dreaded symptoms; it does not occur very frequently, but when it does, it is almost impossible to control it without packing the nasal cavities; it has frequently led to death. Such hemorrhages may occur spontaneously or as the result of very slight injuries to the nasal mucosa, particularly from blowing the nose violently. Immermann believes that the reason for the primary involvement of the gums and for their being the apparent place of predilection for scorbutic lesions is the fact that it is almost always necessary in scurvy that some external injury supervene before the hemorrhagic lesions occur. He expresses the opinion that this marginal stomatitis is secondary, and is brought about by the many mechanical, chemical, and thermic injuries to which the gums are exposed during the biting off and chewing of food, by spices, hot drinks, etc. This view is justified, particularly when we consider how delicate the histologic structure of the gums is, and further, when we remember that the affection of the gums occurs only where teeth are found in the alveoli—that is, where the act of chewing is performed.

The writer might mention here that the gums are not always the chief point of attack, or, at least, not always the seat of the first typical lesions, but that very severe cases are on record in which the gums were not affected at all. Altogether, the order of the different symptoms and the number of organs that are affected in this disease are inconstant.

Occasionally *hematemesis*, more frequently *hemorrhages from the bowels*, are observed. The latter usually occur when the intestine is stimulated to active peristalsis; for instance, after the administration of laxatives. Their origin is probably in these cases due to slight mechanical injuries, as in the case of epistaxis after blowing the nose; it may also be a symptom of an existing diarrhea; at the same time hemorrhages from the uropoietic apparatus are occasionally observed; also from the lungs, but in the latter instance, chiefly if some other disease, as tuberculosis, pneumonia, etc., coexist.

In addition to these hemorrhages that occur on the surface or in organs that communicate with the surface, hemorrhages may occur into the cavities of the body or into internal organs. Such an occurrence always constitutes a serious complication, will always increase the loss of vitality, and may, of course, produce death. *Pleural* and *pericardial*

exudates of this kind are the most important; they may be considered as non-inflammatory extravasations, leading in some instances to an inflammation of the serous membrane, or as primarily inflammatory hemorrhagic exudates. Niemeyer observed 2 cases in which the exudates were reabsorbed.

Hemorrhage from the *meninges* has also been described. This accident is rare and usually leads to death, with the clinical picture of apoplexy. Hemorrhage into the *eyes* and their surroundings is more frequent; particularly hemorrhage under the conjunctiva, leading to the separation of this tissue from its base, and reaching such dimensions that it protrudes below the lid and covers the eyeball to a great extent Hemorrhage into the anterior chamber, combined with iritis and hemorrhagic choroiditis, is also observed; these lesions may disappear or may become permanent. In very severe cases bilateral panophthalmitis occurs that is horrible to see, and ultimately leads to the complete disintegration of the eyes. These cases are always fatal.

The lesions seen in the *bones*, the *cartilages*, and the *joints* are distinctive. In the bones, particularly if some slight mechanical injury occur subperiosteal hemorrhage or inflammatory exudation takes place, resulting in the formation of firm, acutely painful swellings that may either slowly disappear or lead to local necrosis and formation of sequestra. In the region of the epiphysis a separation of the cartilage occurs. Most frequently the long bones of the lower extremity are involved; next in order of frequency, those of the upper extremity; quite often the ribs, in which the process leads to separation from the sternum. In case there are fresh bone cicatrices, scurvy will produce a softening of the callus, acting in this instance as everywhere else—that is, producing an aggravation of whatever accidental lesions may exist. Hemorrhagic exudates into the joint cavities are very important, particularly because they produce violent arthritic pains. If a cure of the disease be brought about at all, these exudates are usually reabsorbed without leaving ankylosis. In addition to these typical symptoms of scurvy, a swelling of the *spleen* is usually noticed that is not at all specific. Malaria seems to be a predisposing disease, or possibly is easily acquired when scurvy is present, and the swelling of the spleen may even be attributed to this complication; it may also be found in uncomplicated cases. What has been said of malaria applies with equal force to dysentery. The *kidneys* are usually only slightly involved; occasionally albuminuria is found.

Nothing characteristic has so far been found in the *blood* aside from the doubtful monads of Klebs. The blood-picture in general is that of a severe secondary anemia. The quantity of hemoglobin is diminished, and in grave cases the red blood-corpuscles are reduced in number as well as in their individual hemoglobin content. Poikilocytes and microcytes are often present, and particularly the pessary forms described above. Penzoldt reports the presence in the blood of granular, partially refractive bodies; these he considers rudimentary red blood-corpuscles; it is also stated that macrocytes have been seen in great

numbers. According to Laboulbène, the number of white blood-corpuscles is increased. The writer has not been able to verify this statement in his own cases.

Reports on the iron of the blood are contradictory. According to Opitz and Schneider, it is increased; according to Duchek, approximately normal; according to Becquerel, Rodier and Chalvet, reduced. The latter author claims to have determined a reduction in its potassium; v. Jaksch found bile pigment. [Moderate increase in the number of leukocytes has come to be regarded as a fairly constant finding in scorbutic blood. While the increase is usually confined to the polynuclear neutrophile elements, Da Costa has observed a relative lymphocytosis accompanying it in cases of infantile scurvy. Denys noticed unusual fragility of the leukocytes and an increase in the number of degenerated forms. Decreased alkalinity has been observed by Bush, Garrod, Ralfe and Wright, the latter believing that the intoxication of scurvy is due to acidosis.—Ed.]

The *urine* is frequently dark in color; Kretschy attributes this to an increase of its normal pigments caused by a great disintegration of red blood-corpuscles. The quantity of the urine in severe cases, particularly during the development of the disease, is greatly reduced. We have already mentioned the presence of albumin in variable quantities, and may add that quite frequently peptonuria occurs. According to v. Jaksch, the peptone is not derived from the blood, but from the hemorrhages into the skin and subcutaneous tissues. He also designates these exudates as the source of urobilin, which is found in large quantities. Naturally a great deal of attention has been given to the plus or minus of potassium in the urine, but the observations made are contradictory. It is said that phosphoric acid is increased. There can be no doubt that the quantity of uric acid is very great, particularly at the height of the disease. According to v. Jaksch, this quantity decreases as soon as improvement begins.

If we review the large number of individual symptoms and compare the disease picture with the one seen nowadays in Germany, we notice that we rarely see the disease in its severe form. Frequently the symptoms are limited to great lassitude, pain in the joints and limbs, isolated hemorrhages into the skin and gums, without other anatomic changes in the gums or other organs. The course of the whole disease is relatively short.

Scurvy may terminate in death or in complete or partial recovery.

The latter, as a rule, proceeds very slowly, and it usually takes weeks and months for the single processes to heal. The lesions of the gums, provided no destruction of the tissue has occurred, are usually completely cured; the swelling disappears and a restitution to normal ensues. Sometimes permanent changes remain, assuming the form of hyperplastic thickening of the tissues, but causing no symptoms. Where loss of tissue has occurred, large and small scars naturally remain. The small hemorrhages in the skin run a simple course; they pass through all the stages of blood-pigment changes, and ultimately

disappear completely. The ulcers also assume a benign character; as the patient improves, the surfaces become cleaner and are ultimately covered with skin. The site of the ulcer is distinguishable for a long time by a darker color; the swellings of the muscles and of the connective tissue also recede gradually, but so slowly that evidences of these lesions can frequently be felt for a long time after recovery. Occasionally, as in the case of the gums, connective-tissue proliferation occurs, resulting in permanent contractures that may either assume the form of fixation of muscles or of joints, as, for instance, club-foot.

A peculiar complication involving the nervous system must be mentioned. This lesion is *per se* independent of scurvy, but occurs now and then in the course of the disease; the writer refers to hemeralopia, so-called night-blindness, in which vision is more or less impaired at dusk and at night.

Diagnosis.—In view of the typical character of the symptoms, the pronounced epidemic character of the disease, and the extraordinary circumstances under which it develops, the diagnosis of scurvy is rarely difficult; only where sporadic cases occur may it be difficult to arrive at definite diagnostic conclusions, and even here a careful anamnesis, involving the previous mode of living and surroundings, and determining the region from which the patient came, will usually lead to the goal.

If by way of recapitulation we remember that the great majority of epidemics of scurvy aboard ship, in fortresses, in isolated bodies of troops, and in closed institutions, almshouses, etc., and that in addition definite etiologic factors must obtain, as, for instance, unhygienic conditions or deficient and inappropriate food, it will be a comparatively easy matter to recognize the disease when it first appears. Further, it is rare to find only one or the other symptom in this or that locality of the body; as a rule, the disease breaks out in different places at once, so that we may say that individual cases of a very mild character are the only ones which may really present diagnostic difficulties.

We have learned to recognize the external symptoms: first, the general cachexia, which occurs spontaneously with the appearance of local symptoms and progresses steadily; second, the various kinds of hemorrhagic extravasations into the skin, the subcutaneous connective tissue, and the muscles; third, the occasional presence of rheumatoid pain in the joints; fourth, above all, the lesions of the gums. The number of diseases with which this condition could be confounded is very small; the most important are hemophilia and morbus maculosus Werlhofii, which form a group with scurvy. Neither one of these, however, is epidemic in character, and as we are to discuss them at length in the following sections we need not refer to them here.

Cutaneous hemorrhages, particularly petechiæ and small ecchymoses, are found in a great variety of cachectic conditions (for instance, malignant tumors) accompanied by the hemorrhagic diathesis. If rheumatoid or articular pain be present, scurvy may occasionally be con-

founded with peliosis rheumatica; if in such a case the diagnosis should remain doubtful a significant symptom is the inflammatory rupture of the hemorrhages of scurvy, whereas in the other disease this is not the case. Finally we must emphasize the excellent therapeutic measures for scurvy which usually lead to the disappearance of many of the symptoms, whereas we are utterly helpless in regard to the other diseases mentioned above.

In small children, particularly in infants who are artificially nourished, scurvy is undoubtedly often confused with Barlow's disease, especially if we are dealing with isolated cases. Perusal of the voluminous literature on scurvy in children carries the conviction that in the majority of cases the authors are dealing with Barlow's disease.

[This seems to imply a distinction between Barlow's disease and scurvy in infants. In one sense, possibly, such a distinction is permissible. Infants may acquire the disease during an epidemic either by sharing the conditions that produced it in the adults, or, in the case of sucklings, by nursing from scorbutic mothers. On the other hand, the disease may occur sporadically as a direct result of improper diet, independent of the prevalence of an epidemic. Cases of the latter group are often, but not always, associated with some of the manifestations of rickets, so that the clinical picture becomes complicated. For this reason the true nature of the affection was for a long time unrecognized. Litten may include the former group as scurvy, the latter as Barlow's disease. However, in 1881 Barlow described a series of cases of this kind and made accurate autopsy records, confirming beyond doubt the belief then growing that they were identical with true "sea" scurvy. The term Barlow's disease was used in acknowledgment of this work, and is, hence, synonymous with scurvy in infants. It is dealt with fully in the following section.—Ed.]

Prognosis.—Whereas the prognosis of scurvy was very bad in the days that are now happily historic, it is nowadays good, particularly if we are dealing with milder cases. It is true that we must be careful in making a prognosis even in the milder cases, as complications that may lead to an unfortunate issue are never excluded. The sooner treatment is begun, the shorter the course, although even under these conditions it usually takes a long time, many weeks or months, before the patient has progressed to such a stage that he can perform all his duties. A complete restitution to normal is only to be expected in those cases in which the disease assumes its lightest form; in every other case recovery is incomplete, and only where no loss of tissue has occurred may we expect a complete *restitutio ad integrum*. As we have already seen in our discussion on the symptomatology, ulceration of the gums leads to scar formation or permanent thickenings. Cutaneous ulcers leave scars; affections of the bones, and particularly the connective-tissue proliferations, the contractures of muscles, and suppurations in the joints—all lead to ankylosis or lasting impairment of function.

If the disease terminate with death, the patient usually suffers for a long time and must go through many phases before general exhaustion

leads to the end. At the same time an early termination may occur in advanced years. Fatal hemorrhages from the gums and nose, from arteries that are eroded by cutaneous ulcers, from the digestive tract, and from the bladder may occur. Complications like dysentery, croupous pneumonia, less frequently malignant endocarditis, caused by the entrance of infectious germs from the ulcers, may cause death. Further, pleural and pericardial effusions may assume dimensions large enough to threaten life; and, finally, life may end from sudden heart failure so that the patient may drop dead after some sudden movement or on getting up suddenly from the bed.

Treatment.—Investigations on the etiology of this disease have not yet determined positively what the primary causes of scurvy are. They have, however, revealed with sufficient clearness what factors co-operate to cause an epidemic of the disease, so that we have ways and means at our disposal to prevent by prophylactic measures the occurrence of the disease, and by giving the patient that which he lacked before we can, at least, arrest the progress of the disease. Particularly in the case of scurvy has prophylaxis accomplished wonders. Figures are eloquent when the tremendous mortality incident to sea expeditions in the fifteenth and sixteenth centuries is compared with that of later periods. In the English navy, from 1856–61, there occurred but 1.05 per cent. of cases; in the Austrian navy, from 1863–71, only 1 per cent. of cases; in the Austrian merchant marine, during 1871–72, 0.34 per cent.; and in the German navy, from April, 1875, until March, 1880, only 16 cases of scurvy and 76 cases of scorbutic mouth diseases, an average of 0.475 per cent. of the total crew. According to Lissunow, the number of scurvy patients found in the Russian army varied from 0.3 to 22.3 pro mille, with an average of 1.8 pro mille in the whole army from 1888–92.

The *general hygiene and the mode of life* should be improved both on water and on land. Garrod's discovery that a lack of potash salts may produce the disease indicates another direction in which prophylaxis must be exercised. It will be necessary to introduce an abundant quantity of this substance, best in the form of good, fresh potatoes, fresh vegetables, spinach, watercress, radishes, sorrel, sauerkraut, carrots, turnips, onions, artichokes, asparagus, salad, deciduous fruit, oranges, milk, fresh-meat extract, and well-preserved meat. The greatest difficulty is to equip ships with a sufficient quantity of such articles of food for long sea voyages; particular attention must be given to sailing vessels that are going long distances, as they are less conveniently arranged for storing large quantities of fresh food than larger and more luxuriant steamers.

Arctic expeditions are still particularly dangerous, not on account of the climate, for we have seen that scurvy may occur in all latitudes, but because the members of such expeditions have to stand great bodily exertions and deprivations, and are frequently deprived of fresh vegetable food. That good management and foresight can accomplish wonders in this direction is shown by Nansen's last expedition, which

lasted fully three years; here all the members remained healthy up to the last day. Nansen based his precautions on the idea that "in long Arctic expeditions the preservation of meat and fish by salting, smoking, or incomplete drying is insufficient and to be condemned. The main precaution in providing nourishment for a long journey must be to preserve food either by complete and careful desiccation or by sterilization with heat. I also attempted to procure not only nourishing and healthy provender, but also as great a variety of food as possible. We took with us meat of all kinds in hermetically closed tins; fish, both dried and preserved; potatoes, both dried and in cans; all kinds of preserved and dried vegetables, boiled and dried fruit, preserves and marmalade in large quantities, also condensed milk with and without sugar; preserved butter, dried soups of different kinds, and many other things. Our bread was chiefly Norwegian ship bread made from rye and wheat, and English ship biscuit. In addition we took flour, in order to be able to bake our own bread. Each article of food was chemically examined before it was accepted, and especial attention was given to the packing; even the bread and dried vegetables were soldered into zinc-lined cases. Our beverages for breakfast and supper were chocolate, coffee, and tea, occasionally milk; at dinner we had beer in the first half-year; later we had lemon juice with sugar and syrup. In addition, all arrangements were made for a comfortable mode of living aboard ship; the living- and sleeping-cabins were warm, and there was a plentiful supply of clothing, a well-stocked library, and a number of musical instruments, so that life never became monotonous." Nansen also took a large supply of illuminating material for the endless polar night; in this way the depressing influence of the long darkness was mitigated.

For a long time lemon juice has been used to cover the demand for vegetable alkali. The English navy instituted this in the case of their sailors; England has pointed the way to all other nations for the bettering of the hygiene and feeding of sailors. After the first fortnight of a voyage the crew of English vessels receive daily 30 gm. of lemon juice (10 parts lemon juice, 1 part brandy) with 45 gm. of sugar. It is not practical to substitute crystallized citric acid for this mixture, for the reason that citric acid is frequently adulterated, and that it is also important to use precisely those salts contained in the expressed juice of the lemon itself. Other fruit juices can be used in the place of lemon juice, as can also preserved fruits and berries. Nansen took with him a large supply of preserved cranberries and mulberries (Rubus chamæmorus), following in the latter case the recommendation of Nordenskjöld. Neale recommends fresh meat still containing the blood, which, of course, is very hard to procure on long sea voyages; an excellent substitute, particularly in respect to its antiscorbutic action, is Liebig's meat extract, which, it is true, contains no albumin, but precisely those salts that are demanded in this instance. Corn-beef, on the other hand, is altogether useless, because these salts are absent.

Good drinking-water is of paramount importance. If necessary, it

can be procured from salt water by distillation. Nansen recommends during polar expeditions to melt those portions of the salt-water ice which protrude above the surface of the sea, for the reason that these parts have been exposed to the rays of the sun all summer and have lost the larger part of their salt. He does not consider it necessary to distil water procured in this way before drinking, and says that the danger of scurvy is not increased by the presence of a small quantity of salt. Of other beverages that can be considered, we may mention tea, beer, wine, and cider, particularly the kind of beer called pine beer, which is manufactured by adding either Turiones pini or essence of spruce to the fermenting mass.

What applies to appropriate food on board ship is also valid for large bodies of troops during war; particularly in fortresses great care should be taken, especially as we have seen that among the land epidemics reported the great majority occurred during war. Proper care of the clothing and the procuring of suitable quarters where the men can sleep are as important as proper food, and means should never be omitted to raise the spirits of the troops as much as possible.

The prophylaxis against scurvy that can be exercised in institutions is based on the same principles; it is very important here to avoid a monotony in the diet. The principal indication is, as we have said, a well-executed system of hygienic rules.

Bornträger, on the supposition that the infection in scurvy occurs from the intestinal tract, makes a series of prophylactic suggestions that apply chiefly to the disinfection of the dejecta, etc. If Babes, on the other hand, is right in his supposition that microbes enter *via* the gums, then the above rules of Bornträger are fictitious.

The *treatment* of scurvy is a general one. We have already called attention to the fact that Garrod's potassium theory is not valid in all cases, and that patients who have a plentiful supply of appropriate food may still be scorbutic. In such cases no advantages can be gained by giving potassium salts. Sometimes all that is needed is to place the patient under favorable local conditions. A classic example of this kind is the removal of a number of scurvy cases in 1847 from the moist and poorly situated hospital in Givet to an elevated point in the vicinity; this transportation led to the recovery of almost all the patients. Mari recommends the employment of hydrotherapeutic measures. The patients, as a rule, do well if warm baths are frequently given.

Special treatment is purely symptomatic, for we know of no specific against scurvy, and the great majority of the plant preparations that have been recommended in reality constitute a modification of the diet. Since antiquity, Herba cochleareæ occupies first place. The following is a very popular prescription:

℞ Herb. cochlear. rec. conc.,	50.0
Sem. sinap. cont.,	12.5
Vin. gall. alb.,	300.0
Macera per biduum., colat. adde. spirit. æther chlor.,	6.0

Sig.—One-half wineglassful t. i. d.

Whether this remedy really exercises a special effect is very doubtful. It is more probable, as Immermann has said, that the reputation of Herba cochleareæ is due to the fact that it is the only plant found in the inhospitable regions of Spitzbergen and Greenland that the sick members of polar expeditions could use; and, as it contains a great deal of potassium, it probably was of great benefit to them.

The administration of vegetable acids is not particularly beneficial. The salts made from these acids are better; of the potassium salts the bitartrate, citrate, and acetate, or the ferrotartrate, on account of its iron, are preferable. Iron is useful because of the anemia that always supervenes. Certain tannates, bitter and aromatic tonics are also occasionally employed; for instance, tannic acid, cinchona, cascarilla, myrrh, rhatany, calamus, and gentian.

The administration of brewers' yeast, pure or mixed with water and sugar, in doses of from 200 to 300 gm. daily is advised; this contains much potassium.

The best prophylaxis against involvement of the gums is the removal of all defective teeth early in the disease. Later on this measure is useless, and the affection of the gums must be treated locally with astringents. The gums are then painted with silver, alum, and tannin solutions, with very weak potassium chlorate and permanganate, or with tincture of myrrh, catechu, rhatany, or with decoctions of the bark of oak, willow, or cinchona.

The ulcers of scurvy are best treated by the application of bandages saturated with a 0.3 per cent. solution of permanganate of potash. The general principles of modern surgery apply to the treatment of all scorbutic wounds. It is best, however, to avoid all surgical procedures, as the tissues of a scorbutic patient are exceedingly sensitive to all mechanical inroads. Simple compression from bandages may lead to hemorrhages in the tissues and to extensive ulcerations.

It is best to refrain from using drastic purgatives in case of constipation; it is better to attempt the relief of this symptom by carefully administered enemata or by laxatives of the mildest kinds, as, for instance, tamarind. If too violent a peristalsis be produced, fatal hemorrhages from the bowels may result. Styptics, like secale or iron sesquichlorid, usually do little good in these cases; the best remedy is the application of ice internally and externally. In large external hemorrhages packing, styptics, and the cautery are useful.

If pleuritic and pericardial effusions threaten life they must be aspirated.

LITERATURE.

The literature on scurvy is very voluminous. A good review of the literature up to 1865, with brief extracts, is found in:

Krebel, *Der Scorbut in geschichtlich-literarischer, pathologischer, prophylaktischer und therapeutischer Beziehung*, Leipzig, 1866.

Complete accounts will be found in:

Immermann, *Handb. der allg. Ernährungsstörungen, v. Ziemssen's Sammelwerk*, Leipzig, 1879.

Aug. Hirsch, *Handb. der historisch-geographischen Path.*, section II., 2d ed., Stuttgart, 1883.

Hoffmann, *Lehrb. der constitutionellen Krankh.*, Stuttgart, 1893.

In the preparation of the above sketch on scurvy we have consulted the following books:

Babes, "Ueber einen Gingivitis und Hämorrhagie verursachenden Bacillus bei Scorbut," *Deutsch. med. Woch.*, 1893, No. 43.

Bornträger, "Scorbut auf Schiffen," *Vierteljahrsschr. f. gerichtliche Med. u. öffentliches Sanitätswesen*, vol. vi., No. 4 and Sup.

Contù, "Communicazione preventiva intorno al contagio scorbutico," *Raccoglitore med.*, August 30, 1881.

v. Jaksch, "Zur Kenntniss der Peptonurie bei Scorbut, nebst Bemerkungen über den Ikterus und die Harnsäureausscheidung bei derselben Krankheit," *Zeits. f. Heilk.*, 1895, vol. xvi.

Kretschy, "Beitrag zur Lehre vom Scorbut," *Wien. med. Woch.*, 1881, No. 52.

Kürgkula, "Zur Aetiologie des Scorbuts." *Ibid.*, 1873, No. 27.

Kühn, "Ueber leichte Scorbutformen," *Deutsch. Arch. f. klin. Med.*, 1880, vol. xxv., p. 115.

Lissunow, "Beiträge zur Erforschung des Scorbuts," *Diss.*, 1895.

Mari, "L'idroterapia nello Scorbuto," *Rivista clin. di Bologna*, December, 1881.

Murri, "Intorno al contagio scorbutico," *Ibid.*, April, 1881.

Petrone, "Nuova teoria infettiva miasmatica dello Scorbuto," *Ibid.*, 1881, vol. iv.; "Sulla nuova teoria miasmatica dello Scorbuto," *Ibid.*, vol. vi.

Rosenell, A. G., "Zur Aetiologie des Scorbuts," *Wratsch*, 1892, Nos. 28 and 29 (Russian).

Seeland, "Ueber Scorbut und passive Blutungen in ätiologischer Hinsicht," *Petersburg. med. Woch.*, 1882, Nos. 2 and 3.

Villemin, "Cause et nature de scorbut," *Bull. de l'Acad. de méd.*, 1874, pp. 680, 739.

Wieriúzkij, "Untersuchung des Blutes Scorbutkranker auf Mikroorganismen," *Wratsch*, 1890, pp. 208 and 303.

[INFANTILE SCURVY.

Scurvy Rickets; Barlow's Disease.

Definition.—Infantile scurvy is the phase assumed by scorbutus when it occurs in the infant. It is often associated with some of the manifestations of rickets, so that the disease picture is at times complicated. It differs, however, in no essential feature from the form seen in adults, but like that form depends for its origin upon a deficiency in the fresh elements of the food, the administration of which produces a cure; it shows the same impoverishment of the blood with the tendency to hemorrhages into various parts of the body, the same progressive cachexia, and, under like conditions, the same spongy alteration in the gums.

History.—For a long time scurvy in infants was only known as it occurred along with adults during epidemics. Sporadic cases were unrecognized. Between 1859 and 1873 several were reported in the German literature by Bohn, Mohler, Hirschsprung, and Senator, not as scurvy, but as "acute rickets." The first writer to suggest the true nature of these cases was Ingelev, of Sweden, who reported a single case in 1872. In 1878 Cheadle, of England, described 3 cases, expressing the belief, based upon the clinical features, that they were scorbutic in nature. Barlow says, "Cheadle laid down the original lines of the true interpretation of the disease, and I do not think that anything has invalidated the soundness of his conclusions."

It remained for Barlow himself, however, to close the discussion,

in 1883, when he added "the anatomic substratum which explained the symptoms found." His original report included 31 cases, and exhaustive descriptions of the postmortem findings in 3. Again, in 1894, in his Bradshaw lecture,[1] he reviews the entire subject in the light of later events. Previous to Barlow's report, Gee had, in 1881, given a brief but accurate account of the findings in 5 cases, which he designated as osteal or periosteal cachexia.

Confirmatory reports have come in large numbers from America, England, and Germany. In this country cases are numerous, owing to the widespread use of artificial foods. Holt, Rotch, and Starr were able to collect a series of 106 in their report to the New York Academy of Medicine in 1894. In 1891 Northrup, in an able report, analyzed 11 cases. Among the English contributors may be mentioned Gee, Goodhart, Railton, Sutherland, and others; among the Germans, Rehm and Heubner.

Etiology.—It has been conclusively shown that infantile scurvy is the result of depriving the individual of certain elements found only in fresh foods. Milk contains the antiscorbutic element in small amount, although enough to prevent the disease if used in sufficient quantity. Artificial treatment of milk may deprive it of the element more or less completely, depending upon the process used. Sterilization, evaporation, so-called "humanizing," and peptonizing abolish its antiscorbutic power. Bringing the milk to the boiling-point and then allowing it to cool is generally permissible, though cases of scurvy have been known to develop after prolonged feeding on milk altered only in this way. Pasteurization appears to be a harmless process. Return to a diet containing juices of fresh vegetables or fruits produces wonderful cures. As in the adult form, potato is particularly efficient.

What the principle in fresh food is we do not know. Its easy destruction is suggestive of a complex organic structure; while the view that the potassium salts play some rôle in this process seems too well supported to be ignored. Possibly we have to deal with a ferment-like body dependent for its action upon the presence of certain inorganic salts. Other views have been discussed at length in the preceding section. The association of rickets and scurvy is best explained on the ground that those foods which are deficient in antiscorbutic elements are often lacking in the antirachitic as well. Thus, the farinaceous foods so often responsible for the appearance of scurvy contain little or no proteid, fat, and phosphates. That the occurrence of scurvy is not in any way dependent upon rickets is proved by the numerous cases in which rickets has not been present.

Pathology.—In general the postmortem findings closely resemble those found in the adult form. The only differences lie in those organs which, because of their early developmental stage, present conditions not found in the adult at all. Thus, we see the same sodden, blood-infiltrated muscles, the hematomata and hemorrhages, and the same inconstant alterations in the serous membranes and viscera. The spleen is

[1] *Brit. Med. Jour.*, vol., ii. 1029, 1894.

sometimes enlarged. The gums are involved if the teeth have been cut, or if they approach the surface of the gums, otherwise not; for, as explained in the preceding section, alterations in the gums occur only when the gums have a functional relation to the teeth.

The *osseous system* in early life differs physiologically and anatomically from that of the adult. The same processes operating here might be expected to produce a somewhat different picture, a premise in accord with the facts; hence, the bone-findings merit a separate description. The essential features of these findings are excessive vascularity and tendency to hemorrhages, particularly in the regions of the greatest physiologic activity. An affected bone presents a thickened, highly vascular, sometimes edematous periosteum, which alone is capable of giving the shaft a thickened appearance. Under this altered membrane local or general blood-extravasations occur, further altering the contour of the shaft. As a rule, the first changes of this kind occur just above the epiphyses, in the lower and upper ends of the femur, and the upper end of the tibia. In severe cases the periosteum of the scapulæ, humeri, and ribs may be similarly lifted. The layer of blood interposed between shaft and membrane gives the bone, apparently, a much increased diameter. Surgeons have occasionally incised such bones during life for diagnostic purposes or in the belief that they had to deal with osteomyelitis. Continuing to functionate, the periosteum sometimes produces a shell of bone on its inner surface, accounting for the firm envelope recognized by clinicians during life. The bone marrow becomes soft and hemorrhagic, the regions of active bone formation close to the epiphyses being most affected, sometimes to such an extent that separation occurs. Hemorrhages of various sizes are also seen in the shaft. Around them softening is extreme. The cancellous portions are absorbed and partially replaced by non-calcified tissue. The compacta may be reduced to a thin shell, so that even in the middle of the shaft spontaneous fractures may occur.

Microscopic examination of the periosteum reveals great vascularity and hyperplasia, occasionally edema, but rarely any cellular infiltration indicative of inflammation, unless it be near the site of a fracture, where irritation of the fragments has induced it. The bone itself shows marked thinning of the trabeculæ and cavernous increase of the interspaces, which are occupied by highly vascular tissues and loose blood. Jacobsthal states that while cartilage cells proliferate freely but atypically, the cartilage is not replaced by bone. In those cases associated with rickets, characteristic areas of rickety ossification may be seen.

Changes like the above may occur in any of the bones, sometimes exclusively in certain ones, thus accounting for many odd clinical manifestations.

Symptoms.—Children may be affected at any age, rarely earlier than four months, most commonly during the second nine months of life. Often, but not always, the subject shows signs of rickets. A period characterized by debility and pallor generally precedes the appearance of definite symptoms, which then establish themselves with

abruptness. At first the child becomes fretful, depressed, and disinclined to be handled. Later it prefers to lie quietly in bed with the legs drawn up, violently resenting any attempt to move it or to handle the limbs. Examination reveals tenderness, particularly in the region of the epiphyses of the lower limbs; later, perhaps in the upper limbs and in other bones of the body. In advanced cases tenderness and pain on movement become extreme and the child assumes a characteristic posture, with the lower limbs extended and everted. The slightest movement or pressure calls forth violent manifestations of pain. The absolute quiet of the limbs suggests a paralysis. Generally the limbs show some degree of change in keeping with the pathologic conditions. The skin will be pale, the muscles flabby and probably irregularly thickened by extravasations of blood into their substance. The bones may present uniform enlargement or knob-like fluctuating tumors in the epiphyseal regions, indicative of localized subperiosteal hemorrhages; there may be edematous swellings above the ankles, or the alterations may be so slight as to be readily overlooked. After some days' duration the boggy fluctuation may give way to a firm resistance without decrease in the size of the swelling, due to the formation of a bony sheath by the periosteum; or extreme tenderness, false motion, and crepitus may indicate that the bone has fractured or the epiphysis separated. Other bones of the body may be affected, abscess-like enlargements occurring above the wrists, below the shoulder, on the ribs, or on the scapulæ. As a rule, however, there are no evidences of inflammation. The body temperature may be normal, subnormal, or as high as 102° F. When fresh hemorrhages occur the temperature is apt to rise for a number of hours. *The joints remain unaffected.* In atypical cases, bones of various parts of the body may be the first or only ones involved; though commonly, if involved at all, it is in company with those of the lower extremity. Hemorrhage under the orbital periosteum may be the first local manifestation. It is evidenced by a sudden protrusion of the globe and a discoloration of the lids. A peculiar sinking of the sternum, as described by Barlow, may result from softening of the chondrosternal attachments; and tender softening may appear in the face or head as a result of hemorrhages under the periosteum in these localities. Spongy, bleeding gums occur when teeth have been erupted or when they approach the surface of the gums. Sometimes the gum changes comprise only a purplish color and tenderness on pressure.

The symptoms produced by hemorrhages into the skin and serous and mucous membranes, and the changes occurring in the viscera, differ in no way from those seen in the adult. The disease may progress rapidly, the pallor and cachexia become extreme, and death ensue; or death may occur suddenly as a result of accident or intercurrent infection. It may become chronic in character, improving and relapsing from time to time, or it may disappear rapidly under appropriate treatment.

Diagnosis.—Advanced cases offer no difficulties in the way of diagnosis. The combination of deathly pallor, motionless, exquisitely

tender limbs, and spongy gums is pathognomonic. Rheumatism, with which such cases are at times confounded, can be excluded by the absence in scurvy of joint involvement and local temperature, and by the presence of characteristic changes in the periosteum. Infantile paralysis has usually a different distribution, and in scurvy examination proves that no genuine paralysis exists. Rickets often occurs in company with scurvy, but rickets *per se* never shows any tendency to hemorrhages and does not clear up under antiscorbutic treatment. Cases showing irregular and incomplete signs may offer considerable difficulty. Thus, in early stages the debility may be mistaken for that of simple malnutrition or enteric disorders. Infants in whom the teeth do not approach the surface of the gums do not show the typical alterations in that location, and the typical periosteal changes in the lower limbs may be preceded by similar changes in other bones of the body, such as the ribs, face, and cranial bones, so that a sudden bulging of the eye due to hemorrhage into the periosteum of the orbit, or the appearance of a tender swelling on the face or head, may be the first signs to attract attention. Once suspected, other signs of scurvy can usually be demonstrated in other parts of the body by a systematic examination. The history will also give some clew, such as that of improper feeding and preceding depression of the patient. In all doubtful cases, particularly if rickets be already present, the patient should be put upon antiscorbutic treatment for a time, when, if scurvy be present, rapid recovery may be expected.

Prognosis.—The outlook is good if treatment be instituted in time. Recovery is then wonderfully rapid and generally complete. Of 39 cases reported by Cheadle, only 3 were fatal. The wasted muscles recover slowly; thickenings about the joints may persist for a time, but unless faulty union occurs at the sites of fracture, no permanent defects persist. Intercurrent infections once established make the chances for recovery slender.

Treatment.—Infantile scurvy can be prevented by including in the dietary a sufficient percentage of fresh food, either in the form of fresh milk or the juices of fresh meat, fruits, or vegetables. Simple pasteurization of milk, or bringing it to a boil, as in scalding, generally has no bad effect. Peptonizing, sterilizing, evaporation, and so-called humanizing processes destroy the antiscorbutic principle. The cure of the disease can be accomplished by supplying antiscorbutic food. Milk is feebly efficient once the disease has developed, so that recourse must be had to the juices of fresh fruit and vegetables. Potato is the strongest antiscorbutic we have. It can well be used for infants according to the method of Dr. Baily as described by Cheadle. The potato is well steamed, reduced to a light flour, and beaten into boiled milk in quantity sufficient to give the consistence of thin cream. This may be added to the regular food in teaspoonful amounts at each feeding, or, in the case of children a year old, a tablespoonful at a time. Raw-meat juice is feebly antiscorbutic, but aids in restoring the quality of the blood, and may, hence, be well employed. Vegetables may be boiled

in water and the strained fluid added to the milk. For children old enough to tolerate it, fruits, such as grapes, lemons, oranges, etc., may be used to advantage, as in the case of adults. In addition to the diet, care should be taken to provide plenty of fresh air and sunlight, as these factors materially hasten the recovery.

Local treatment is mainly protective. The patient should be kept quiet and made as comfortable as possible with cotton pads and cushions. Applications to the limbs are not, as a rule, grateful. Inequalities in the bedding should be avoided, since they cause pain and, often, extravasations of blood. Should fractures occur, care must be exercised to prevent union in a faulty position. Medicines of all kinds are unnecessary and are best avoided, since they interfere with digestion.—ED.]

HEMOPHILIA (Bleeders' Disease).

Definition and Etiology.—Hemophilia is a peculiar congenital constitutional anomaly characterized, on the one hand, by the occurrence of hemorrhages following trauma that resist all known artificial means of control; and, on the other, by a peculiar tendency to spontaneous hemorrhage. So far no anatomic cause for these frequently repeated hemorrhages has been discovered. Combined with this peculiar symptom we frequently find rheumatoid pains and swellings of the joints. This definition is the only explanation of hemophilia that can be given. Particularly striking are the congenital and hereditary features of the disease and the repetition of the hemorrhages. According to current opinions, these two peculiarities characterize the disease picture. If we assume this definition, hemophilia can readily be differentiated from all other lesions that are grouped under the name of the hemorrhagic diatheses, particularly scurvy and morbus maculosus Werlhofii. The former is differentiated from hemophilia by its epidemic or endemic character and by the fact that it rarely occurs sporadically. Still more characteristic is its dependence on external conditions. Scurvy constitutes an expression of serious disturbances of nutrition that may be produced by essential diseases or by long-continued defects in the nourishment of the body. Morbus maculosus Werlhofii is differentiated from hemophilia principally by the fact that it undoubtedly constitutes an acquired disease, heredity playing no rôle in its causation; this also applies to scurvy. In contrast to the sufferer from scurvy, a bleeder may be well nourished and strong; in fact, perfectly healthy with the exception of his tendency to spontaneous hemorrhages. In comparing hemophilia with the other diseases of the group of hemorrhagic diatheses, one peculiarity of the disease is particularly striking: it is not, in contrast with other affections, a disease *process*, but a *permanent condition*, that manifests itself as a result either of known causes (traumatic hemorrhages) or of unknown causes (spontaneous hemorrhage). Hemophilia, for this reason, has been called a "*vitium primæ formationis*."

Some authors have attempted to draw another distinction from the fact that bacteria have been found in the other "hemorrhagic" diseases,

but not in hemophilia. It is best, however, to suspend judgment in regard to this point until our knowledge is more advanced.

Hemophilia is in the majority of cases a congenital, and nearly always a hereditary condition. From the first the exquisitely hemorrhagic character of this disease commanded the interest of all observers. Grandidier calls it "the most hereditary of all hereditary diseases." It is very rare that an isolated case of hemophilia has been observed; as a rule, a number of cases occur in the same family. Reviews of the known cases of hemophilia and their distribution in families show that at least 3 bleeders are found in every family of bleeders. In some cases the hereditary transmission is direct from the parent to the child; more frequently, however, the transmission of the disease occurs according to a very peculiar law of heredity. This is particularly striking, as a very distinct difference is observed in the tendency of the two sexes to transmit or acquire hemophilia by heredity. The female sex has a proportionately increased capability of transmitting the disease; the male sex, on the other hand, has a peculiar disposition to acquire the disease; the latter disposition is manifest by the fact that there exist more male than female bleeders. There is still another peculiarity attached to the tendency of the female sex to transmit hemophilia—that is, a woman in a bleeder family can transmit the disease to her offspring without having hemophilia herself, the disease thus skipping a generation.

This mode of transmission seems to be the rule. In earlier days, before we had such abundant material, the belief prevailed that only male subjects could acquire hemophilia, that females were immune and that, on the other hand, the disease could be transmitted by women only. Hence popular parlance and, later, science designated the women of bleeder families as "conductors." More exact investigations and increased experience, however, have taught us that females can also become affected with hemophilia, though not as frequently, in proportion, as males. We calculate that 1 woman is affected to every 13 men. It has also been found that the supposition that women alone can transmit the disease is not strictly correct, as a number of deviations from this rule seem to have been observed.

Grandidier has formulated the facts in regard to predisposition, transmission, and hereditary character in hemophilia in the following two paragraphs:

1. Men of bleeder families who are bleeders themselves do not necessarily have hemophilic children with women who are not members of bleeder families; on the contrary, the children of such a union are, as a rule, healthy and not hemophilic. Inversely, it appears that the children of women who are bleeders will be regularly hemophilic.

2. Men from bleeder families who are not themselves bleeders hardly ever generate hemophilic children with women from other families. On the other hand, among the children of women who are members of bleeder families, but not bleeders themselves, almost without exception some will be found who are sufferers from hemophilia.

In view of the striking character of hemophilia, its persistence in a certain family, and the severe hemorrhages commonly preceding the fatal issue, it is readily understood why we have reports on bleeder families which extend very far back, particularly as the interest in this condition was augmented by the popular knowledge of the disease and by its mysterious character. Grandidier, in his well-known monograph, enumerates 200 bleeder families, with 609 male and 48 female bleeders, a proportion of 13 : 1. In a family of bleeders described by Stahel in 1880, only male bleeders (24 in number) were found in 4 generations; although the female sex is less frequently afflicted, transmission occurs decidedly through the female members of the family. According to Bollinger's summary, it seems that hemophilia, like color-blindness, is most frequently found in the sons of daughters whose fathers were bleeders.

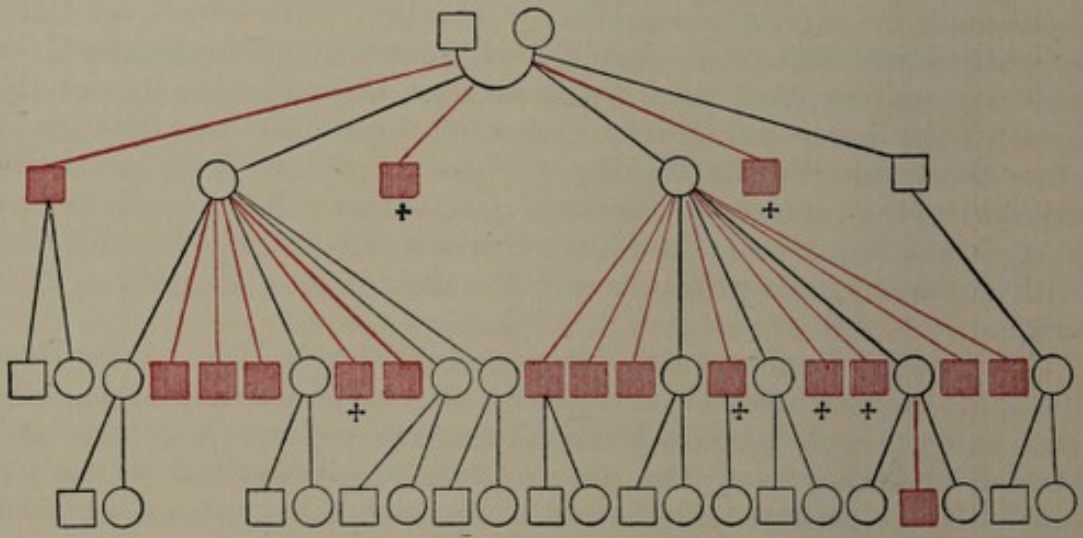


FIG. 2.—Family tree of the bleeder family Mampel, according to Lossen: □, Male; ○, female. The red figures represent the bleeders. The members designated by + died from hemorrhage.

Notorious bleeder families are those of Tenna, in Graubündten; the American family of Appleton-Browe, and the family Mampel, from Kirchheim, near Heidelberg, whose family tree Chelius formulated in 1827; Mutzenbecher described it again in 1841, and Lossen has recently continued it.

We see from this family tree that the tendency of hemorrhages is transmitted exclusively by the female members of the family, who themselves are not affected by the disease. On the other hand, the issue of marriages between male bleeders and female subjects who are not bleeders is healthy.

The proportion of boys and girls in the different generations is also quite remarkable. In the first generation 4 boys and 2 girls are found. Of the former, 3—that is, 75 per cent.—are bleeders; of the latter, none. In the second generation there are 14 boys and 9 girls; of the former, 13—that is, 93 per cent.—are bleeders; of the latter, none. In the third generation, among about 50 children, there is only 1 male bleeder, who is the son of a mother not a bleeder. It seems, therefore,

that a considerable decrease of the disease occurs in the third generation; this is probably due to intermarriage with members of healthy families.

M. Fischer, in his dissertation of the year 1889, described another family tree of a large family of bleeders. The description is that of a family living in a village in Würtemberg, whose case had never until then been described. The tendency to hemophilia in this family extended over 4 generations, and was interesting for several reasons. The founder of the family, who was a bleeder (he married twice, and one of his wives was certainly not hemophilic, yet some of the children of both families were bleeders), had himself transmitted the disposition; whereas, as a rule, this only occurs in women. Further, 2 of the female conductors were themselves bleeders, which is considered contrary to the rule. Altogether, of 114 members of the family, 17 were bleeders; of these, 13 were males and 4 females, showing that the participation of the female sex was abnormally high. The age at which the bleeders died varied from three-quarters of a year to sixty-two years. In addition, as has been frequently observed in other cases, nearly all the members of the family, particularly the bleeders, were sufferers from other diseases, chiefly rheumatic affections, congestions, and dental troubles.

It is impossible to state whether the disease can persist beyond the fourth generation or whether it is so attenuated in the mothers of the third generation that it does not appear again after that. In order to determine this point, it will be necessary to have genealogic observations extending over a longer period of time.

There are exceptions to the rule that healthy women transmit hemophilia—that is, act as conductors; a direct hereditary transmission through male descendants may occur. This was, for instance, observed in a family in Bremen, in which hemophilia was transmitted from the father to the male members of 3 generations. In the bleeder family from Wald, in the Canton of Zurich, 1 such transmission is reported. In the majority of cases in this family a healthy mother transmitted the disease to her sons; the first generation consisted of 16 persons, 7 of whom were bleeders; the following generation consisted of 28 members, with 16 bleeders; the third generation had 12 members free from hemophilia and only 1 bleeder, a remarkable reduction.

The most persistent cases of continued transmission are found in the families of the small village of Tenna, in Granbündten, the population of which is only 170 people. Here the hereditary transmission could be traced through 6 and 7 generations. In this instance, however, bleeders twice married into the family, so that this probably explains the persistence of the diathesis. Several times the disease seemed to be absent through 2 generations, but reappeared in the third. In the direct descendancy still longer pauses occurred, but it is probable that only the most severe cases were recorded and remembered.

The hereditary form of hemophilia is unquestionably the most frequent. It seems, however, that there is a so-called congenital form of

the disease; by which we mean that children who are bleeders may be born to parents who are themselves healthy and come from healthy families. From the children the disease can, of course, be again transmitted by heredity. [Possibly these cases represent reversion to the type of some distant ancestor whose hemophilia was unrecorded.—Ed.]

Particular attention has been called to the significance of intermarriage of relations in the genesis of hemophilia; also to the effect of certain psychic influences (as terror, anger) during pregnancy. So far we have no scientific basis for the assumption of such views.

It is positive that the disease can originate spontaneously only in a very great minority of the cases—that is, without hereditary influence; the twenty-second year is the time boundary at which subjects who have been healthy up to this time may develop hemophilia. These statements, which are not at all positive, are still more confused by reports on so-called *spontaneous cases of hemophilia* occurring later in life that manifest themselves by purely localized hemorrhages restricted to one or another organ.

In regard to the *geographic distribution* of the disease, Germany seems to furnish a great majority of the cases. Other countries, however, are not free from it. The following table formulated by Grandidier gives us information in regard to this question:

Country.	Bleeder families.	Bleeders.	Bleeders. Male.	Bleeders. Female.
Germany	93	258	236	22
England	46	141	134	7
France	20	80	75	5
North America	15	61	60	1
Russia	7	11	7	4
Switzerland	5	48	48	—
Sweden-Norway	3	9	6	3
Holland	2	9	7	2
Belgium	1	4	4	—
Denmark	1	3	2	1
East Indies	1	6	5	1
Totals	194	630	584	46
			92.6 %	7.4 %

The real causes of hemophilia are entirely unknown, and so far we have nothing but hypotheses. Two factors chiefly attract our attention —that is, the *constitution of the vascular system and of the blood itself.* As hemophilia is not a transitory, but a permanent, disease, a condition, moreover, that may be congenital or acquired, we shall necessarily have to assume that the disturbance is one of "*primæ formationis*" involving a part of the connective-tissue layers—that is, that from which the vascular system develops. All hypotheses that have been formulated in this direction have failed to stand a rigorous scientific examination, so that we are dependent, so far as actual facts are concerned, on the very scanty anatomic findings that have been recorded here and there. At

best these afford us but little insight into the mysterious character of the disease under discussion.

It was assumed for a time that, owing to an abnormal constitution of the vessel walls, these were readily ruptured; it was claimed that the arteries had very thin walls, were very narrow, and were situated close to the surface. Even should this finding be more constant than it actually is, such changes in the vessels would hardly account for the hemorrhages, particularly the spontaneous ones, as similar conditions are found in chlorosis and in so-called narrowing of the aorta without the occurrence of hemorrhages. We will recur to this subject when we discuss the pathologic anatomy. The writer will only mention here that some observers, as Hooper, Liston, Fischer, and others, have found the walls of the arteries to be very thin and in a condition of fatty degeneration in hemophilic subjects. Virchow lays special stress on an observation that he made in a bleeder of twenty-four years, whose aorta was not only very thin, but also very narrow, almost of the dimensions of a child's; at the same time the vessel was very elastic; the capillaries, however, showed no changes. In a case of this kind the arteries, very narrow and elastic, would drive the blood with excessive force into the capillaries, and Virchow claims that the hemorrhagic diathesis, or at least the continuous hemorrhages, could be attributed to this concatenation of circumstances. Further, such a narrowing of the arteries was not the result of any special disease of the vessel walls, but a disturbance of development similar to that of chlorosis, and thus an additional feature in accord with hemophilia, since it was of an hereditary character.

Whether fatty degeneration of the intima that has been seen in some, not in all, cases is a result of the anemia, or whether it is the cause of the hemophilia, cannot be determined. As hypertrophy of the left ventricle and thinness of the walls of the aorta have been found in several cases of hemophilia, some observers have attempted to draw conclusions in regard to the cause of the hemorrhages from this finding. If the blood be driven with great force into narrow, thin-walled arteries, and the left ventricle be at the same time hypertrophied, the increased pressure is said to burst the vessel walls. Aside from the fact that hypertrophy of the left side of the heart is comparatively rare, it must be remembered that a great part of the hemorrhages occur by diapedesis and not by rhexis. As different investigators realized how insufficient these explanations were, the opinion became prevalent that a deficiency existed in the coagulative powers of the blood. The latter hypothesis was formulated for the reason that in hemophilic subjects it is very difficult to stop any hemorrhage, however small it may be. That the blood, however, will coagulate in these cases is readily seen on the surface of wounds; if these are not disturbed, it will be seen that coagulated masses form quite readily, but that new blood oozes from underneath, and in its turn coagulates and enlarges the blood-clot; ultimately the oozing stops and the hemorrhage is arrested. In very severe cases of hemorrhage it may possibly happen that the production

of fibrin ferment stops, so that the blood gradually loses some of its powers of coagulation; as a result, the hemorrhages into the tissues assume larger dimensions and death occurs. This is seen in epistaxis, in hemorrhages following extraction of teeth, occasionally in intestinal hemorrhages, etc.

Microscopic and chemical examination did not reveal that the blood was changed in any way; no deviation from the normal could be found in regard to the quantity of inorganic salts found in the blood, nor in the quantity of the fibrin-forming constituents. The organized constituents were normal both in regard to the numeric proportions of the blood-corpuscles and the percentage of hemoglobin; fibrin was not found reduced, contrary to all expectations; thus, Heyland found 5 pro mille of fibrin; Gavoy-Ritter, 2.6, and Otte, 4.3 pro mille.

The coagulability of the blood is naturally a subject of great importance in the discussion of hemophilia. Some authors, as Grandidier, Lossen, and others, state that the coagulability of the blood is reduced. As against this we know that such a reduction only occurs in the very last stages of the disease, after very much blood has been lost (Hoffmann[1]). These two views are not in opposition to each other. Grawitz calls attention to the fact that under normal circumstances, if long-continued hemorrhages have occurred, the coagulation of the blood is more rapid, and the last portions of blood frequently coagulate at once. In view of this fact, the reduced coagulability in the latter stages of hemophilia demonstrates most conclusively that the general coagulability of the blood is reduced.

Alex. Schmidt has recently corroborated this view, and confirmed it by his findings in a case of hemophilia; the blood of this patient coagulated in four and a half minutes after leaving the vessel, which Schmidt considers as an exceedingly long time, in view of the quantity of blood previously lost. In this case the action of a zymoplastic substance that Schmidt had isolated was tested. If added to the blood of a hemophilic patient in the test tube, it showed a remarkable ability to hasten coagulation, so that instead of occurring four and a half minutes after leaving the body, it now occurred in ten seconds. Local application of this zymoplasm to the bleeding gums showed it to be an excellent styptic as soon as the contraction of the vessels and the temporary arrest of the hemorrhage had been brought about by injections of cocain, in order to permit the coagulating substance to act.

Cohnheim's assumption that the blood contains fewer functionating red blood-corpuscles, and consequently has a tendency to hemorrhages, is absolutely undemonstrated. The writer can give the assurance that he has repeatedly submitted to blood-experts blood from hemophilic patients, stained by various methods, and never have they been able to discover any abnormality. Repeated blood-counts revealed normal proportions. It is said that the blood-plates are somewhat increased in number. G. Cohen reports a very remarkable finding in a case of hemophilia; the blood was barely colored red, did not coagulate when

[1] *Text-book of Constitutional Diseases.*

beaten, and on standing precipitated a number of isolated granular, white coagula of fibrin of the size of a pin. Microscopically, the well-known poikilocytosis of a secondary anemia was seen, with absence of rouleau formation.

In regard to the origin of hemophilia, a number of different theories are reported in the literature, of which the writer will mention only the best known. The most important and best known was the one originated by Immermann, and is based on certain demonstrations by Virchow that the writer shall mention below. Immermann summarizes his theory as follows: "Hemophilia is a form of hemorrhagic diathesis, usually congenital and habitually persistent, characterized by frequently occurring and readily producible hemorrhages. These may be exceptionally violent (obstinate) and dangerous, for the reason that a *congenital disproportion between the volume of the blood and the capacity of the vessels exists. As a result the blood-pressure within the latter is inordinately increased.* Functional erythism of the heart and an increased development of the musculature of this organ also play a rôle in many cases of this disease, and may aid in the causation of hemorrhages and the general abnormal clinical symptoms presented, by causing an exaggerated tendency to fluxion. Finally, may be superadded, certain neurotic influences that increase the diathesis."

Oertel[1] expresses himself similarly to Immermann in regard to the nature of hemophilia. He, too, is of the opinion that this disease is a form of hydremic plethora of very high degree. G. Cohen,[2] following the ideas of Immermann-Oertel, has formulated a general treatment of hemophilia, the essence of which is the treatment of this hydremic plethora by an energetic increase of cataphoresis and diuresis. It is possible that we can adduce the marked improvement seen by Cohen in his one case as evidence for the correctness of the Immermann-Oertel theory.

The patient was a woman, born in 1852, thirty-eight years old at the time of treatment. She was the third youngest of 11 brothers and sisters. Her father had been a sufferer from violent epistaxis and from agarophobia; her grandfather had died of morbus maculosus with hemorrhagic extravasations into the joints and hemorrhages from the kidneys. One of her sisters cannot walk in the street without a companion; if she go out alone, she is afflicted with a feeling of terror and palpitation of the heart, which she also experiences if at least 2 of her brothers and sisters do not remain at home with her. The first violent hemorrhages observed in this patient occurred when she was twelve years old, following the extraction of a tooth. A year later she began to menstruate. In 1866 a violent metrorrhagia, induced by overexertion from walking, followed menstruation on the fourth day. Following this came her first attacks of epistaxis; in 1868 convulsions; the patient is now forced to remain in bed. In 1870 frequent epistaxis and violent hemorrhages from the uterus; severe edema of the feet. In 1872 still more frequent occurrence of epistaxis; regular injections of ergotin for periods of from six to eight weeks without arresting the hemorrhages. In the following year she cut her finger, and this insignificant accident was followed by hemorrhages that persisted for several weeks. Hemorrhages from the uterus now became almost continuous, and ergotin no longer seemed to exercise any effect. In 1874 violent hemorrhages, following the extraction of a tooth, again appeared. Two years later, following a very violent attack of dysentery with

[1] *Therapy of Diseases of the Circulation.* [2] *Zeit. f. klin. Med.*, Festschrift, 1890.

hematemesis and enterorrhagia, epistaxis increased so rapidly that it was necessary to keep the nose plugged for a long time; later, epistaxis lasting several hours; galvanization of the sympathetic combined with ergotin administration seems to have improved the health for the time being. In 1881 large blood-spots appeared for the first time on the left arm, accompanied by great swelling that was painful. Menstruation lasted without interruption from November of this year until February, 1882; regular application of tampons was necessary. In March, 1882, the first hemorrhage occurred from the skin and an uninjured finger. Following this occurrence such hemorrhages recurred with great frequency. In January of the following year several uninjured fingers and the nose bled daily; subcutaneous hemorrhages occurred; the blood broke through the skin of the right thigh and the left arm, covering large surfaces. In 1884 violent diarrheas and frequent vomiting accompanied by enormous hemorrhages. In addition, rises of temperature that sometimes persisted for months; the urine was very scanty, $\frac{1}{8}$ to $\frac{1}{4}$ liter in twenty-four hours, colorless, containing no albumin, and of a very low specific gravity (1002 to 1005). The daily loss of blood in twenty-four hours amounted to 1 pound; galvanic baths seemed to decrease the number of hemorrhages. Treatment directed toward an increase of the scanty urine seemed to lead to improvement, combined with energetic diaphoresis persistently carried out for three years. Injections of pilocarpin alternately with packing or infusions of jaborandi and Flor. tiliæ [European linden]; in addition, digitalis was administered in large doses. The patient was cured after the disease had lasted for twenty-five years.

The advocates of the Immermann-Oertel theory of the etiology of hemophilia must consider both chlorosis, which, according to Virchow's deductions, belongs to the same class of diseases, and in addition still another disease picture, in which the *small size of the aortic system* plays an important rôle—that is, congenital narrowing of the aortic system. The symptoms produced by this congenital anomaly are not at all similar to those of hemophilia, notwithstanding the fact that the anatomic findings in both are identical. It might be argued that in hemophilia an *abnormal constitution of the blood* is superadded to the small size and narrowness of the vessels of the arterial system, and that hemophilia is a result of this combination of abnormalities. As against this we must refer to the fact that examinations of the blood have never revealed any constant or positive abnormalities in hemophilia, and only in isolated cases have poikilocytosis, microcytosis, and absence of roll formation been observed. Reduction of the hemoglobin of the individual erythrocytes has been observed so frequently in cases that were anemic and weakened by repeated hemorrhages that this symptom cannot be regarded as characteristic, and certainly not as pathognomonic. All the hypotheses, therefore, that attempt to explain hemophilia by changes in the constitution of the blood are not based on facts scientifically established.

v. Recklinghausen assumes that hemophilia is a neurotic diathesis. We shall speak at length in the next section on spontaneous hemorrhages that occur through the agency of the vessel nerves, and in this place we shall only emphasize that v. Recklinghausen's theory seeks a probable cause in the rather striking nervous phenomena frequently observed in this affection. It seems only natural, however, that a patient who is suffering from a general disease like hemophilia should be in a constant state of tension and excitement, owing to the fact that the main symptom of the disease—hemorrhage—may occur at any time

and unexpectedly. It appears probable, therefore, that the nervous system, if it be at all involved, is only secondarily affected.

We must finally briefly mention the views of W. Koch. This investigator regards hemophilia as a *toxic infectious disease.* In his book on diseases of the blood he gives a critical review of the various theories of hemophilia. He particularly examines and sifts the material that has so far been adduced in support of the different views, and calls attention to the scantiness and insufficiency, and in many instances the contradictory character, of such data. His final conclusions are as follows: "Hemophilia is no specific disease in itself, but a general infectious disease and identical with scurvy. According to my opinion," says Koch, "the blood in hemophilia penetrates the vessel walls, the permeability of which is in nowise altered, because certain toxins are mixed with the blood. I consider hemophilia an infectious disease, like scurvy, chiefly because the symptomatology and the anatomic changes observed are similar to those seen in the latter disease. In support of the parasitic nature of this affection, I can only call attention to the well-established congenital form of hemophilia, in which all the typical symptoms occur as soon as the patient is born, and which can only be transmitted from hemophilic parents. Such a congenital condition can never be explained in the same manner as, for instance, a congenital club-foot or a congenital meningocele—that is, as a *vitium primæ formationis*—and I do not believe that purely anatomic changes, however complicated they may be and whatever secondary symptoms they may produce, can be responsible for the severe disturbances of function which we observe. For nearly one hundred years an anatomic substratum for hemophilia has been looked for, and notwithstanding the fact that our modern methods of examination are so perfect, only anomalies in the vascular system have so far been recorded, and these certainly have only a negative significance, otherwise they would be found in the majority of cases and not only in so small a proportion.

"In contradistinction to this anatomic theory, I offer the view that congenital hemophilia is closely allied to congenital syphilis. As a further argument in favor of the infection theory I consider the simultaneous occurrence of hemophilia and wounds or ulcerative processes, as, for instance, tuberculous and syphilitic skin eruptions, tuberculosis of the glands, discharge from the ears, suppuration of the umbilicus, etc. The craving of certain hemophilics for sand, dirt, chalk, coke, acid and biting vegetables is also interesting and significant. Again, other patients are subject to fever or perish with surprising rapidity notwithstanding the absence of great hemorrhages. Nearly all the patients, in addition, have an enlarged spleen. These are all facts that, in my opinion, have a significant bearing on the connection between hemophilia and infection. Such a connection, so far as I know, has never been emphasized nor discussed, but it seems to me fully as important as the contention that telluric, instead of hereditary, influences underlie those cases occurring in families during several generations who never remove from their home, particularly in view

of the fact that in many members hemorrhages did not appear until late in life."

Koch's theory that hemophilia is a toxic infectious disease is so little grounded on fact, both in its general aspects and in its details, that it can hardly be discussed. The coincidence of hemophilia with tuberculosis of the glands, tuberculous and syphilitic ulcers, discharges from the ear, rise of temperature, and other processes that he has mentioned is so rare that other authors have not even mentioned it. The same applies to the occurrence of tumor of the spleen; Koch declares that it is constantly found, and attaches a great deal of importance to it in proof of the infectious nature of the disease. Other symptoms that he emphasizes are not peculiar to hemophilia, but are found in all cases of anemia due to hemorrhages. So long as the organism said to produce the infection has not been discovered, his theory is without foundation, and all examinations made in this direction, particularly by Klebs, have yielded an altogether negative result. It seems to the writer that his attempt to adduce miasmatic influences is most unfortunate and uncalled for, particularly as he tries to place so fictitious a postulate in place of the well-established hereditary influence in this disease.

From all this discussion we must decide that the cause of the disease is altogether unknown; even the two etiologic factors most frequently mentioned—the abnormal constitution of the vessel walls, consisting in a great fragility, and the deficient coagulating powers of the blood—are so little convincing and so little based on actual fact that they do not stand the light of critical illumination. We shall refer to these two factors, particularly the former, in a subsequent paragraph. In view of the great importance assumed by heredity in the etiology of this disease, we must mention that frequently a neuropathic tendency is discoverable in the ancestors of hemophilics. It must also be remembered that the statements of relatives must be accepted and utilized with a great deal of discretion. There are, however, a great many cases of well-established anamneses that distinctly emphasize the existence of a neuropathic taint in the relatives of bleeders. This is particularly the case in the patient of G. Cohen. The father of this patient was a very excitable man, and was particularly affected with vomiting and agarophobia on the slightest emotional excitement—for instance, if he were starting on a journey. He died of a heart lesion. One of his sisters was subject to hysteric convulsions; another was very nervous. One of his children could not walk alone in the street; another (a bleeder) was not comfortable unless at least two of her brothers or sisters were in the house; if they were not there, she immediately developed palpitation and became frightened.

Pathologic Anatomy.—Anatomic examination so far has revealed neither characteristic nor constant findings. The number of scientifically performed autopsies on individuals who had died of this disease is small; consequently, the records in regard to its pathologic anatomy are scanty. In general the following is reported: The corpse of a bleeder is very anemic, the skin waxy; in the skin are found petechiæ,

ecchymoses, blood-tumors, and signs of injuries if death has occurred from hemorrhage following trauma. The internal organs are anemic, watery blood oozing from the severed vessels; the spleen is the most interesting of the abdominal organs, all of which frequently show signs of old hemorrhages. The spleen is usually enlarged; occasionally normal. A great deal of importance has been attributed to this enlargement of the spleen in hemophilia, particularly by those authors who have attempted to prove the infectious nature of the disease. At present, however, since the inconstancy of this finding has been established, the infectious theory has been relegated to the background. The superficial position of the cutaneous and subcutaneous arteries and veins has been frequently described; the heart muscle is frequently in a state of fatty degeneration; the volume of the heart is sometimes normal, sometimes hypoplastic, or sometimes hypertrophic, particularly the left ventricle. In a number of cases the large arteries and their first ramifications had a very narrow lumen. In many instances a thinness and translucency of the intima were noticeable wherever the structure of the larger and smaller arteries was carefully examined; in some cases partial fatty degeneration could be determined. Virchow particularly has described smoothness of the heart, narrowness of the vessels, and thinness of their walls in hemophilia and in chlorosis. In view of the rarity of scientifically correct autopsy reports on this disease, it is interesting to refer to the record that the author himself has made on a case of hemophilia which he observed and dissected.[1]

"The blood did not contain less fibrin than normal. This corresponds to similar findings in the other cases of hemophilia. The examination of the arteries and veins showed no large ruptures nor any other conspicuous changes; we are therefore justified in concluding that the hemorrhages started from the capillary system. The veins were very wide, the arteries very elastic and narrow; the capillaries and nerves showed no abnormalities. In the central parts of the vascular system lesions were found that were undoubtedly congenital; the thymus gland was very large, the heart was pale and small, *the aorta small, its wall thin*, very elastic, and, owing to *fatty degeneration of the intima*, showed wave-like elevations. This condition was particularly conspicuous in the descending thoracic aorta; the whole picture resembled very much that seen in chlorosis, which I (Virchow) have already described. The development of the heart and aorta is apparently arrested in chlorotics, and the enlargement of the heart usually does not occur until later. Hemorrhages occur quite frequently and with great violence in cases of chlorosis, and it is possible that they are to a certain degree caused by the changes that I have observed in the arteries. An additional factor in support of this view is the peculiar arrangement of the round gastric ulcers seen in chlorosis that correspond exactly to the distribution of the single arteries in the stomach walls. A great many other arguments can be adduced in favor of the congenital character of chlorosis, or, at least, of the early development and the predisposition to this

[1] *Deutsch. Klin.*, 1859, No. 23, and *Canstatt's Jahresb.*, 1859, 4.

disease. These statements can be made for hemophilia with the same or greater force; the blood from this case decomposed very rapidly on standing, crystals of xanthoglobulin and of triple phosphate and leucin were precipitated. This case teaches us that in hemophilia it is not the particular thinness or dissolution of the blood that causes the hemorrhages; blood containing a good deal of fibrin will still produce a hemorrhagic diathesis in this disease as well as in scurvy. In the autopsy under discussion *no exceptional fragility of the vessel walls was present;* the question arises, therefore, whether in this disease, as in chlorosis, the narrowness and the greater elasticity of the arteries did not increase the blood-pressure in the capillaries to such a degree that a predisposition to hemorrhage was caused. Such a hemorrhage when it once occurs is difficult to stop. In this one case, therefore, the cause of the hemorrhagic diathesis would be an arrested development of the vessels, and it is a striking fact that the thymus gland persisted for so long a time."

Virchow therefore considers the arrested development of the vessels as a valid and important pathologico-anatomic finding in hemophilia; on the other hand, he calls attention to the fact that very similar conditions are found in chlorosis. The discussion in regard to the question why arrested development of the vessels should be found in two diseases that are so different is not yet concluded. If we wish to be very critical we can deduct from this peculiarity that arrested development of the vessel walls cannot be a cause of hemophilia. Notwithstanding this, Virchow's description and deductions are of paramount importance; they form the basis of the Immermann-Oertel theory of hemophilia which we have discussed above.

In contradistinction to the positive findings chronicled by Virchow and found in a number of other cases of hemophilia we have a much larger number of autopsy reports, made by careful and skilled anatomists, that have revealed nothing.

The *microscopic examinations* of Buhl and of Birch-Hirschfeld on the changes in the vessel walls in hemophilia are particularly important. The former found an *excessive increase and growth in the loops of the capillary vessels* in a hemophilic clergyman of fifty-four, who was suffering from chronic dermatosis. In the walls of these capillaries a great increase and rearrangement of the nuclei were seen; Buhl himself does not consider this anomaly peculiar to hemophilia. Birch-Hirschfeld examined the heart, the large vessels, and pieces of the spleen and the skin of a child of one year who had died of congenital hemophilia. He remarks in regard to these tissues as follows: "Nothing abnormal was found in the heart and the vessels connected with it. In the negative sense it might be emphasized that the size of the heart corresponded to the age of the child. Only slight indications of fatty degeneration were found in the heart muscle; the valves and the intima of the large vessels were delicate and normal in structure. The muscularis and media of the arteries were also normal. Within the kidneys a slight swelling of the cortical canals and a finely granular clouding

of the epithelium were seen. Within the spleen nothing abnormal was seen excepting a very slight hyperplasia of the stroma. Finally, with a great deal of reserve, an observation may be chronicled that was made concerning the capillaries and the connecting vessels of various organs, particularly the liver and the kidneys. In several places in these vessels the endothelial cells were apparently enlarged and contained swollen nuclei, and here and there granular deposits within their protoplasm. In a number of specimens treated with silver solutions, that, by the way, were not mechanically perfect, the epithelial outline seemed to be very irregular, distorted, and the single cells separated by wide spaces. I do not venture to attach particular importance to this peculiar finding, as it is frequently impossible to determine which of these very delicate changes have been caused in the manipulation of the specimen. It must be remembered, moreover, that such changes may be found in various chronic diseases in their later stages."

Kidd describes in the finer vessels of the subcutaneous connective tissue and the muscles a peculiar increase in the endothelia, a hydropic swelling of the muscularis, and a proliferation of the nuclei. These changes Legg could not find in another case. The simultaneous occurrence of hemophilia and of multiple sarcoma is, finally, worthy of mention.

We see from all this that pathologic anatomy furnishes no basis for an understanding of the disease picture. Even the periodically increased blood-formation mentioned by several authors is only weakly supported; the same applies to the hypothesis that the narrow, possibly fragile vessels of hemophilics are engorged with blood owing to hypertrophy of the heart, and that, as a result, the blood that is formed in excessive quantities at times bursts the distended capillaries.

Symptomatology and Course.—The disease may be observed in different stages of its development. It does not necessarily appear with the same intensity in all cases. Particularly has the study of whole families of bleeders demonstrated that it is possible to observe all the stages of the disease in different members, from the mildest and most rudimentary forms to the most violent and pronounced manifestations. The milder forms, it is true, are characterized by a striking tendency to hemorrhages; these, however, never directly threaten life.

In nearly three-fourths of the cases the first hemorrhage occurs before the expiration of the second year. The outside limit for its appearance has been placed at the twenty-second year. Only in 1 or 2 isolated cases has the first hemorrhage been observed in later years. An increased tendency to hemorrhage seems to exist in bleeders during the epochs of physiologic development (periods of dentition, puberty, climacteric). The majority of bleeders die in the first years of life, most of them before they reach the tenth year; only rarely do they attain great age. A few bleeders, however, have been known to reach seventy and above. With increased age the hemophilic tendency is more and more reduced until it finally disappears.

It is often enough discovered by chance that a subject is hemophilic,

particularly if he be not a member of a bleeder family or has no older hemophilic brothers or sisters. Thus, such a discovery may be made when the child begins to bleed freely and profusely after some slight injury sustained during play. In other cases the disease has been discovered when boys whipped by their teacher have developed bloody streaks and cutaneous hemorrhages wherever they were struck. In other cases, again, surgeons, in performing an operation, have made the disagreeable discovery that they could not control the hemorrhage from the incision, and that they were dealing with hemophilia. Its earliest manifestation occurs in newborn children when violent hemorrhage ensues after separation and ligation of the umbilical cord; bleeding of this kind has been known to persist uninfluenced by any measures adopted to stop it, and even to have led to the death of the child. Of course, all umbilical hemorrhages in the newborn must not be interpreted as hemophilic in character, for we know that umbilical hemorrhages may occur in the newborn as a result of bacterial infection of the blood. The next period at which the disease is frequently discovered is during the operation of ritual circumcision, which is usually performed on the eighth day after birth. The scratches from vaccination, on the other hand, are relatively harmless.

It is quite possible for the disease to remain latent and not become manifest early in life, being discovered only under certain conditions; for instance, during the period of first dentition violent bleeding from the gums may occur and be the first manifestation of hemophilia. In the case of female bleeders the first hemophilic symptoms may occur at puberty, although the girl may have been free from all manifestations during her childhood. Profuse and prolonged hemorrhages may then occur during menstruation and be repeated every month. Labor in hemophilics is frequently dangerous, and very severe, even fatal, hemorrhages have been observed, so that Kehrer has proposed induction of premature labor in hemophilic women in order to interrupt pregnancy.

The most prominent symptom of hemophilia is the sudden occurrence of violent hemorrhages without any demonstrable cause, or as the result of very slight and insignificant external injuries. In about 50 per cent. the mucous lining of the nose is the seat of the hemorrhage; in 12 per cent. of the cases the gums and the intestine are affected; and in about 6 per cent. the lungs, the kidneys, and the stomach. The most frequent hemorrhages are from the skin, the alimentary mucous membranes, the joints, and the uterus. Hemorrhages into the serous membranes without demonstrable cause are comparatively rare with the exception of hemorrhages into the joints, of which we will speak later. Bleeding from the conjunctiva has occasionally been observed, and may become so violent as to cause death. An observation of this kind has been made in the cases of two brothers, both very young and both hemophilics. Sometimes the hemorrhages are so profuse that death occurs within a few hours. It is remarkable what enormous quantities of blood hemophilics may shed and still recover. In Cohen's case the patient lost a pound of blood per hour, and another case lost 24 pounds of blood

within eleven days. Occasionally, as a result of anemia of the brain, a fainting spell occurs, accompanied by a reduction in the blood-pressure to a minimum; this usually stops further hemorrhage; as the blood-pressure increases the hemorrhage is renewed. The fact that the blood regenerates so rapidly in this disease has been attributed to the increased hemapoietic function of the bone marrow (Fischer). This assumption is purely hypothetic.

In hemophilia two kinds of hemorrhages can be distinguished—namely, traumatic and spontaneous hemorrhages. In making this classification, however, it must be remembered that hemorrhages are called spontaneous chiefly for the reason that no demonstrable cause can be discovered. When we consider that in the very nature of the hemorrhagic diathesis even minimal causes will provoke bleeding, and that lesions may be so slight that the patient has not perceived them, we can readily conceive how part of the so-called spontaneous hemorrhages may belong to the traumatic groups. We further classify hemorrhages, whether they be spontaneous or traumatic, as *the superficial* and *the interstitial.*

Superficial traumatic hemorrhages can occur in all superficially located parts of the body, in all parts of the external skin and superficial mucous membranes, and also in those mucous membranes whose products are carried away *per vias naturales.* We include also the serous membranes of the thorax and abdomen. Bleeding into the skin and mucous membranes that are exposed to view may result from a fall, scratch, bite, surgical procedure, or otherwise. It is of interest to note that the ragged, accidentally inflicted abrasions give rise to much more severe hemorrhages than do those made by surgical operations. Scarred and ulcerated portions of the skin form a *locus minoris resistentiæ.* Of all regions in the body, the head is conspicuous as the site of severe hemorrhages. Extraction of teeth has led to alarming bleeding, and one fatal case followed rupture of the hymen. It is a curious fact that small wounds bleed much more profusely in relation to their size than large ones. Fordyce controlled the bleeding in one case by enlarging the cut with a knife. Superficial traumatic hemorrhages are usually solitary; blood oozes from them as from a wet sponge, and rarely is a spurting artery visible.

Interstitial hemorrhages following trauma occur chiefly in the subcutaneous and cutaneous connective tissue; they usually follow very slight external causes; a rough push, a slight blow, pressure from sitting or lying in one position, may be enough to provoke them. Blood-tumors —so-called hematomata—result, particularly in those parts of the body that are subject to pressure in ordinary life, the glutei, the upper posterior portions of the thighs, and the back being the chief places of predilection.

Diffuse hematomata are found chiefly in the soft tissues of the arms and thighs, and occasionally in the psoas muscle. They frequently resemble a phlegmon, with tense, shiny, engorged cutaneous covering; they are frequently very painful. Subcutaneous hemorrhages may

assume large dimensions; occasionally suppuration and gangrene of the skin have been observed. The fluid evacuated from the subcutaneous hematomata is chocolate-colored.and mixed with gangrenous shreds.

Superficial spontaneous hemorrhages occur most frequently from the mucous membranes; that of the nose is the commonest site, and the mucous lining of the buccal cavity is the next in importance; then come the mucosæ of the urinary organs, the female sexual organs, and finally the lungs, the stomach, and the intestine. Superficial spontaneous hemorrhages of the skin are chiefly found near the scars of cut wounds or of ulcers. In these cases hemorrhage usually occurs when continuity is being restored. Spontaneous hemorrhages into the mucous membranes are frequently combined with cutaneous hemorrhages.

Spontaneous interstitial hemorrhages occur most frequently in the hairy scalp and in the face; next in frequency in the scrotum, less frequently in the extremities, and least frequently in the trunk. Sometimes the points of the fingers are involved, and blood seems to ooze from them as from a sponge that has been dipped in blood. While these hemorrhages appear to be *spontaneous*—that is, cannot be traced to any external cause—we can assume with certainty that they are caused by insignificant, hardly demonstrable mechanical insults, in the same manner as the "traumatic." Intraparenchymatous hemorrhages hardly ever occur in internal organs or in locations that are entirely protected from external violence (the kidneys form an exception). Strümpell attaches a great deal of importance to this fact, and attempts to characterize it as a valuable point in the differential diagnosis between hemophilia and the acquired hemorrhagic diathesis.

Spontaneous hemorrhages often occur without any premonition. Frequently, however, the patient is forewarned of their advent by distinct premonitory phenomena or auras. They occur regularly before every severe hemorrhage, usually as cardiovascular phenomena, such as flushing of the face, roaring in the ears, palpitation, dizziness, or feelings of oppression. Sometimes frequent and forcible pulsations can be seen in the peripheral arteries. Psychic disturbances are produced thereby, and the patient becomes restless, depressed, or filled with anxiety. Another characteristic symptom of the disease is the remarkable persistence of the bleeding. Herein lies the cause of its fatality and the reason why bleeders rarely attain advanced ages.

An open hemophilic hemorrhage has the characteristics of a parenchymatous hemorrhage; the blood continues to ooze for many hours from the whole surface that has been denuded by the traumatic dissolution of continuity. The most careful inspection fails to reveal the presence of a spurting vessel.

It is impossible to predict in any individual case when the hemorrhage will be arrested; the great loss of blood itself seems to exercise a beneficent effect in the direction of controlling the hemorrhage. The patient frequently faints, and the hemorrhage ceases soon after this accident. Occasionally, on the other hand, it persists for so long a time that the patient bleeds to death. During the hemorrhage an

increased action of the heart is observed in the beginning; later, as the anemia progresses, the pulse becomes small, frequently quite imperceptible, the patient grows pale and faint, and in very severe cases hallucinations, convulsions, and delirium may occur.

The blood at first appears normal. As the bleeding continues the character of the blood changes and it becomes lighter and more watery. Chemical and microscopic examinations have so far revealed nothing worthy of mention. The plethora that Immermann postulates in support of his theory lacks definite foundation.

The interstitial hemorrhages in the external cutis present the appearance of bullæ that may assume various colors, depending on the stage of transformation of the blood-pigment; they are similar in this respect to all other deposits of blood in the body. Occasionally a blood-tumor of this kind may suppurate and perforate. It is evident that these hemorrhages damage the nutrition and the general constitution of the patient, the more so as these unfortunates are usually sufferers from other complications that we shall discuss below. The mind and the nerves of a hemophilic are further necessarily deeply affected by the knowledge that they are afflicted with so hopeless a disease.

Among the most characteristic complications of hemophilia a tendency to "rheumatic" lesions of the muscles and joints is important, for the reason chiefly that these complications are analogous to those found in the hemorrhagic diatheses in general. The arthropathies that may appear in any of the joints originate spontaneously or from very slight traumata; quite frequently they are of an undoubtedly rheumatic nature, and hemophilics in general show a tendency to react to "rheumatic" irritation. We shall discuss the peculiar relationship between the hemorrhagic diathesis and diseases of the joints in the next section. The knee and elbow joints are the seats of predilection for hemophilic arthropathies; the lesions begin with pain and swelling, tending to stiffness and flexion, as in subacute inflammations of joints or in "tumor albus." The differential diagnosis between these joint lesions is not always easy, and can occasionally only be made from the fact that hemophilic symptoms have been reported. Such affection of the joints occasionally occurs in attacks unassociated with other evidence of hemophilia. These are evidenced by pain and swelling of certain joints, with fever-like attacks of rheumatic polyarthritis. The course may be very chronic. Young male individuals are most frequently affected with this form of arthritis.

The above-mentioned symptoms are caused by hemorrhages occurring into one or several joints *while these are being used;* in this manner the irritation from motion is superadded to the irritation of the blood, so that the typical picture of arthritis is produced. Finally the arthritis may lead to the partial destruction of the joint, severe contractures, ankylosis, and manifold deformities.

Franz König[1] subdivides the joint lesions of bleeders into 3 stages: The first stage, the one of hemorrhage, is similar to that of a genuine

[1] *Samml. klin. Vorträge*, No. 36.

hemarthrosis. If proper treatment be instituted the disease may not progress beyond this stage and the hemarthrosis may heal. In case such a termination is not brought about the blood within the joint constitutes an irritant, resulting in the development of the second stage, characterized by a peculiar form of inflammation, a panarthritis, similar in its pathologic anatomy and clinical symptoms to those of joint tuberculosis. This stage may be designated as the inflammatory stage (the form of bleeders' joint corresponding to "tumor albus"). In the third stage retrogressive metamorphoses occur. It is here that the joint tissues become obliterated or adherent; that the surfaces of the joint change their relative positions. It is the stage of contractures, ankyloses, and deformities.

In case a patient, in addition to a fresh arthritis of this type, shows evidence of previous inflammations in the form of one or more deformed joints, or if, while under observation, fresh effusions into other joints occur, then the diagnosis of hemophilic arthritis in different stages becomes very probable; if, in addition, the patient should make the statements that the first joint affection occurred suddenly, that the joint in the beginning was painless and its function unimpaired, and that, finally, the arthritis grew progressively worse, then the diagnosis of hemophilic arthritis is almost positive. The symptoms of the third stage are similar to the lesions of tuberculosis of the joint in a corresponding stage. In hemophilic arthritis, however, there is never any tendency to the formation of abscess or fistula. Frequently several of the joints rapidly heal within a short time, and a clinical observer may be staggered by observing several apparently tuberculous joints suddenly heal in a young individual.

The first hemorrhagic exudate into the joints of a bleeder frequently disappears without leaving any traces; on the other hand, it cannot be expected that a joint will recover from the lesions of the second stage with unimpaired motility. We may always expect a more or less severe disturbance of function, particularly as the violent movements, formerly deemed so desirable, are of highly doubtful value. Usually a bleeder who is at all inclined to hemorrhages into the joints will be affected with arthritis in more than one place.

According to Gayet and Th. Hirsch, hemophilic arthritis resembles either an acute or subacute inflammation of the joint in regard to the clinical symptoms that are observed—viz., pain, swelling, possibly fever, stiffness of the joint, and flexion. The above authors believe that rheumatic influences in addition to hemorrhages are concerned in the pathogenesis of this form of arthritis.

Another complication of particular importance is the neuropathic disposition, which manifests itself in all imaginable forms, particularly in female patients. Neuralgia and occasionally neuritis are relatively frequent in hemophilics. In isolated cases a continuous type of fever has been observed for a long time without any local cause. Finally the appearance of circumscribed, hard, and painful infiltrations of the skin and the subcutaneous tissue is worthy of mention. The skin over these

extravasations remains perfectly normal in color; the swelling may go through the different stages usually observed in other extravasations, or may be absorbed without any further changes.

Local Hemorrhages in Hemophilia.—In the last few years a number of cases have been reported characterized by more or less profuse hemorrhages from one of the kidneys. The organ from which the bleeding occurred was found to be absolutely intact, so far as could be determined by clinical observation and after operation. In these important cases it became necessary to answer the query, What caused this hemorrhage? As early as 1887 Lauenstein published his fundamentally important case, and his report was followed by a series of similar observations (by Sabatier, v. Schede, Anderson, and Legueu, in the years 1889 and 1890). It was not until Senator published his first report on renal hemophilia, in 1891, however, that scientifically authoritative statements were made. The writer gives a brief abstract of Senator's case:

A girl of nineteen, toward the end of 1887, discovered blood in the urine immediately after menstruation. An examination of the bloody urine revealed a high percentage of hemoglobin, but did not show any erythrocytes. At the end of two years, during which the strength of the patient had been failing, and she had developed a cough that made tuberculosis probable, this hemorrhage was repeated; at this time it was more severe, and lasted with intervals for half a year. Urinalysis showed a genuine hematuria, and the blood excreted by the kidneys was not different from pure unmixed blood. Toward the end of February, 1890, Senator could determine the following: The patient is well built, very pale but not emaciated; the internal organs show no abnormalities; the lungs and the kidneys are apparently normal. Voiding of urine is painless, possibly a little more frequent than normal, but not accompanied by tenesmus. The urinary sediment consists exclusively of red blood-corpuscles; crystals, pus, and other pathologic constituents are absent; no fever. An examination was made under anesthesia, but revealed no changes in the kidneys, the bladder, nor the sexual organs. Cystoscopic examination showed that the blood flowed from the right ureter.

After the ordinary causes of hemorrhage, as lithiasis, tumor, and tuberculosis, had been excluded Senator made the diagnosis of hemophilia. This was strengthened by the anamnesis, for it was found that the patient was a member of a family in which hemorrhages had often occurred; 4 sisters and a brother (who died at the age of seventeen) had always shown a great tendency to epistaxis; her father, who was perfectly healthy at the time, had been a sufferer from epistaxis and hemoptysis as a child, without lesions of the lungs; 11 brothers and sisters of the father are or were sufferers from epistaxis. One of the patient's uncles, who had been a sufferer from nose-bleed for a long time, had suffered an attack when he was twenty that lasted twenty-four hours, and was followed by the appearance of hemorrhagic spots on the whole body, and by vomiting of blood. The disease ended fatally in two weeks. Another uncle is the father of 2 children, who have inherited from him a tendency to epistaxis. The father's mother suffered with violent and profuse menstruation up to the time of her death. Undoubtedly, therefore, the patient was a member of a bleeder family, and although she had up to the present time showed no symptoms of hemophilia, Senator thought he was justified, in the absence of any other demonstrable cause for the occurrence, in assuming a hematuria of hemophilic origin. The continuous hemorrhages produced a severe anemia that resisted all medication, and it was finally determined to perform a nephrectomy.

The kidney was removed, although during the operation it looked perfectly normal. The subsequent course of the disease was very favorable. Two days after the operation no blood was found in the urine and never recurred thereafter; four weeks afterward the patient, in the best of health, left the hospital. An

examination of the extirpated kidney revealed small foci of inflammation and small areas of extravasation; otherwise the organ was absolutely normal.

Two other analogous cases are found in the literature; both are from Leyden's Clinic, and have been described by Klemperer.[1]

A man of thirty-five came to the clinic on April 15, 1893. The patient's father had died from typhoid; his mother is still living and has been a sufferer since childhood from frequent subcutaneous hemorrhages and violent bleeding, even after insignificant injuries. Her brother died from hemorrhage following an amputation; another brother is also disposed to hemorrhages. The patient himself bled violently from the umbilical cord immediately after he was born. During his childhood epistaxis and other hemorrhages frequently occurred, following insignificant traumata. Beginning with his third year he was afflicted with swellings of the joints in the upper and lower extremities; as a rule, these swellings appeared suddenly without any cause, usually in the morning. They were very painful, and disappeared again toward evening. The patient never regained the complete use of his limbs for several months after such an attack. When the patient was fifteen he fractured his thigh bone, and healing of the fracture was delayed by a violent subcutaneous hemorrhage. The first attack of hematuria occurred when he was sixteen years old, and was accompanied by a dull pain in the region of the right kidney that soon became colicky, and was followed by a tendency to vomit, and finally by vomiting. The urine was colored blood red or black. This condition lasted for several months, and hemorrhages recurred at intervals of a year and a half to two years; one of the attacks of hematuria lasted thirteen weeks. The patient did not consult a physician because he considered himself to be a hemophilic, and looked upon the hematuria simply as a symptom of the general disease. During the attacks he kept quiet and stopped his pain with large doses of morphin; he had learned the use of it at the time of his first joint swelling. The patient had come to the clinic chiefly in order to get rid of the morphin habit. The subject is pale and nervous. His internal organs are sound. Four days after admission to the hospital a hemorrhage from the kidneys, lasting two weeks, occurred. Nothing but blood was found in the urine. On May 15, 1893, the patient was dismissed in good health; toward the end of his sojourn two hemorrhages into the wrist joint occurred. Similar arthritic hemorrhages occurred frequently thereafter. Since March, 1896, however, no hematuria has occurred.

The third case is that of an official, aged twenty-six, with only a slight hereditary taint. Since his sixteenth year, almost annually, attacks of hematuria would occur, sometimes recurring several times during the year and lasting hours or weeks; they were accompanied by insignificant pain in the region of the right kidney. The patient only consulted a physician if the hemorrhage lasted more than a week. On November 2, 1895, pain occurred in the region of the right kidney, and on November 9th he passed bloody urine. Examination revealed nothing abnormal, and nothing pathologic was found in the urine excepting the blood. Despite the numerous remedies administered, the hemorrhage continued and the anemia grew worse. On December 28th all treatment was stopped and a course of hydrotherapy instituted. The patient received a daily bath for ten minutes, followed by a "showering" of the region of the kidney; the bath was begun at about 35° C., and the temperature gradually reduced to 24° C. The temperature of the shower varied from 28° to 16° C. Gradually the hemorrhages decreased and the urine became clear. On January 15th the patient left the hospital, cured.

The fourth case is reported in the pamphlet of S. Grosglik, entitled *Hemorrhages from Anatomically Intact Kidneys.*[2] This patient was a pronounced bleeder, and both his parents had been bleeders. Hematuria had occurred after he had suffered from all other possible kinds of hemorrhages, which disappeared as soon as the hemorrhages from the kidney made their appearance.

Grosglik reports on 18 cases of unilateral hematuria that were not

[1] *Deutsch. med. Woch.*, 1897.

[2] *Samml. klin. Vorträge*, No. 203.

caused by lithiasis, tuberculosis, or neoplasms. In the majority of these cases the kidney was exposed and incised, inspected, sewed together, and replaced; by this method of examination it was clearly demonstrated that no anatomic cause for this unilateral hematuria existed. In another series of cases the bleeding kidney was extirpated. Clinically, all the cases resembled each other in the most striking manner.

The most important point in the 4 cases reported above is that they were all associated with hereditary hemophilia. Senator's patient is conspicuous by the fact that she never showed any tendency to hemorrhage before, and even later the kidney was the only source of bleeding. We know, however, that many bleeders do not develop hemorrhages until they are twenty-two, or even twenty-five, years of age, and Senator's patient was only eighteen.

Other cases of unilateral hematuria (to which belong the cases that were reported before Senator) are clinically indistinguishable from those reported, with the exception that they did not have a hemophilic disposition: Preceded by more or less violent pain, occasionally severe colics, bloody urine is passed containing nothing abnormal excepting the corpuscular elements of the blood; occasionally oxalates and once granular casts were found. After the bleeding has persisted for a short or long period of time it disappears, only to recur again at varying intervals. In those cases in which hemorrhage was so severe as to threaten life an operation was decided upon, and usually a simple incision into the kidney or opening the pelvis was sufficient to produce a cure; in one case a high incision into the bladder was all that was necessary; all the cases recovered. Usually blood was passed for from one to three days after the operation. Overexertion from riding a bicycle was made responsible for some of the attacks; in others, certain nervous influences were thought to be concerned in the etiology of these hemorrhages. So much is certain, that in lighter cases, where the intensity of the hemorrhage does not originally call for an operation, a cure can be effected without surgical procedure.

The fact must be chronicled that, according to frequent observation, the occurrence of hematuria in hemophilic cases seems to put a stop to hemorrhages in other parts of the body.

Senator was the first to call attention to the hemophilic form of hemorrhage from the kidney and to explain it correctly. He deserves a great deal of credit for this elucidation; but notwithstanding his statements, we are justified in doubting whether in his case the patient was really affected with renal hemophilia or was simply a sufferer from angioneurotic hemorrhage. Particularly in his case is the hemophilic character doubtful, because, as a rule in this affection, very violent, uncontrollable hemorrhages occur after surgical procedures, whereas in this case a cure was rapidly obtained.

Hematuria is not the only form of local hemorrhage seen in hemophilia; we occasionally find hemorrhages from the lungs and the stomach in bleeders who had not had any hemorrhages at all until the age of puberty. For this form of hemorrhage no anatomic reason can be

found. Cases of hematuria are particularly interesting for the reason that they may occur on one side only, and that it has been possible to make an exact and positive diagnosis during the life of the patient. This, of course, does not apply to other organs, like the stomach and the lungs. [For a further discussion of "renal hemophilia" see the section on Hematuria, etc., in the work of Senator on the kidneys, published in this volume.—Ed.]

Prognosis.—The prognosis is not favorable; 60 per cent. of all bleeders succumb before their eighth year, and only 11 per cent. reach twenty-two. After puberty the outlook is a little better, but even in later life a slight injury may be fatal. In a hemophilic family from Finland 14 died from direct hemorrhages; there were 5 generations of bleeders in this family, which originated from a couple that were not hemophilic themselves. Here the first symptoms of the disease became apparent after the children had attained the age of six months.

Treatment.—General Prophylaxis.—In view of the hereditary character of the disease and its transmissibility, particularly through women, it is apparent that restrictions of marriage among such people may limit the spread of hemophilia. From considerations of this character certain rules have been formulated to regulate intermarriage in bleeder families. Grandidier, who has had a great deal of experience in this disease, expresses himself as follows: "First, all female members of bleeder families, regardless of whether they are bleeders themselves or not, should be advised against marriage; second, all male members who are not hemophilics themselves may be allowed to marry; third, a male bleeder should only be advised against marriage if a case or cases are known in his family in which hemophilic men have had hemophilic children, and provided, of course, that those men married healthy daughters of healthy families. Intermarriage among relatives has also been made responsible for the appearance of hemophilia. It is difficult to determine in how far such an assumption is correct; we are in the same position in regard to rendering judgment on this question as we are in general in regard to intermarriage among relatives. There is no doubt that the interdiction of marriage made by a physician is rarely obeyed, and the desire to see a daughter married is probably more pronounced in a bleeder family than the scruples that may arise from the fear that bleeders may be the issue of such a union.

Individual prophylaxis is very important in the fight against hemophilia. This should begin with the earliest days of life and be continued rigidly during the first years of childhood, particularly since in this period of life hemophilics are exposed to the greatest danger. On general principles all operative procedures should be waived in the case of nursing infants in whom hemophilia might be suspected. Congenital deformities of all kinds should be let alone, and such operations as hare-lip, palatal fissure, severing of the septum of the tongue, syndactyly, removal of a nevus, etc., should not be performed; the physician should advise against ritual circumcision in children of Orthodox Jewish or Mohammedan bleeder families. In the

case of the Jews, religious scruples can readily be allayed by calling attention to the fact that in their books on religion the danger of hemophilic hemorrhage is given as a valid reason for omitting ritual circumcision. In the case of girls the customary piercing of the ears should not be performed. The experience of many observers seems to point to the fact that vaccination does not cause dangerous hemorrhages in hemophilics, so that vaccination may be performed in the newborn, or in children who have been vaccinated once, without misgivings. In bleeder families particular attention should be given to the care of the teeth in the children; it is necessary to have the teeth inspected periodically by a competent dentist, and to have the slightest damage to the teeth repaired at once, so that they may be kept as healthy as possible.

In view of the great danger of surgical inroads within the buccal cavity, particularly of extractions of teeth, care should be taken that such procedures are rendered unnecessary. Leeches, vesicants, and cups should not be applied in bleeder children or in hemophilic adults. As soon as the children learn to move about by themselves, their playing with other children should be supervised; the nurse should be instructed that the children be not allowed to injure or hurt themselves in any way; the playthings should be of a kind that cannot inflict injury. Hemophilic children should not be punished. As soon as the children have become old enough to understand, they and their playmates should be instructed in an appropriate manner that injuries by falling, pushing, or pricking with a needle or a pin may in their case readily cause serious damage. It is a practical idea for the family physician to consult with the child's teacher, and to instruct him, so far as his supervision of the child in the school demands, in regard to the symptoms of hemophilia; in this way the teacher may learn what attitude he is to take toward such a hemophilic pupil, and what instructions he is to give the classmates of such a subject in regard to their intercourse with him. Hemophilic children should never be allowed to perform gymnastic exercises, nor should they ever be punished in school.

In the choice of their calling hemophilics are usually restricted. To begin with, they are usually weaklings, and they will select the calling that does not demand violent bodily exercise. Subjects of moderate means should be advised to take up office work or to become draftsmen; they should not be allowed to take up a trade in which they are exposed to slight injuries, as watchmaking and engraving; nor should they be allowed to become wall-paper hangers, goldsmiths, or barbers. Bleeders with means should take up some learned profession; if they are students, duelling should be forbidden. Hemophilics should be exempt from military service.

General Treatment.—Hemophilics should limit themselves to a special diet and avoid all beverages that excite the vascular system (alcohol, tea, coffee); milk and lemonade are advised. Solid food should be bland, and strong spices should be avoided; a vegetable diet, particularly fresh vegetables and salads, is recommended. The general

nutrition may be increased by bathing, particularly sea-bathing, cold ablutions followed by rubs, and life in the country.

Special Treatment.—The attempt has frequently been made to influence the course of the disease by the administration of drugs. In one case reported by Wickham Legg the administration of chlorid of iron is said to have caused some improvement. Other drugs that have been employed in this direction are mineral acids, subacetate of lead, sulphate of magnesia, and sulphate of sodium.

The salines probably act by relieving the congestions that play a certain rôle in hemophilia. General strengthening and tonic remedies have frequently been employed in the periods between the hemorrhages; during this period, or as soon as any sign of approaching hemorrhage was noticed, ergot, acetate of lead, hydrastis canadensis or opiates, and nitrate of silver have been administered. In general very little can be expected from the medicinal treatment of hemophilia.

The treatment of hemorrhage in a hemophilic in a given case should be directed primarily toward mechanically stopping the bleeding. The limb in which the hemorrhage occurs should be elevated, and occasionally this simple action will be sufficient; in the second place, local styptics may be used; for instance, the chlorid of iron and sometimes the cautery. Occasionally, packing is useful, or bandaging of the bleeding extremity with rubber bandages and compression of the nearest large artery. Sometimes it is necessary to ligate one of the large vessels. Hémard in one case ligated the common carotid in order to arrest a hemorrhage following the extraction of a tooth. Of internal remedies, Secale cornutum and its derivatives must be considered; their action in the fully developed disease is doubtful.

In hemorrhage in hemophilic women during pregnancy artificial abortion or premature labor (Kehrer) is indicated.

The treatment of the *joints* in hemophilics is, for therapeutic reasons, exceedingly important. The writer follows the recommendations of F. König in the following: A recent case of hemarthrosis in a hemophilic should, above all, be treated by rest, and the patient instructed not to use the joint; moderate compression aids resorption considerably. König recommends puncture of the joint, notwithstanding the fact that operative treatment seems contra-indicated in hemophilia. He performed puncture of the knee joint 3 times in 2 cases, followed by irrigations with carbolic acid. In no case did the operation do harm; in 2 cases the patients improved, and one was cured. König advises limiting operative inroads to this simple procedure. In 3 cases where this author performed an incision into the joint by mistake, assuming that tuberculosis was present, he had disastrous results; all of these cases bled to death, and in another hemorrhage occurred for a long time and the motility of the joint was permanently impaired. According to Gayet, the treatment of hemophilic arthropathies in the acute stage should be expectant; later, he also advises either puncture of the joint or incision and removal of clots. He claims that in this way a restitu-

tion to normal is encouraged, and that relapses from hemorrhages into the joints are less to be feared.

[Gelatin, by virtue of the hemostatic properties, is a valuable agent in the treatment of hemophilia. Compresses or tampons soaked in a 20 to 25 per cent. solution and applied directly to the bleeding surface at times check oozing not susceptible to pressure or ligation. It may also be used subcutaneously in cases of severe bleeding and bleeding from inaccessible places. Since tetanus has followed such injections in a certain number of cases, care must be taken that the solution be absolutely sterile. Various strengths of solution have been employed, from 2 to 20 per cent., 10 to 25 c.c. being given at one time. Hesse gave a hemophilic boy 200 gm. of a 10 per cent. gelatin solution by mouth daily for six months with very good results; and Tschuselmer, in the case of a hemophilic female, administered 50 to 80 gm. of gelatin a day with the food. Under this treatment the menorrhagia from which she suffered was held in abeyance for nine months. At the end of that time the treatment was discontinued, and the hemorrhages promptly reappeared. Treatment was now resumed, 40 gm. of gelatin being given per day, and at the end of two weeks the bleeding had again stopped.

On the supposition that the immunity of females might depend upon the restraining influence of some internal secretion, Lachlan Gromut[1] gave to a hemophilic boy 2½ gr. of ovarian extract three times a day. He reports beneficial results.—Ed.]

MORBUS MACULOSUS WERLHOFII.

(Purpura Simplex, Haemorrhagica, Rheumatica Seu Peliosis Rheumatica Schonleinii.)

Definition.—Blood-spots are so conspicuous that they have been described even by physicians of antiquity. It is also quite natural that, at a time when it was not known whether blood-spots were the chief symptom or only an insignificant manifestation of a variety of diseases, all such lesions should be described together irrespective of their significance. From the great number of diseases in which blood-spots are found in the skin, Werlhoff, in 1775, separated a specific disease picture that he called *purpura hæmorrhagica*. Later, further subdivisions were made, a *purpura simplex* was distinguished; and finally a *purpura urticans*. Schönlein later described a *peliosis rheumatica*. We may state that such a definition was justified at the time—in fact, was demanded—and particular value was to be attached to a subtle distinction between the different clinical symptoms. Still, in this way great stress was laid on an individual symptom; thus, the formulation of a "peliosis rheumatica" was based on the observation that purpura is occasionally accompanied by a joint affection. It seems to have been overlooked that such a complication was not at all rare, and that it was seen as a result of various kinds of hemorrhagic diseases, not only in

[1] *Lancet*, Nov. 19, 1904, p. 1414.

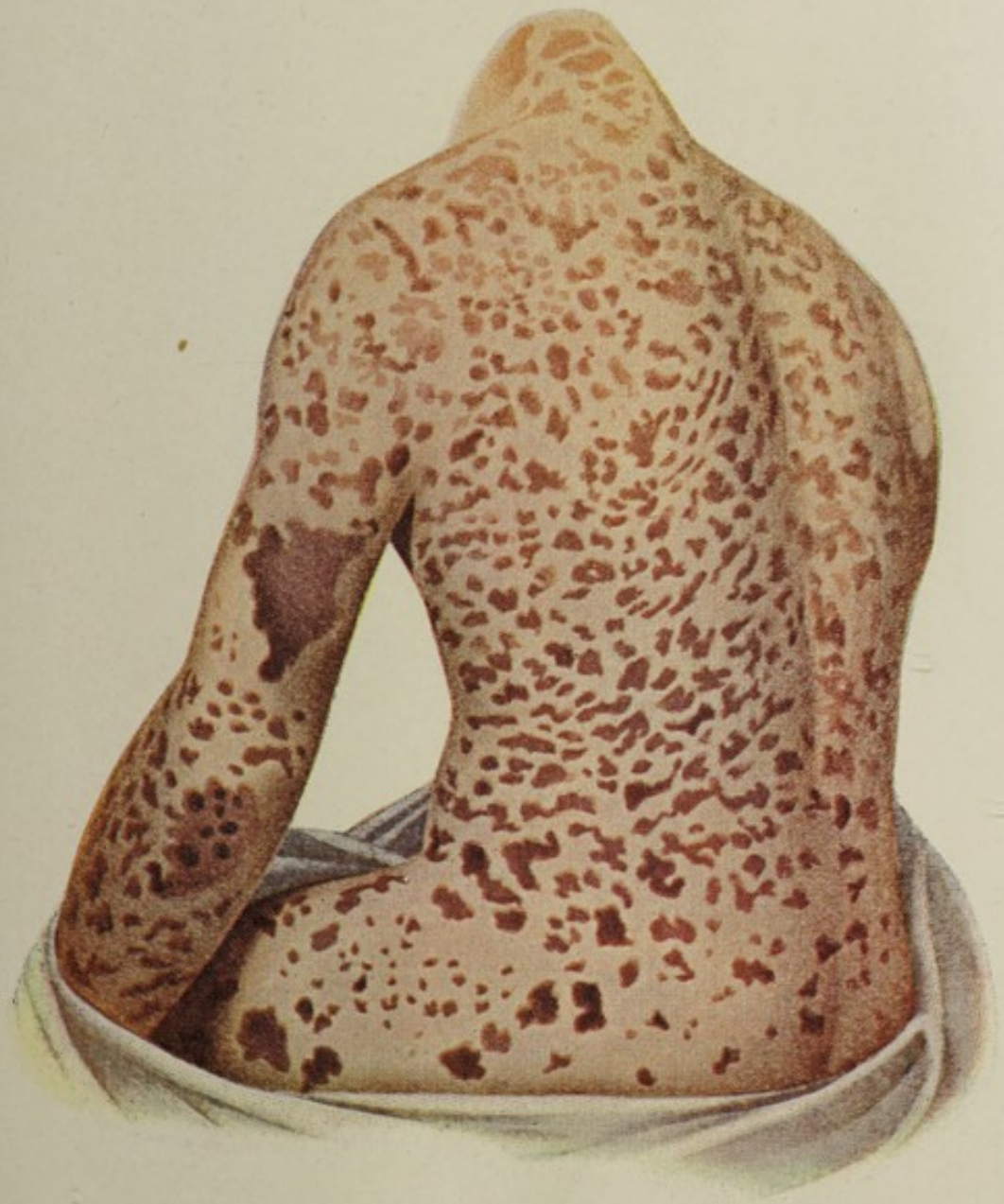
those that strictly belong to the class of purpura, but also in the course of scurvy and of hemophilia. With a recognition of this fact, the differentiation of the various forms of purpura is naturally not justified to the same extent as formerly. Since the seventies a tendency to group the various forms of purpura has become manifest, and with it an inclination to discuss from a common point of view the various forms that formerly were considered as independent diseases. Personally, the writer is of the opinion that in all the different forms of purpura we are unable to distinguish any essential characteristic features; the only differences observed are in the intensity of the disease. The differences then are of degree and not of kind. It is true that sometimes these differences in degree may clinically present such different pictures that an inexperienced observer might be led to the conclusion that he is dealing with different diseases entirely unrelated. This attempt to establish an identity for each manifestation of purpura has been exaggerated by some authors, and they have gone even beyond this and attempted to draw scurvy into this group of diseases (Schwimmer and Scheby-Buch); other authors include hemophilia.

Aside from the facts adduced by bacteriology of late years, which we hope will be corroborated in the future, we must consider the disease under discussion as the result of unknown noxious substances; it occurs sporadically and manifests a transitory tendency to hemorrhages of different kinds. In contradistinction to hemophilia, a congenital or hereditary influence cannot be determined; in contradistinction to scurvy, it does not appear epidemically nor endemically, nor does it produce severe disturbances of the general health. In the case of scurvy, the fact that it appears not only sporadically, but also epidemically or endemically, is characteristic; still more so its dependence on external conditions. We have seen that scurvy is almost without exception the expression of serious disturbances of nutrition, produced either through certain diseases or through the effect of long-continued reduction in the quantity and quality of the food. Morbus maculosus Werlhofii is differentiated from hemophilia particularly by the fact that it is never transmitted by heredity. The latter distinction applies also to scurvy. In contradistinction to scurvy the hemophilic is frequently well nourished and strong; in fact, may be considered perfectly healthy, with the exception that he shows this peculiar tendency to spontaneous hemorrhages. In comparing hemophilia with related diseases in the group of the hemorrhagic diatheses, one peculiarity of hemophilia is particularly striking; it is not, in contradistinction to all the other diseases named, a true disease process, but a permanent condition that becomes manifest from time to time through known or unknown causes.

With the facts in view we shall discuss the different purpuric diseases together, not forgetting, however, the older clinical divisions; further, we shall remember that transition forms exist between those different diseases, and, finally, that the distinctions drawn are, after all, superficial.

When we group all the forms of purpura and discuss them in a

PLATE VII.



Purpura Hæmorrhagica.

special section on Pathology, we purposely exclude all those diseases that produce hemorrhages into the skin, but in which such lesions are not an essential determining symptom, but are merely symptomatic of some recognized infection or intoxication. In this category are hemorrhagic small-pox, typhoid fever, typhus fever, acute atrophy of the liver, phosphorus-poisoning, sepsis, ulcerative endocarditis, pernicious anemia, leukemia, yellow fever, snake-venom intoxication, etc. We can only speak of a purpura if hemorrhages occur by themselves and dominate the whole disease picture, though we must remember that certain results of hemorrhages, such as anemia, may occur and change the aspect of the disease.

[Purpura, as has been said by Litten, is a disease condition that lends itself with great difficulty to an accurate classification. Until something more is definitely known concerning the etiologic factor that is at work in these cases, classifications are more or less artificial. There is room for a great deal of accurate clinical observation and for laboratory and experimental work before the mystery of purpura is entirely cleared up. While no classification is entirely satisfactory, the writer believes it is not without some value that the student and physician have pretty clearly fixed in their minds some working scheme for the identification of this group of diseases. The one adopted by Osler in his text-book is both simple and fairly accurate. I give a brief outline of the same.

The purpuras may be divided into the symptomatic and the arthritic.

The *symptomatic purpuras* are those in which purpuric lesions exist, but they do not dominate the entire picture, and some definite etiologic factor is recognized. Purpura is therefore merely a symptom of some other underlying disease or recognized cause. Under this head one may class: First, the infectious purpuras, as, for example, in small-pox, measles, scarlet fever, typhus; also the purpuric manifestations of ulcerative endocarditis would fit into this group.

Second, the toxic group, as is known, certain drugs, such as quinin, copaiba, iodid of potassium, are followed by purpuric rash; also in certain snake venoms purpura is a striking symptom. Icteric purpura would be classed here.

Third, in conditions of cachexia, as in carcinoma, tuberculosis, Bright's disease, and even in senility. In these, hemorrhages into the skin may be present. Here we could probably class also the purpuras met with in the severer forms of anemia, such as pernicious anemia and leukemia.

Fourth, in certain nervous conditions, though rarely, purpura is seen. It is met with at times following the severe lightning pains of tabes, and is also described as an occasional manifestation of hysteria.

Fifth, from mechanical causes, as very slight bruises, from straining efforts during whooping-cough, and, as in one case of the writer's, following the strangling that occurred in a patient who took an anesthetic badly, purpuric lesions may be seen.

The *arthritic purpuras* may be subdivided into purpura simplex, purpura rheumatica, and purpura hæmorrhagica. As Litten says, the line that divides these various groups is not a hard and fast one. Possibly no attempt should be made to divide them into different groups any more than we should attempt to make two distinct diseases out of a mild attack of scarlet fever and one of the malignant variety. In the purpura simplex, however, the joint symptoms are entirely absent or are very slight. In the so-called rheumatic purpura the joint symptoms come to the front; while in the so-called hemorrhagic purpura the hemorrhages from mucous membranes are the striking features. As said before, these classifications are more or less artificial, and yet for practical purposes they are of considerable value.—Ed.]

Etiology.—Within the numberless ecchymoses that are distributed all over the body we are often able to see that the capillaries are occluded, thus revealing the dyscrasic nature of the disease. In the multiple capillary hemorrhages of septic diseases little white centers can sometimes be seen within the areas of extravasation; further, it can be demonstrated that the capillaries and capillary veins are occluded by colonies of micrococci in the case of hemorrhagic smallpox. The same may be seen in the hemorrhagic efflorescences, not only of the skin, but also of the internal organs—the spleen, the kidneys, and the lungs. The writer was also enabled in septic retinitis or in retinal hemorrhages occasionally to see vessels that were occluded with masses of micro-organisms. In other cases that were just as clearly septic he did not succeed in making this observation. The attempt to demonstrate occlusion of vessels has not always been successful in cases of hemorrhagic exanthemata. In many other diseases and intoxications distinguished clinically by hemorrhagic states (cholera, plague, yellow fever, anthrax, snake-bite poisoning, petechiæ typhus, etc.), occlusion of the capillaries in the center or the periphery of ecchymoses has not been discovered, and the different observers were forced to the conclusion that zymotic substances, ferments, ptomains, or toxins produced the hemorrhagic diathesis. How these act—that is, whether they change the blood directly, and in this way produce occlusion of capillaries, or whether they affect the structure or the muscular or nervous function of the vascular apparatus—is a problem yet unsolved.

Whether in morbus maculosus or purpura hæmorrhagica certain parasites or their toxins are circulating in the blood we do not know; the assumption is very tempting, however, that such foreign bodies are present, and that they exercise a deleterious influence on the vessel walls and thus lead to the ecchymoses characterizing these diseases.

Ajello, who was able to demonstrate methemoglobin spectroscopically in a case of purpura, assumes that purpura hæmorrhagica is the result of the auto-intoxication produced by the absorption from the intestinal tract of certain substances generated by the decomposition of albumin. Schwab also assumes that toxins play a rôle in the causation of this disease. In certain forms that have been known to follow infectious diseases (see below) the blood has been examined for bacteria,

and in some instances with a positive result. Some of the older authors (as Batemann and Grisolle) considered certain forms of purpura as infectious. In some of the cases of purpura, recent investigations have positively demonstrated that they are bacillary diseases. Thus, the following investigators have found bacilli: Klebs, Ceci, Reher, Demme, Vessalle, Gendre-Gimard, Simon-Legrain, Jones, Tizzoni, Giovannini, Kolb, Petrone, Babes, Letzerich; Hanot and Luzet, Widal, and Thérèse found streptococci; Lebreton and the writer found staphylococci in one case; other authors, like Marfan, Legendre, Demys, and others, report negative findings.

Letzerich believes that he has demonstrated by bacteriologic examination that purpura hæmorrhagica is, in fact, an infectious disease. Petrone particularly postulated such a view of this affection. In 1884, in the blood of a female of twenty-five, who was affected with a long-lasting attack of this disease, but was finally cured, he found small, shiny, round bodies. In cultures these bodies were seen to be the spores of a bacillus described and delineated by this author as the Bacillus purpuræ. A large number of rabbits were injected with several generations of this culture; an inoculation made into the peritoneal cavity led to positive findings in each case. The animals in a short time showed circumscribed dilatations of the capillaries in the region of the ears, followed by hemorrhages, enlargement of the gums, etc. If the animals were destroyed, similar hemorrhages and ectases of blood-vessels were found in different parts of the body. Microscopic examination showed that these bacilli or their spores were present in the blood-vessels of different parts of the body; they are most developed in the enlarged liver. Letzerich calls attention to the frequent enlargement of the liver in the human form of the disease; he also found conglomerations of red blood-corpuscles in different organs of the animals on which he experimented, and, as a result, stasis within the capillaries. In addition, he saw hyaline plugs at the dichotomous ramifications of the smallest vessels; the latter had probably originated from the effect of the chemical poison of the bacteria on the albumin of the blood. He concludes that the hemorrhages within the organs, and certain circulatory disturbances are due to these occlusions of vessels. It is possible that the bacillus penetrates the mucous membrane of the mouth and throat and thus enters the human organism. From his experiments, Letzerich considers purpura hæmorrhagica as a chronic infectious disease, and points to its analogy with syphilis and malaria. It is remarkable that three years after these experiments, Letzerich himself became affected with a long-lasting purpura complicated with a large tumor of the liver. The bacillus described by him could be cultivated from his blood.

A few words in regard to the biologic properties of Letzerich's Bacillus purpuræ will not be out of place here. The organism resembles the bacillus of anthrax, particularly in its method of growth. Both form rather irregular colonies (flakes) in Koch's stab culture. The center of a colony is formed by a ramified mass of threads that,

toward the periphery, merge into little bundles, partially bent backward into loops. They are, however, differentiated by their size and the form of their spores. Both present the appearance of long threads, in which the different bacilli are seen arranged in chains; but in purpura they are smaller, both in regard to their length and their width; further, the spores are small and absolutely round, as against the long, oval structures of Bacillus anthracis. In addition, the Bacillus purpuræ liquefies gelatin very slowly, sometimes not at all, or only at higher temperatures (25°–30° C.) and in the immediate surroundings of the growth. In the petechiæ of human beings and animals the bacillus is frequently found arranged in sheaths or in long chains. The surface of the stab culture in Koch's gelatin presents the appearance of flat meniscus-like depressions that can only be seen on careful inspection.

The differences are particularly marked in regard to the chemical peculiarities of the two organisms. The bacillus does not form so toxic a substance as the Bacillus anthracis; the ptomain of the former organism is a weak poison. This is manifested by the slight occasional evening rise of temperature. Purpura is differentiated in this manner from other acute infectious diseases that are accompanied by the appearance of petechiæ, as these owe their origin to other micro-organisms.

Letzerich was able to produce purpura in rabbits with cultures from a third recurrence. In transverse sections through small petechiæ conglomerates of purpura bacilli, stainable with simple methyl-violet solutions, can be seen in the lumena of the capillary vessels, particularly where they ramify and subdivide.

The various developmental stages of the Bacillus purpuræ cannot be seen in each petechia; sometimes toward the end of the disease or in recurrences nothing is seen but little heaps of free spores or a few isolated bacilli. In such cases it is necessary to section a great many petechiæ in order to observe the developmental cycle of the micro-organism. Particularly in the relapses of this disease spore emboli are frequently seen that on superficial observation might be considered as micrococcus emboli. If these are more carefully inspected, the fact that they are embedded in gelatinous plugs will throw light upon the subject, and will reveal that they owe their origin to little rods and fibers.

Lockwood considers purpura to be of an infectious nature, and agrees with Letzerich in considering the bacillus described as the true carrier of the infection and the cause of the disease. Certain acute forms of this disease that begin like other infectious diseases speak particularly in favor of an infectious origin. Of these forms Lockwood describes 17 cases that he finds in the literature; 13 of these died within a short time, varying from seven hours to twenty-one days. He is also inclined to the opinion that purpura simplex and rheumatica are the same infectious disease, varying only in intensity.

H. Neumann reports some cases of the hemorrhagic diathesis in the newborn. In his first case the Bacillus pyocyaneus β was found in addition to the Staphylococcus pyogenes aureus. The author is not

inclined to see a connection between the former and the hemorrhagic diathesis, since the diathesis in this case might possibly have been dependent on syphilis.

In another case (melena) the Bacillus lactis aërogenes was found, but no pathologic significance was attached to it.

Lebreton describes a case of severe fatal purpura that occurred acutely in a young girl, following a sudden fright. It was characterized by the presence of large ecchymoses, from which cultures could be obtained that developed the Staphylococcus albus and aureus. This disease was interpreted as an infectious form of purpura.

Wikner also found the Staphylococcus pyogenes albus in a case of morbus maculosus Werlhofii.

We must now mention a group of investigations that were based partly on anatomic examinations of the blood-vessels and partly on a series of experiments.

Silbermann based his experiments on the well-known investigations of Armin Köhler. This author published a work on thrombosis and its relations to the fibrin ferment (that appeared in Dorpat), and by infusing blood very rich in ferment was able to produce in dogs a picture similar to Henoch's purpura (see below). A short time after infusion multiple capillary ecchymoses appeared in the subcutaneous connective tissue, with vomiting of blood, bloody diarrhea, and intestinal colic. The animals all died very soon after the injection, owing to the severe character of the process that developed; this in turn was the result of the high percentage of ferment contained in the blood injected. Silbermann modified the experiment, so that the animals did not die so rapidly or did not die at all. In his cases the purpuric spots were more numerous and distributed over the whole skin.

He conducted his experiments as follows:

Before injecting the ferment the dogs received small doses of pyrogallic acid (0.05 gm. for each kilo of dog); this produced a moderate stasis in the veins and capillaries. The property of pyrogallol to produce this effect in small doses seems to depend on its inducing fragmentation of the erythrocytes and the formation of shadows. In dogs in which such a stasis in the veins and capillaries of the whole circulation had been produced by suitable doses of pyrogallic acid, Köhler's experiments were repeated; it was expected that the capillaries of the skin, which were under high pressure, would also exhibit, like the other capillaries of the body, a greater permeability for the ferment blood. The experiments showed that in animals prepared in this manner ferment injections produced thrombosis and hyaline changes in the vessel walls that were always present in the internal organs, less constantly in the skin; these were followed by multiple hemorrhages that, according to Silbermann, occurred by diapedesis and as the result of the stretching of the vessel walls. Microscopically no rhexis of the vessels could be demonstrated; it is hardly possible, however, to exclude this with absolute certainty. The changes of the vessel walls, as well as the extravasations, are the result, not the cause, of the disturbances in circulation;

alterations in the vessel walls never occur alone, but are always found in connection with thrombosis; the reverse, however—that is, the occurrence of thrombosis without alterations of the vessel walls—may often be found. The retardation of the blood-current within the capillaries is probably responsible for the occurrence of thrombosis within these vessels, as a reduction in the rapidity of the flow of blood is an important factor in the production of all forms of coagulation. The stases that occur in the lighter cases are usually followed by thrombosis, and injure the vessel walls in such a manner that they become permeable for blood; in fact, they may produce fatty degeneration and even necrosis of the cells of the vessels.

It is, then, possible to produce in an animal an experimental "purpura," complicated by swelling of the joints, vomiting of blood, bloody diarrhea, and intestinal colics, as the direct result of a dyscrasia of the blood. The question arises whether primary disease of the blood can ever be made responsible for purpura, of whatever kind, in human beings. Silbermann answers this question in the affirmative, for the reason that, aside from important findings in the blood, the connection of the symptoms of this disease with a primary disease of the blood is apparent.

The hemorrhages into the skin and the intestinal tract, the bloody vomiting, the colic, the swellings of the joints, all seen in severe cases of purpura, can easily be explained by *primary alterations of the blood* which, according to Silbermann, lead to a slowing of the blood-current, stasis, and thrombosis. As a result of these disturbances of circulation we have, on the one hand, hemorrhages from stasis; on the other hand, hemorrhages that follow a necrosis of the vessel walls, the latter again being the result of the occlusion of vessels by thrombi. The stasis and thrombosis of the capillaries produce the same serious lesions in the liver, the kidneys, and the heart muscles as they do in the intestinal tract, the pathologic change consisting in a fatty degeneration of the cells and in necrobiosis. These processes were all recently recognized by Tizzoni and Giovannini in the organs of a girl who had died of a severe purpura. The same occlusion of vessels that, on the one hand, leads to hemorrhages and tissue necrosis will, on the other, lead to those changes in the vessels that are observed in human beings and animals affected with purpura. Silbermann believes that these degenerations of the vessel wall are of a secondary nature, because it is possible to follow experimentally all the stages in the development of this change of the vessels, and to demonstrate that hyaline deposits follow secondarily.

In the literature we also find reports that resemble very much the one mentioned above in regard to the nature of purpura; thus, Green, DuCastel, Dusch, Mackenzie, Krauss, and others express the belief that an alteration of the blood exists in certain forms of purpura. Leloir, who also observed stasis in the vessels, distinguishes between a purpura "par modification des vaisseaux" and a purpura "par modification du sang." Riehl and v. Kogerer consider the alterations of the vessels as the primary lesion, and alterations of the blood—that is, the thrombosis

—as the secondary one. The latter, in his dissertation on the origin of cutaneous hemorrhages, says: "No doubt can exist in general that the thrombi observed are the direct cause of the hemorrhages. The thrombi in their turn are produced by the joint action of local and general causes. The blood-vessel changes probably play the most important rôle; this is apparent from the constant appearance of such changes; in fact, they may be considered a *conditio sine qua non.*" Silbermann agrees with v. Kogerer that the thrombi originate from general and local causes, but considers the alterations of the blood as the general cause; a pathologic change in the blood-current of the capillary, produced by the presence of ferment, as the local cause. v. Kogerer, basing on the constant anatomic findings, assumes a primary disease of the blood-vessels, whereas Silbermann considers these lesions as secondary. Other observers, as, for instance, Leloir, did not report so constant an occurrence of vessel lesions. The latter author considers the occlusion of vessels, which v. Kogerer and Silbermann declare to be thrombotic, as embolic.

v. Kogerer summarizes the result of his investigations in purpura diagrammatically as follows:

(*a*) Lesions of the blood-vessels.
(*b*) Thrombosis.
(*c*) Blood-extravasations.
(*d*) Pigmentation.

Silbermann, on the other hand, summarizes his findings as follows:

(*a*) Thrombosis.
(*b*) Lesions of the blood-vessels.
(*c*) Blood-extravasations.
(*d*) Pigmentation.

As we see, these two authors agree in regarding the lesions of the blood-vessels as the cause of the hemorrhages. Silbermann, however, looks upon stasis, the formation of thrombi in the small veins and capillaries, as the primary factor leading to lesions of the blood-vessels; whereas v. Kogerer considers the lesions of the blood-vessels as the primary factor leading to the formation of thrombi. The blood-vessel lesions in all cases produce hemorrhages.

We must refrain from discussing the paper of v. Kogerer in detail; we shall only mention that he has examined 13 cases of different diseases accompanied by hemorrhage, as scurvy, heart lesions, carcinoma of the stomach, tuberculosis of the lungs, senile marasmus, lobar pneumonia, sepsis, progressive paralysis, ulcerative endocarditis, and purpura hæmorrhagica. In all these cases careful examination revealed the presence of thrombi; they were usually found in the small venous branches, occasionally in the smallest arteries. In addition many of the small arteries and capillaries were filled with fibrin coagula and blood-corpuscles. In several of the cases, however, it could not be positively determined whether a thrombosis was present or whether a blood-infarct had been formed. The degeneration of the vessel walls was very conspicuous; Riehl and v. Kogerer had found changes in the blood-vessels

of the cutis and the subcutaneous connective tissue with great regularity in cases of scurvy, morbus maculosus Werlhofii, purpura rheumatica and cachectica. v. Kogerer, too, found endarteritis with thickening of all the layers of the vessel walls, hyaline degeneration and partial degeneration with narrowing of the lumen and proliferation of the endothelium in all cases of scurvy and morbus maculosus; in addition, a considerable round-cell infiltration was found in the connective tissues and the fat surrounding the vessels.

In the hemorrhagic places recent or slightly changed blood-extravasations were found, or coarsely granular or flaky blood-pigment; this was seen lying between the layers of connective tissue and the cell infiltrations.

In purpura rheumatica and peliosis cachecticorum lesions of the blood-vessels and infiltration of the perivascular connective tissue, resembling in all respects the hemorrhages into the skin, could be seen.

In all the cases the larger arteries situated in the reticular layer of the cutis were most severely affected; after this the vessels of the adipose layer, and finally, only slightly, the vessels situated in the subpapillary layer.

As these lesions of the blood-vessels were seen in all the cases characterized by hemorrhages into the skin, we are justified in assuming that these vessel changes bear a definite causal relation to the hemorrhages.

In addition to the investigations cited, we must mention later ones by Hayem and Stroganow, and recently by Leloir and Riehl, to which we have briefly referred. All these authors corroborate the described changes in the blood-vessels in the reticular layer of the cutis and in other parts of the body, and agree in their statements that the changes consist in thickening, hyaline degeneration, fatty degeneration of the endothelium, and the formation of thrombi. Notwithstanding the fact that these changes in the vessel walls have been found in all anatomic examinations of the capillaries, the small veins, and the arteries of the ecchymosis, no clinician will, in the writer's opinion, be inclined to attribute to them a primary etiologic rôle. One who has seen a normal skin change within two days in such a manner that it resembles the skin of a leopard (compare the colored plate (Plate VII.) that represents such a case) will unquestionably deny the assumption that such lesions of blood-vessels can produce purpura hæmorrhagica.

Such an assumption is, in addition, made most improbable by the fact that the affection appears and disappears within a short time; it may break out and recede at varying intervals, and finally disappear altogether—two facts that contradict a general involvement of the vessels extending over the whole surface of the skin. It is natural that the vessels should appear congested in all the hyperemic portions of the skin after blood-extravasation by diapedesis, since diapedesis itself is the result and expression of any extensive stasis. A hyaline degeneration of the vessels can never be the cause of an acute purpura hæmor-

rhagica involving the whole body, including the mucous and serous membranes. In certain very severe and fatal cases (particularly chronic forms) of marasmus senilis, peliosis cachecticorum, and pulmonary tuberculosis, in which hemorrhages into the skin, particularly when chronic, are only a secondary and unimportant symptom of the primary disease, the writer will concede that degeneration of the vessel walls may be the cause of the hemorrhages; but he cannot, however, agree to the theory that in the mild, transitory forms of ordinary purpura such conditions obtain. In his opinion the hemorrhages here are not caused by stasis and hyaline degeneration of vessels, but by *internal causes that are at present unknown*. What rôle infection plays in this interpretation of the disease must remain doubtful until we can demonstrate to what extent the Bacillus purpuræ or some other microbe may be considered a constant finding in the blood of patients with morbus maculosus. If later experiments should demonstrate that this bacillus is constantly present, the question might arise whether the toxins and ptomains of this bacillus circulating in the blood could lead to extended stasis in the capillaries and small veins, or whether they could change the blood direct and thereby cause occlusion of capillaries. Finally, the question might arise as to whether these bacilli were capable of changing the structure of the vessel walls or of affecting the function of the muscular and nervous apparatus in such a manner that a stasis would result from a paralytic dilatation of the smallest vessels.

The writer has no doubt that the most severe cases of purpura, those terminating fatally in a short time (aptly termed purpura fulminans, of which he will give a striking example later), are of an infectious nature, and probably due to the operation of a very harmful pathogenic microbe.

The disease is not a very frequent one. The female sex, according to the majority of observers, is more disposed to it than the male; an age limit does not exist, although the disease occurs most frequently in the middle years of life; old people and infants are rarely affected. It is not true, however, that the disease is never seen before the fifth year.

Immediate causes can rarely be demonstrated. The disease seems to occur spontaneously as a primary affection, to run its course or to recur. In some cases the disease continues for many months or even years.

Moist dwellings, deficient food, cold and damp have been regarded as causes with insufficient reason; bad hygiene, improper habits of life, and unfavorable external conditions reduce the resisting powers, and in this manner produce a disposition for all diseases, naturally including the hemorrhagic diathesis. Here, too, individuals that are poorly nourished and have a poor constitution furnish the majority of sufferers from this disease, but this does not exempt the millionaire who lives in a palace and enjoys every luxury of life. The disease always occurs sporadically and in isolated cases; never, like scurvy, which is frequently

confounded with it, endemically or epidemically. In a few cases, intoxication with coal gas has been considered the cause, but undoubtedly some confusion exists here. On the other hand, it seems fairly well demonstrated that purpura may occur in convalescence from typhoid and malaria, or some time after these diseases have been cured.

Dohrn observed the case of a child suffering from purpura, born of a mother affected with the same disease during pregnancy. If confusion of this case with the hemorrhagic diathesis as a result of septic infection does not obtain, we may conclude from it that the vascular systems—that is, the blood and the vessels—of both mother and child were affected by the same deleterious substance.

In conclusion we must mention the fact that here and there severe cases of purpura have been observed following violent *nervous shocks*, terror, and fright. The case of Lebreton is instructive. He observed a purpura that terminated fatally in a young girl, the disease beginning acutely after a violent fright. In the skin large confluent hemorrhagic spots were seen. In another case of Bobrizki's morbus maculosus developed in a girl of twelve years as the direct result of a severe nervous shock (an attempt at rape); the same was observed in a second case, that of a boy of ten, who was frightened by a fire. Bobrizki believes that the nerve centers are irritated by fright and that a paralysis of the vasomotor apparatus results, this permitting an extravasation of blood by diapedesis.

[Under the head of Etiology of these purpuras may be mentioned a thought that has recently been brought out, particularly by Dr. Flexner, that some of the purpuric lesions may be due to the action upon the endothelial cells of the capillaries of some peculiar substance that may be designated as endotheliolysin, some substance having a peculiar affinity for the endothelial cells, causing their partial or complete destruction, and therefore permitting of the escape of fluid. Whether any such cytolysin is present in the blood in these particular diseases must be determined by future investigation.—Ed.]

General Disease Picture.—By the name purpura (Blutfleckenkrankheit) we understand a disease that occurs spontaneously, and is characterized by transitory hemorrhages into the external skin, the serous and mucous membranes, and even the parenchyma of the different organs.

In this place we shall discuss only those hemorrhages that occur independently either on the free surfaces of the different membranes or interstitially, and that are not the result of any general febrile disturbances; for instance, sepsis or acute inflammatory rheumatism. If these hemorrhages occur into the skin alone, the disease is called *purpura simplex;* if into the mucous membranes, the serous membranes, and the internal organs (parenchymatous hemorrhages), it is called purpura hæmorrhagica; or if involvement of the joints with swelling and pain be present, we speak of *peliosis* or *purpura rheumatica*. As we have already stated, these different forms of the disease are all due to the same cause—*i. e.*, the hemorrhagic diathesis. They have a tendency to

present different clinical pictures or to merge into one another. They all are essentially the same hemorrhagic disease, but of different degrees and intensities. The definition we have given of this disease excludes any other primary disease. Purpura simplex is the mildest form of purpura; we never know, however, whether the disease will continue in this form or will develop into the more severe forms of purpura hæmorrhagica, or whether, finally, involvement of the joints or other complications may not supervene. For this reason, if for no other, we cannot agree with some authors, who consider each form of hemorrhagic diathesis as a particular species of disease; we are more inclined to consider the whole group as a morbus maculosus that varies clinically with individual peculiarities of the patient.

The *simplest* and *mildest form* is that in which isolated blood-spots, usually assuming the form of very small petechiæ, appear in the skin as the only clinical symptom. Sometimes these occur very suddenly without any prodromal symptoms. The eruption may rarely be accompanied by gastric disturbances, lack of appetite, pressure in the region of the stomach, depression, vomiting, or a mild type of fever; it usually persists for several hours, sometimes for several days, and in exceptional cases may last for one or two weeks. The hemorrhages themselves appear as small or large, round, dark-red or bluish-red spots, their chief places of predilection being the legs and the feet; sometimes they appear on the abdomen and on the arms; usually the disease exhausts itself with a single crop. On pressure the color persists, especially in recent cases. They are distinguished from flea bites by the absence of the circumscribed circular area most always found in fresh bites. The face is usually not involved. The extensor surfaces of the extremities are more involved than the flexor surfaces. The size and shape of these cutaneous hemorrhages resemble those of petechiæ—that is, the spots are about as large as a needle prick or the head of a pin; here and there isolated larger hemorrhagic spots are seen that may attain the size of a pea. The older hemorrhages change color and go through the varying color shades of blood-pigment, from brownish red to blue, green, and yellow. After having persisted for several days they pale off and disappear; this usually terminates the disease. Occasionally a second group may appear before the first has disappeared. The patients, who are usually somewhat anemic, recover and the disease is completely cured. Occasionally a relapse occurs, sometimes several relapses, all of them assuming the mild form of the first attack.

Purpura hæmorrhagica is a more severe and more persistent form of the disease, characterized by the appearance of hemorrhages into the mucous membranes in addition to hemorrhages into the skin. This form may develop without any prodromal symptoms, and may run its course without any elevation of temperature. It is distinguished from the preceding form by the greater number and the more severe character of the hemorrhages; the whole body sometimes appears spattered with blood. In addition to punctiform hemorrhages, so-called suggillations occur that occasionally extend deep into the cutis and form hard infil-

trations. Here and there large confluent blood-spots are seen, or streaky or circular figures. Sometimes single spots will run together and form hemorrhagic areas of irregular outline; when this occurs, large areas of the skin or the whole cutaneous surface may be involved, so that only single spaces of the skin between the large areas of hemorrhagic extravasations remain free. Deep-lying, streaky hemorrhages are very characteristic, and they are frequently found in the popliteal space or on the arms and thighs. The skin over these places assumes all the colors of the rainbow.

The patients usually notice the yellowish-green or bluish-red color of their skins, and have the impression that it has been caused by a blow or fall or by pinching. Similar discolored areas are seen in scurvy, and are here also caused by deep extravasations that are undergoing the ordinary pigmentary color changes of extravasated blood. Such extravasations may be situated within the musculature, and may even form hematomata of considerable size. Fever may be completely absent; if an evening rise of temperature is observed, it is usually slight and rarely exceeds 38.5° C. More frequently this form is not accompanied by fever. Occasionally, but not always, hemorrhages into the mucous membranes occur; they are first seen in the mucous lining of the nasal cavity, and may lead to more or less severe epistaxis. Then hemorrhages are seen in the lips, the cheeks, the mucous membrane of the palate, and the gums; never, however, does loosening of the teeth occur, as in scurvy, nor is swelling, a spongy change in the gums, or ulceration observed. Occasionally severe gastric crises or violent pains in the joints are seen; the latter, however, are never swollen. The process may recur frequently and persist for a long time (six to fifteen months), so that the patient becomes very much reduced. Severe degrees of anemia with palpitation, vertigo, and fainting spells are quite frequently seen in such cases. If the disease be accompanied by fever and complicated by albuminuria, the general loss of strength proceeds more rapidly.

Different authors have distinguished a particular form of the disease called *purpura urticans*, in which wheals that may assume a hemorrhagic character are formed in the external skin. As in other forms of nettle-rash, gastric symptoms are found in this form of purpura.

The forms of purpura described so far make their appearance without any prodromal symptoms and without the appearance of any local disturbances. There are other forms, different from these, in which slight prodromal symptoms of an indistinct nature, as depression, headache, loss of appetite, precede the appearance of hemorrhagic symptoms by several days. In other cases a peculiar drawing sensation in the muscles and pains in the joints are experienced. Here slight fluctuations in the temperature may persist for several days, with painful sensations in the joints, particularly of the lower extremity. Finally the blood-disease itself makes its appearance. This leads us to that form of purpura that is called *peliosis* or *purpura rheumatica*. Schönlein deserves credit for having first recognized that a connection exists between the hemor-

rhagic diathesis and certain articular lesions. By not recognizing, however, that this connection is general, and declaring that it is found only in a limited and circumscribed form, he has delayed our correct understanding of the hemorrhagic diathesis.

Hippocrates first uses the word peliosis (ἡ πελίωσις), which signifies an extravasation of blood. As we know, this meaning has been extended by Schönlein, who called a whole group of diseases peliosis, and added the epithet "rheumatica."

According to the well-known lectures of Schönlein, published by "some of his auditors," the following symptoms are characteristic for peliosis rheumatica: "The spots are never confluent. The patients have either at some time previously suffered from rheumatism or else rheumatic symptoms appear simultaneously with the disease, such as slight, periodic, lancinating pains in the joints (in the ankles and the knee, even in the joints of the hand and the shoulder), accompanied by edematous swelling, and pain on pressure. The peculiar spots of the disease appear in the majority of cases first in the extremities, particularly in the lower, and extend only as far as the knee. The spots are small, no larger than a lentil or a millet seed, bright red in color, do not extend above the level of the skin, and gradually assume a dirty-brown color and desquamate. The eruption occurs in batches and may persist for several weeks. Each rise in temperature is followed by a new crop. The disease is usually accompanied by fever of a remittent type. This disease has been confounded with morbus maculosus Werlhofii, from which it differs in the following respects: The absence of so-called 'purpitäten' [purpuric] symptoms in the mouth, which is usually free from all lesions; the absence of all hemorrhages; the character of the eruption which is limited to the extremities, and appears there first, never assumes the size of the eruption in morbus maculosus, is never confluent, and is bright red in color; the lesions of the joints that are absent in the other disease, and the lack of nervous symptoms, the great depression, and the loss of strength.

"The disease is found in individuals with a tender, vulnerable skin, who have either at one time been sufferers from rheumatism or who are suffering from rheumatic arthritis, in addition to presenting the symptoms of peliosis. Both affections may be considered as the result of catching cold." So much for Schönlein.

If we omit all those cases that have been described in the literature as peliosis rheumatica which do not conform to the above description, only one case of the disease on which an autopsy was performed can be found. This case was published by Leuthold, from Traube's Clinic. The case is particularly important and merits especial attention because Traube was for a long time Schönlein's clinical assistant, and consequently knew exactly what Schönlein understood by "peliosis rheumatica."

The case, briefly, is the following:

A carpenter, thirty-nine years of age, after having lifted some heavy object came to the clinic, complaining of sensitiveness in the joints,

edema of the feet, and a crop of small dark-red spots; the latter were about as large as pinheads or lentils, and were on the dorsum of each foot, did not protrude above the level of the skin, and did not disappear on pressure. The malleoli and all the articulations of the foot were extremely sensitive to pressure; these areas, too, were covered with spots. Soon a rise of temperature occurred, followed in a few days by a distinct swelling of the right knee joint. In the following night violent pain in the joints appeared, accompanied by a second eruption of petechiæ, in particularly large numbers, on the arms and legs, also in groups or isolated on all parts of the body excepting the thorax and the face. In addition, edema of the hands and a redness of the joints of the fingers developed; in these areas large extravasations of blood occurred, so that the skin was raised and assumed the shape of tensely distended vesicles that seemed filled to bursting. This eruption was followed by a new crop of petechiæ and a swelling of the left knee joint. A part of the petechiæ now began to pale and disappear; at the same time new batches of hemorrhagic spots followed, accompained by the recedence of the joint swelling. The fever during this time assumed a partly continuous, partly intermittent type; albuminuria of considerable degree existed.

The writer will only mention the autopsy findings in regard to the diseased joints: In the right knee joint a large quantity of a colorless, tough, stringy, semifluid substance is found; the cavity of the joint is somewhat dilated, the synovial membrane is pale, only here and there small brownish flecks confined to the upper part; the fatty portions are injected, the semilunar cartilages are of normal translucence and tinged with yellow near their margins. In the left knee joint also there is a large quantity of synovial fluid, and in the tissues surrounding the patella a spongy condition with slight edema and an injection of the vessels; under the tendon of the extensors recent and old brownish extravasations are seen. (Compare the section on Pathologic Anatomy.)

"The pathologic findings in this obscure process that Schönlein has described under the name of peliosis rheumatica are not different in any respect from the changes found on autopsy in the joints of acute articular rheumatism." The significant remark is also made that "these lesions are not very different from the findings in gonorrheal rheumatism."

A patient, following an attack of gonorrhea, contracted typhoid fever, and died at the beginning of the eighth day. The autopsy report reads as follows: "The right knee appeared somewhat thicker than the left. In the external parts very little abnormality is visible. In the interior parts, however, there is a very marked, fine, dark-red injection of the crucial ligaments and of the whole capsule of the joint. In addition a gelatinous swelling, which is greatest in the region of the patella. The articular and semilunar cartilages show no abnormalities. The fluid within the joint is small in quantity, viscid, and darker than normal."

"General rheumatism and gonorrheal rheumatism seem to resemble each other also in regard to their sequelæ; this is made probable by the discovery of an endocarditis that followed an attack of rheumatism, which in its turn was the result of a long-lasting gonorrhea. The two former lesions must therefore be considered dependent on the latter one." [It is now well recognized that an endocarditis, as well as the more frequently seen arthritis, may be caused by the gonococcus. These cases have nothing whatever to do with true rheumatism.—ED.]

So much for the facts. We must let each individual investigator decide whether he wishes to believe in the existence of the disease picture described and designated by Schönlein as peliosis rheumatica. Everyone, however, will agree that if we accept the name given by Schönlein, we shall have to designate with this name that condition only which he intended to have designated in this manner; in reality, however, we find the term given to a variety of diseases in nowise resembling the disease picture delineated by Schönlein. The writer need only refer to the well-known cases of v. Bamberger. The author begins his description with the following words: "So-called peliosis rheumatica of the lower extremities is occasionally seen in Bright's disease. I find a record of 5 such cases among my own material. In the majority of these cases the purpuric spots persisted unchanged for several months. It is not clear what connection exists between these two conditions, and I shall refrain from generalities. Only 2 cases went to autopsy." The writer would like briefly to sketch these cases:

CASE I.—A man of thirty-nine, previously healthy, came to the clinic for painful hemorrhagic spots that had appeared on the lower extremities. After a few days edema occurred; albumin was found in the urine; pleuritis finally supervened, and the patient died. On autopsy hemorrhages in the skin, the mucous lining of the stomach, and in the kidneys were found.

CASE II.—A woman of thirty-six suffered from stenosis of the mitral valve and congestion of the liver, in addition to the ordinary manifestations of Bright's disease. The purpuric spots in the lower extremities had existed for over a year. Death occurred from apoplexy. Autopsy: fresh hemorrhagic focus in the brain, stenosis of the mitral valve, wedge-shaped infarct of the spleen, pneumonia, and chronic nephritis.

These cases do not resemble in the slightest degree the disease picture of Schönlein, but were simple cases of chronic nephritis with purpuric spots; the latter were undoubtedly the result of a hemorrhagic diathesis due to the cachexia (peliosis cachecticorum). v. Bamberger employs the word peliosis as synonymous with purpura, and he is certainly not justified in speaking of the rheumatic form, since he does not mention any involvement of the joints. If he be seeking for an etiologic connection between all the symptoms, he need only consider the great loss of albumin, the cachexia, and the hemorrhagic diathesis resulting therefrom. The writer has frequently observed cases like those described by v. Bamberger. He mentions v. Bamberger's descriptions chiefly that he may show how, within a relatively short time after Schönlein's

dissertations, even so eminent a clinician could so confuse the original picture that practically nothing remains of it but a certain form of cutaneous hemorrhage. A perusal of the literature on the subject shows that these hemorrhages have always been considered the main symptoms of the affection.

In looking through much that has been written on this subject we are impressed by the fact that it was most arbitrary to isolate one of the many forms of purpura that run their course complicated by joint affections, and to designate it as a particular disease. The more material is gathered, the more it becomes clear that joint lesions of all kinds may occur in any hemorrhagic disease. Shortly after Schönlein, nearly all cases were described as peliosis rheumatica in which the two symptoms, skin hemorrhages and joint lesions, were found. Such descriptions were not criticized at the time; moreover, wherever a case did not coincide with Schönlein's picture, a peliosis "with atypical course" was constructed. Thus it came about that neither a distinct form of hemorrhage nor of joint affection was reserved for this disease, and that no attention whatever was paid to the etiology of these two lesions. Finally, owing to this lack of critical discussion, cases of ulcerative endocarditis with purulent inflammations of the joints and multiple hemorrhages of the skin and the internal organs were included in the same category, and the hemorrhages in Schönlein's disease attributed to embolism.

But aside from these enormous errors and this great lack of critical review, we encounter almost at every step numerous cases in the literature that have been described as peliosis rheumatica, but have nothing in common with it save the association of hemorrhages and joint lesions. Little attention was paid to any definite kind of hemorrhage, so that instead of isolated non-confluent petechiæ as large as lentils and limited to the lower extremity, according to Schönlein, we find in their place every form of cutaneous hemorrhage, of hemorrhage into mucous membranes and into internal organs. If we attempt to find our way through this labyrinth of disease pictures that have been described under the same name, we encounter simple purpura, purpura hæmorrhagica, purpura urticans, morbus maculosus, scurvy, peliosis rheumatica, and finally erythema nodosum. In all these forms of cutaneous hemorrhages, to which the writer might add hemophilia, joint lesions occur as an occasional complication. The writer will discuss this point at some length below when describing the special symptomatology. In view of all this, etiology furnishes the only important factor in determining the nature of this condition. The seat, the size, or the confluence of the hemorrhages; or the involvement of the mucous membranes, serous linings, or internal organs; and, finally, the sequelæ of these individual symptoms have no bearing on the nature and the character of the disease.

The etiology of the disease, as already mentioned, must be sought for in those changes of the blood that we have designated as the hemorrhagic diathesis. Patients, as a rule, have pale, delicate skins, showing a tendency to bleed on slightest provocation; and show the well-

known symptoms of chlorosis and anemia. It is probably due to this vulnerability of the skin and to its sensitiveness to temperature changes that such individuals are more frequently affected than others by rheumatoid diseases.

It seems altogether arbitrary to isolate a single group out of all this complex of diseases etiologically related because this one group happens to show a slightly different localization of the petechiæ. In looking over the splendid publication of Scheby-Buch, who has carefully collated the clinical material at the Hamburg Hospital during forty years, many cases will be found corresponding exactly to the description of Schönlein's, except that the hemorrhages varied slightly in form and were also found on the mucous membranes. What right have we to designate the one as peliosis rheumatica, and not the other? The writer has a large mass of anamneses collected with the purpose of finding some relation between hemorrhagic diseases and lesions of the joints. This question has always interested him greatly. He will recur to the result of this study later on. In this place he simply wishes to endorse Scheby-Buch's opinion, the result of careful study. "The history of peliosis rheumatica alone would be enough to demonstrate the fallacy of declaring it as a special disease even if we had no valid reasons why such a distinction should not be made."

No one would think of calling a case of scurvy with lesions of the joints peliosis rheumatica; but we know of certain well-observed cases of purpura hæmorrhagica with joint lesions that one investigator designates as peliosis rheumatica, another as articular rheumatism with hemorrhages. French and English authors particularly offend in classifying cases of the hemorrhagic diathesis with joint lesions as "acute articular rheumatism with atypical course," thus constructing a new disease picture. This example shows us the danger of disregarding the etiologic bases and formulating diagnoses upon a few objective symptoms. It seems to the writer that a peculiar lack of critical judgment must exist in those who misinterpret the relationship of the different symptoms, for instance, in so well characterized a disease as scurvy; in the cases mentioned last, however, it is slightly different. If the skin lesions are more apparent, some will call the disease purpura or peliosis rheumatica; if the joint lesions are more conspicuous, others will call it rheumarthritis, without, however, remembering that the former picture does not resemble Schönlein's description, and that in acute articular rheumatism hemorrhages into the skin never occur unless certain severe complications coexist.

Whoever has seen a large number of cases of acute articular rheumatism will not readily confound the disease with any other affection; he will also know that it has nothing to do *per se* with the hemorrhages into the skin. In addition, he will observe a tendency to secondary inflammations of the serous membranes and the endocardium, which has never, or only exceptionally, been seen in pure forms of peliosis and of the hemorrhagic diathesis. Further, the latter is never accompanied by the severe prodromal attacks of perspiration and the severe

Number.	Etiology.	Heart.	Skin.	Kidneys.	Other symptoms.
1.	Acute articular rheumatism.	Chronic valvular lesions and recent endocarditis.	Repeated attacks of recurring purpura hæmorrhagica.	Paroxysmal hematuria. Autopsy: large white kidney and recent hemorrhagic nephritis.	Hemorrhagic infarcts of the lungs. Severe anemia as a result of copious loss of blood through the kidneys.
2.	Acute articular rheumatism.	Recent endocarditis and purulent pericarditis.	Numerous hemorrhages recurring over the whole cutaneous surface.	Intact.	Autopsy: verrucous form of mitral endocarditis.
3.	Acute articular rheumatism.	Chronic valvular lesions with fresh endocarditis.	Numerous recurrent hemorrhages of the skin. Skin appears as though spattered with a brush dipped in blood.	Repeated attacks of hematuria. Large white kidney with recent hemorrhagic nephritis.	Numerous retinal hemorrhages. Autopsy: recent mycotic endocarditis and chronic mitral endocarditis.
4.	Acute articular rheumatism in the third month of pregnancy.	Old aortic insufficiency and recent endocarditis.	Skin appears as though spattered with blood.	Intact.	Retinal hemorrhages.
5.	Acute articular rheumatism. Relapses with chorea minor.	Chronic recurring and recent endocarditis.	Skin appears as though spattered with blood.	Intact.	Autopsy: recent mitral and aortic endocarditis.
6.	Acute articular rheumatism.	Fresh endocarditis.	Repeated crops of hemorrhages into the skin.	Intact.	Cyanotic induration of the spleen and kidneys; chorea.
7.	Acute articular rheumatism.	Chronic and recent endocarditis.	Petechiæ scattered over the whole body in patches.	Intact.	Diabetes mellitus. Autopsy: mycotic endocarditis.
8.	Acute articular rheumatism with chorea.	Chronic and recent endocarditis.	Petechiæ scattered over the whole body in patches.	Intact.	Autopsy: hemorrhagic infarcts of the lungs; chorea minor; endocarditis mycotica.
9.	Acute articular rheumatism during the puerperium.	Recent mycotic endocarditis.	Petechiæ scattered over the whole body in patches.	Intact.	Retinal hemorrhages.
10.	Acute articular rheumatism.	Mycotic endocarditis.	Petechiæ scattered over the whole body in patches.	Repeated renal hemorrhages; large white kidney with recent hemorrhagic nephritis.	Retinal hemorrhages.

symptoms in the joints which are found in articular rheumatism. In those cases, on the other hand, in which hemorrhages of the skin and internal hemorrhages, particularly of the retina, occur in acute articular rheumatism, they are always due to a complicating endocarditis. The writer has emphasized this expressly in his monograph on septic diseases. Such cases must be strictly distinguished from those that run a similar course, and in which a bacterial endocarditis exists side by side with purulent inflammations of the joints and numerous petechiæ distributed all over the skin, and with hemorrhages into the retina. The cardinal difference between these two groups consists in the following: In the first instance acute articular rheumatism is the primary manifestation, and is the causative factor of the other complications; in the

second case some wound infection (for instance, diphtheria of the placental site, etc.), or internal suppuration (such as suppurating thrombophlebitis of the pelvic veins following abortion, or of the spermatic veins following gonorrhea) is the primary cause of all the lesions. In the writer's pamphlet on septic diseases quoted above he has mentioned a great number of cases of both series. He would like to mention a few examples of the first group (see table, p. 764).

It would have been possible to increase this number of cases by a great many other examples; these, however, are so similar to those communicated that it would be superfluous. It is evident that, notwithstanding the occurrence of hemorrhages into the skin, which may be so extended that the body seems to be spattered with blood, a resemblance with peliosis rheumatica does not exist.

The writer thinks he has demonstrated that Schönlein's disease picture of peliosis rheumatica has "*no raison d'être*," but that it is essentially a form of the hemorrhagic diathesis complicated by joint lesions. He will, however, emphasize the fact that cases are seen which run the same course as the one described by Schönlein, with this difference, that a definite etiologic cause can be found—namely, gonorrhea. His reason for employing the term peliosis gonorrhœica in his exhaustive work on this subject, to which he wishes to refer in this place, was to teach his colleagues by this term exactly what he wishes to convey by it. At the same time he did not discuss those forms of rheumatic purpura caused by gonorrhea.

In general, Schönlein's description of the lighter forms of rheumatic purpura is correct. We shall elaborate on this when describing Henoch's purpura, so-called. As soon as the blood-spots appear the pains in the joints seem to grow less; occasionally vesicles appear in addition to the purpura spots; also edema of the dorsum of the feet and the ankles. The disease may terminate within a few weeks; recurrences may sometimes be seen, manifesting themselves by renewed pain in the joint and more purpuric spots. There are cases that drag along in this manner for months, even for a year and a half to two years or more. Fever may be present or absent; the more violent the affection of the joints, the higher, as a rule, the evening temperature. In very severe cases, in which the disease picture may resemble acute articular rheumatism, we find long-lasting fever curves of a remittent character. The disease is differentiated from typical inflammatory rheumatism proper by the absence both of profuse sweating and the tendency to endocardial complications. Sometimes the occurrence of hemorrhages into the skin, if the attack be the first, may be attributed to this endocarditis. On the other hand, although rarely, the character of the diseased joints in severe cases of rheumatic purpura may resemble that of genuine acute articular rheumatism; in fact, these two forms of arthritis may be so similar that they cannot be distinguished. In one well-known case from Traube's Clinic, which terminated fatally, Leuthold states that the findings in the joints were different in no respect from the changes found on autopsy in the joints in articular

rheumatism. The writer knows of no instance, however, in which a purulent fluid was found in the joint cavities during purpura rheumatica. If the disease persist for a long time, anemic symptoms appear, anemic heart murmurs among others. The spleen is frequently enlarged.

Hemorrhages into the mucous membranes are usually absent; yet Kaposi in one case found hematuria, and in another, formation of ecchymoses, followed by gangrene of the mucous membrane of the palate. This patient died. Duhring describes bloody discharges from the genitals. These cases resemble *Henoch's* form of *purpura* that will now be described.

This form of purpura was described by the above-named author in 1868 as a complicated form of purpura, in which a series of abdominal symptoms are superadded to the purpuric eruption and joint symptoms. He particularly mentions vomiting, bloody stools, and colic. Henoch states that a spasmodic recurrence of the different disease symptoms is characteristic; they may appear with interposed intervals of several weeks, or even, as in one case, of a whole year. In the older literature on purpura, with the exception of one case described by Willan, no definite description of the disease under discussion, in combination with lesions of the joints and violent abdominal symptoms, is found. We consider this disease, like the other purpuras, as merely a more severe manifestation of the same transitory hemorrhagic diathesis; the latter has the same pathogenesis in all cases.

In presenting the details of this disease picture the writer follows the description given in a short paper by v. Dusch and Hoche, that appeared in the *Festschrift*, published in honor of Henoch's seventieth birthday.

The disease is found particularly in young individuals. In very young children, from the first to the third year, and in older people over forty-six, no case has so far been described; after the third year the number of cases gradually increases, reaching its maximum between the ninth and the twelfth years. The frequency with which the disease is encountered remains the same up to the twenty-fourth year; beyond this age it is quite rare.

Males are more frequently affected than females; of 40 patients in whom the sex is given, 33 were men and 7 women. These statements in regard to age and sex differ considerably from those of other authors. In regard to the sex, the writer has himself observed a conspicuous prevalence among the males.

Bad hygiene, moist dwellings, insufficient nourishment, and a previous attack of inflammatory rheumatism seem to predispose to the disease. On the other hand, among the cases quoted patients are found who are well situated. It is necessary to emphasize this, because many authors still consider purpura as an expression of a certain cachexia.

The disease begins with more or less marked disturbances of the general health—headache, depression, lack of appetite, etc.—followed by rheumatoid pains in different parts of the body—that is, by sensations that cannot be exactly localized, that are drawing or tearing in character; these latter are chiefly manifested in the lower extremities

and the back; sometimes a transitory edematous swelling of the affected regions may be seen. Many of the patients have to remain in bed even at this period; others pursue their usual occupations. Soon, however, violent pains in one or more joints appear without any external manifestations; sometimes one or the other joint begins to swell, the skin over it becomes reddened and feels hot, edematous infiltration is seen in the neighboring tissues exactly as in acute articular rheumatism. In this stage mild fever may sometimes be observed; the temperature may reach 38.5° C., but rarely at this stage or later goes beyond.

As a rule, the pain and the inability to move the joints induce the patient to consult a physician. Sometimes the physician will discover isolated purpuric spots that had appeared without causing any subjective symptoms, excepting possibly a slight itching, particularly if the eruption begins as a slight urticaria. Generally a period of several days intervenes between the appearance of the pains in the joints and the beginning of the first eruption of purpura.

The purpuric spots themselves are usually light red and small in the beginning, distributed irregularly, singly or in groups, and usually become confluent; in this manner large irregular spots are formed, soon undergoing the usual color changes from bluish to yellow or dark brown. They gradually extend from the legs, where they usually, although not always, begin, to the thighs, nates, and genitals; they may extend by continuity or may skip certain areas. Other eruptions appear on both the arms and the body, so that occasionally the whole body, particularly near the large joints, is covered with purpuric spots.

These hemorrhagic points cause more anxiety than annoyance; soon, however, other symptoms appear that are most disagreeable, particularly the disturbances in the intestinal tract; these are exceedingly obstinate and seem to progress uninfluenced by any treatment.

The patients complain of violent colicky pains in the abdomen, situated chiefly in the region of the umbilicus, which may be so severe that the patient doubles up and groans with the suffering. The abdomen is retracted and diffusely sensitive. In the beginning of the attack there is constipation. The disturbances are aggravated by violent vomiting; at first food is vomited, later yellowish-green masses mixed with bile or blood. The pulse becomes small and rapid, the facial expression is one of anxiety, and the whole condition becomes pitiable.

The constipation existing in the beginning is soon followed by a more or less copious evacuation of thin yellowish stools that may be mixed with blood; this frequently terminates the attacks of pain. Colic and vomiting may persist for days; the taking of food is difficult, and sometimes the patients refuse food absolutely. Now and then, probably as a result of the violent movements during vomiting, epistaxis occurs. Gradually all the symptoms decrease in severity; first the vomiting, then the abdominal pain, lastly the thin evacuations; though these may in some instances persist even after the patient's general condition is much improved.

In the meantime the pain in the joints has disappeared and the pur-

puric spots have peeled off, and the patient, provided that none of the complications to be discussed below has occurred, feels comparatively well. Naturally the patient is somewhat exhausted, but he thinks that he is progressing toward recovery.

Sometimes only one attack occurs and convalescence progresses nicely. In the majority of cases, however, the symptoms occur at intervals varying from one day to several weeks, each attack being similar to the one preceding. Finally cure, or in comparatively rare cases death, occurs.

As a rule, the disease does not run such a diagrammatic course; in children it is occasionally seen in this typical form. It will be seen how many deviations and peculiarities of the course may exist when we discuss the different symptoms individually. We will speak of these under the heading of Special Symptomatology (p. 776). In this place we will limit ourselves to some final remarks on this form of the disease.

Among the *atypical forms* we must mention the rare cases in which affections of the joints were completely absent, and in which violent intestinal symptoms were seen in addition to the purpura. The duration of Henoch's purpura varies within wide boundaries, from seven days to nine months; the average duration being from six to twelve weeks.

In children the prognosis is favorable; among 19 cases, death occurred only once, as the result of an acute nephritis. In adults the prognosis is less favorable; 5 out of 22 cases terminated fatally. These small figures do not permit the formation of a definite conclusion.

It remains to discuss one particular manifestation of the disease which was also described by Henoch, in the year 1887, under the name of *purpura fulminans*. The writer saw such a case in the year 1878, observed it very carefully, and described it in 1881, without, however, having given it this very well-chosen name. In all these cases extended hemorrhages occurred into the skin, rapidly leading to death. Henoch saw 3 such cases; Charron, in Brussels, the fourth case, in 1886.

All these cases have in common the absence of hemorrhages from the mucous membrane; they are characterized by the enormous rapidity with which extended ecchymoses occur within a few hours; all the extremities may be colored blue or blackish red; the skin may be hard from infiltrations with blood. In 2 cases vesicles occurred on the skin that were filled with a serosanguinolent fluid. Gangrene has never been observed, nor even a fetid odor. The course is variable; as a rule, death occurs within twenty-four hours after the appearance of the first hemorrhagic spots; the longest duration recorded was four days. Complications were invariably absent; autopsy showed nothing but the signs of anemia. Nowhere could a trace of embolic or thrombotic processes be seen. One of Henoch's cases developed two days after the crisis of a pneumonia; another a week and a half after a mild attack of scarlatina. In the 2 other cases and in the writer's own no etiologic clue is given. Since this time Ström and Arctander have published 2 analogous cases; 1 of these also was a sequel of scarlatina. No

autopsy was made. According to Hervé, Guelliot published 3 similar cases in 1888.

Before communicating his own case, the writer would like to briefly describe one of Henoch's cases:

A boy of five years; crisis of pneumonia on the 22d of November. Since then has felt well. In the night of the 24th sudden pain in the left leg. Toward morning purpuric spots on the chest and thighs; an hour later, on the arms and legs. At 11 o'clock in the morning the whole lower and lateral aspects of the left thigh were bluish black; toward evening the left calf and the right knee also. Temperature 38.8° C. Nothing abnormal in any organ. In the night from the 24th to the 25th the whole right leg, excepting the foot, had turned blackish blue. Great apathy and weakness. Urine normal. At 2 o'clock in the morning death occurred from collapse. Autopsy absolutely negative.

The writer's own case was that of a tinsmith, aged twenty-eight, who entered the hospital on the 23d of March, 1878, and died on the 25th. He was brought to Frerich's Clinic in an unconscious condition. No complete anamnesis could be obtained from the patient or from any of his relatives. It was ascertained, however, that he had been perfectly healthy and was attending to his business within two days before his seizure. The disease began on the morning of the 21st with a violent chill that forced the patient to stay in bed. The physician summoned in the night found the patient with a high fever and ordered his transfer to the hospital. A diagnosis of typhoid was made.

March 23d, 9 o'clock: The patient, a very muscular subject, with large bones, is unconscious, muttering to himself, beating about with trembling hands and tossing to and fro in bed. The face appears swollen, very cyanotic, and feels icy cold. The middle of the upper lip protrudes like a trunk; this prominence of the lip is produced by a bloody suffusion of the mucous membrane, beginning at the margin of the lips and reaching posteriorly nearly to the gums. This suffusion is nearly 2 cm. wide. The mucous lining of the lip is eroded at this place and covered with thick crusts which, when removed, exposed the base of a superficial ulcer, very much discolored. The mucous membranes around the margins of this ulcer are rolled up and separated into shreds. The gums are bluish red, swollen, and in part infiltrated with blood. The lips are covered with sordes. Bloody vomit is forced out between the lips. No changes are seen in the superior maxilla nor in the teeth. The pupils on both sides are very much contracted, equal, and react sluggishly to light. On the conjunctivæ of both sides round hemorrhages are seen as large as millet grains, and some that are more extended. The skin is smooth and dry and yellowish in color, here and there mottled by a great number of pale- to dark-violet irregular hemorrhagic areas, appearing either as very small dots or as suffusions extending over larger surfaces. In some places these spots disappear on pressure; in others they persist. Aside from these spots the skin looks peculiar, presenting a marbled appearance, owing to the unequal filling of the cutaneous vessels with blood.

In the lower extremities are found very large suffusions and hemorrhages several inches in diameter which give the impression of having been caused by trauma. On the external surfaces of the thighs they are symmetrically distributed; also on the back. In the region of the ankles and the dorsa of the feet large reddish-blue suffusions as large as a dollar are found. On the right leg and the dorsum of the left foot are found several ulcers as large as mark pieces [quarters], dry, and covered with black scabs. The feet and the hands are icy cold, like the face. The sensorium is benumbed. Deep punctures with a needle produce no reaction. The pulse is small, undulating, 112 beats to the minute. Apex beat cannot be felt. Heart dulness not increased. Heart sounds clear. Nothing abnormal in the lungs. The spleen, moderately enlarged, extends 3 cm. beyond the anterior axillary line. In the retina the arteries are narrowed and the veins dilated. The papillary boundaries diffuse. No hemorrhage into the retina. Temperature 41.6° C.

Eight o'clock in the evening: The patient is lying on his back with his eyes closed, unconscious, and groaning. The respiration is increased to 32 to the minute; he is snoring. The patient throws both arms to and fro without interruption. The muscles are greatly contracted. Both corneæ are anesthetic.

Half-past eleven o'clock at night: Unconsciousness complete. The face is covered with perspiration, feels cool; the skin otherwise is dry and burning hot. Temperature 42° C. On the left thigh is found a single suggillation, bluish red in color and covering an area as large as two hands. This spot originated from the confluence of a number of smaller foci. When I saw the patient about three hours before, these individual foci were still separated by large areas of healthy skin. Since 8 o'clock several recent light hemorrhages, one of them as large as a dollar, have appeared. The respiration is exceedingly rapid, loud, and snoring; the pulse very small and soft, 120 to the minute. On the right side is a paresis involving the face and the extremities. Ptosis of the right eyelid. No hemorrhages in the retina. Sedes insciæ. Urine acid, containing very much albumin and numerous broad casts.

March 24th, 9 o'clock in the morning: Very little change in the disease picture. Sensorium completely benumbed. Temperature 41.6° C. Numerous new hemorrhages in the skin.

In order to record the picture presented by the skin, I had an artist (Mr. Eyrich) paint the case in water colors. This gentleman began his work on the morning of the 24th, at a time when the hemorrhages were so close together that the single foci, particularly on the arms, had assumed a different shape from that observed when I saw them before. The artist could not draw outlines of the different spots owing to the fact that some of the spots right before his eyes ran together and became markedly larger. As this symptom seemed very peculiar to Mr. Eyrich, he sent for me at once, so that I was enabled to verify his observation, and actually saw a running together and enlargement of these individual spots. What made these hemorrhages particularly unique was the fact that the larger were grouped in concentric rings, and that each of these rings had a different color. This was caused probably by the great rapidity with which the individual spots originated and enlarged. The older center in this way appeared much darker than the more recent peripheral areas. I could observe this phenomenon in different locations. A fresh light-red hemorrhage about as large as a dime would appear; in a short time this would turn dark brownish red, and at the same time around it would develop a new circular hemorrhage that seemed to enclose the first with a band of light-red color. Gradually the color of the center became darker, ultimately violet or black; then the surrounding hemorrhagic ring would turn dark brown, and if a further extension of this focus occurred a light-red ring would surround the whole. This development occurred with such rapidity that the change of color from very light red to the darkest brown red could be observed in the course of a few hours. I never observed hemorrhages that showed more than three such rings; I did, however, see a great number of well-marked hemorrhages with three layers on all the extremities. (Compare Plate, VII.)

Eight o'clock in the evening: Patient collapsed. Examination of the retina shows two small hemorrhages on the left side; one on the right, situated near the center.

At 12:30 in the night death occurred. The temperature post mortem showed a rise as high as 42.7° C.

The results of the autopsy were very scanty. The only important changes found were the following:

Cloudy swelling of the liver, spleen, and kidneys. White bands in the medullary substance of the kidneys. A slight deposit of very fine and almost infinitesimal growths on the free margin of the mitral valves. Multiple hemorrhages in all the serous membranes.

The mitral valves, the kidneys, and different pieces of skin were subjected to microscopic examination. A piece of skin was excised during life, stretched, and immediately put into absolute alcohol. The findings in the skin were completely negative. No emboli nor micro-organisms were found within the vessels; on the other hand, numbers of streptococci were found in the glomeruli and the intertubular capillaries of the kidneys and in the small deposits on the mitral valves.

That the diagnosis of this disease is not simple, and that serious diagnostic mistakes can be made, the following important case may demonstrate:

A man of thirty, who had been healthy previously, suddenly developed chills and a high fever. The occurrence of these symptoms had been preceded by pain in the lumbar region. The patient was brought to the hospital on the day on which these symptoms appeared, and transferred to Frerich's Clinic, where I treated him.

A high fever, a moderate bronchial catarrh, and a few isolated hemorrhages as large as pinheads were observed. No swelling of the spleen could be demonstrated. The patient's sensorium was slightly impaired, but he gave intelligent answers to all questions and complained particularly of pain in the lumbar region. In the course of the next two days, in which a high fever (up to 41° C.) with slight morning remissions was noticed, a very profuse hemorrhagic exanthem developed all over the body; this consisted partly of strictly circumscribed, round, light-red hemorrhages, varying in size from that of a lentil to that of a dollar, partly of large, diffuse, bluish-red suggillations. These hemorrhages were also found in the conjunctiva and in the mucous membrane of the soft palate. In the skin they were so thick that the subject seemed to be spattered with blood. In the meantime the patient became unconscious and delirious. No hemorrhages were found in the retina.

No points could be obtained from the anamnesis. It was stated that the patient had suddenly fallen sick without any premonition. It was also stated that he had complained of slight pain in the lumbar region several days before his seizure. No external injuries could be observed.

So far this disease picture resembles the one described above. On the fifth day, however, the symptoms changed, so that the diagnosis of fulminating purpura could no longer be considered. Profuse hemorrhages occurred from the kidneys, the stomach, the intestinal tract, the nose, and the lungs. Almost simultaneously blood was vomited and passed with the stools. Anatomic findings made post mortem showed that this blood was from the bowels and had not been swallowed. In addition large quantities of blood were poured from the nose, and, by coughing, from the lungs. The largest quantity of very dark-colored blood came from the kidneys. On this and the following day the patient passed 3 liters of urine that seemed to consist almost exclusively of blood. Microscopically it contained almost as many blood-corpuscles as a sample of blood taken for comparison from the patient's finger. The occurrence of these profuse hemorrhages from the different organs, of course, produced a considerable anemia. Soon peculiar distinctly indented pustules appeared on the cheeks and the abdomen, which soon disintegrated and left discolored ulcers. The appearance of this eruption clinched the diagnosis of variola hæmorrhagica.

On autopsy the endocardium was found normal. Hemorrhagic infiltration was seen in the mucous lining of the stomach and intestine; bronchitis, with bloody exudate from the mucous lining of the bronchi, and an enormous hemorrhagic infiltration of the pelves of both kidneys. The spleen was hardly enlarged.

The diagnosis of *hemorrhagic small-pox* may be very difficult owing precisely to the resemblance of this disease picture to fulminating purpura, particularly if the disease runs its course without the formation of pustules and occurs at a time in which no epidemic of small-pox exists (as in our case). In addition profuse hemorrhages into the skin, developing just as rapidly as in the above cases, may occur in the course of severe septic diseases and of acute leukemia.

We must add to the forms of the hemorrhagic diatheses which we have described one other disease that has lately commanded a great deal of interest. Möller described it in 1857 as "acute rachitis." *Barlow*, in 1883, paid particular attention to it, and since that time it has been given his name. Children from six months to three years old are exclusively afflicted with it. It often begins acutely; but not always. After a few days of general discomfort, sensitiveness of one or both of

the lower extremities develops, their motility seems to be impaired, and they are painful and seem to hurt when touched. Children thus afflicted usually lie in bed without moving or stretching their lower extremities. All active or passive motions seem to be painful. Soon a spindle-shaped, smooth, sensitive, soft swelling of an elastic consistence is found over the diaphysis of one or both thighs, less frequently of the leg or of one of the upper extremities. Occasionally crepitation, caused by a loosening of the epiphysis, can be elicited at the epiphyseal boundary.

These deep subperiosteal or subperichondral swellings on the long bones are the pathognomonic peculiarity of this disease. In addition rachitic and scorbutic symptoms appear, but are insignificant as compared with these other manifestations. Pus has never been found underneath the periosteum of the affected bones, either clinically, by puncture or incision, or post mortem. Pure blood is always present. No example is known of the involvement of the capsule of a joint, notwithstanding the fact that these tissues are in such close proximity to the lesion.

To these symptoms are frequently, though not always, added the symptoms of the hemorrhagic diathesis—that is, of scurvy or rachitis. A great tendency to perspire, particularly manifest in the back of the head, must be attributed to the presence of the rachitic complication. Another symptom of rachitis is a puffing of the epiphysis. Scurvy manifests itself by a spongy loosening and puffing of the gums, with fetor and a tendency to hemorrhage, particularly where teeth are already present. Fever and gastric symptoms are frequent. Occasionally purpuric hemorrhages into the mucous membranes, and albuminuria are seen. Henoch mentions hemorrhages under the periosteum and the frontal bone and into the eyelids and the retrobulbar tissues, with exophthalmos. The children look anemic, but rarely die from hemorrhages or other complications. (For a fuller discussion of Barlow's disease see p. 715.)

Pathologic Anatomy.—Cases of uncomplicated purpura rarely terminate fatally. If death occur, it is usually the result of the great anemia following profuse hemorrhages, of complications, or of sequelæ. Autopsy reports are very scanty. Corresponding to the anemia that existed during life, the bodies look exceedingly pale, usually somewhat bloated, and are covered, as a rule, with numerous hemorrhagic efflorescences of that livid color assumed by altered blood-pigment. The musculature and the adipose tissue in the majority of the cases are unchanged. Only after very protracted attacks do we find a decrease in the latter. Depending on the intensity of the disease, we find more or less profuse hemorrhages in the mucous and serous membranes, that sometimes assume considerable dimensions; sometimes these are distributed over large areas in the mucous membranes of the bronchi, the digestive tract (pharynx, esophagus, stomach, intestine), in the pelvis of the kidneys, the ureters, the bladder, etc. Occasionally it will be found that the mucous membrane is eroded beneath the dried blood-crusts that cover it. Fresh blood is occasionally seen in the bronchi, together with bloody mucus, as also occasionally in the pelvis of the kidneys

and in the intestinal canal. In the serous cavities, the pericardium, the pleural, and the peritoneal cavities, as well as in the joints, small ecchymoses are found, and occasionally larger exudates of a purely hemorrhagic character, constituting hemopericardium, hemothorax, hemarthrosis, etc. In addition parenchymatous hemorrhages, particularly into the liver and kidneys, are observed. Occasionally the suprarenals contain hemorrhagic infarcts. The spleen has been found enlarged in a number of cases, but not in all; and it, too, occasionally contains wedge-shaped hemorrhagic infarcts. In protracted cases that ran their course with fever, cloudy swelling of the large parenchymatous glands and swelling of Peyer's patches and the mesenteric glands has been observed.

Extravasations of blood have further been seen in the bone marrow, the endocardium, the intima of the vessels, and in the neurilemma. Ponfick, in an accurately described case, found the former filled with large and small hemorrhages. Hindelang found pigmentary infiltration in the lymph glands, the connective tissue of the liver, as well as in other organs; the pigment probably derived from disintegration of extravasated erythrocytes, had assumed the shape of flaky masses. Chemically, it was found by Kundel to consist of hydrated oxid of iron.

No other constant changes are known; exact reports on the lesions of the membranes of the joints and cavities, particularly in those cases in which rheumatoid pains existed during life, are practically non-procurable. The joints of the knee and of the foot are most frequently involved in those forms of purpura complicated by joint affections. For the present we must content ourselves with establishing this fact, and must patiently await what autopsy findings in these lighter forms of hemorrhagic diseases will teach us. Our present knowledge of this subject is based on a single report of a case of peliosis rheumatica that terminated fatally; this case was from Traube's Clinic, and contains much important information. The autopsy findings were not greatly different from those of acute inflammatory rheumatism or gonorrheal arthritis. The autopsy report reads as follows: "The right knee appears a little thicker than the left. On the external parts nothing abnormal is found; in the interior, however, a very profuse, fine, dark-red injection of the crucial ligaments and of the whole capsule is seen; in addition a gelatinous swelling of these parts, most strongly marked about the patella. No abnormalities in the articular or the semilunar cartilages. Fluid within the joint is scanty, viscid, and darker than normal."

No constant changes have been found about the heart, not even changes that could be attributed to the anemia; the valvular apparatus was always intact. In the case of fulminating purpura that the writer has described a few very minute warty growths were found on the free margins of the mitral segments—no more than may be found in a variety of acute diseases; but even these deposits have never been described in any other case. In the cavities of the heart a little loosely coagulated blood was found.

The writer will recur later to the changes in the blood and its constituents; he will only briefly mention here that some authors have found the coagulability of the blood reduced. This statement remains to be verified.

The spleen and the lymph glands show no constant changes, though the former organ has repeatedly been found to be enlarged and its pulp of a gruelly consistence (Billroth).

The kidneys have been seen in a state of hemorrhagic inflammation; and in those cases where chronic albuminuria existed during life, isolated foci of infiltration have been demonstrated within the cortex. No pathologic significance can be attributed to this.

Hemorrhages into the retina and choroid have been seen, both ophthalmoscopically and post mortem. In other cases meningeal and cerebral hemorrhages have been found, the cause of epileptiform attacks and of paralyses that occurred during life.

The writer has already reported at great length on the changes of the vessels in the neighborhood of the ecchymoses. Under Etiology he has mentioned particularly the investigations of v. Kogerer, Riehl, and Leloir. Hayem mentions that thrombosis of the finer arteries had occurred from agglutination of leukocytes; other authors mention amyloid degeneration of capillaries in the vicinity of the petechiæ. Stroganow, whose investigations have also been mentioned, discovered infiltrations of the intima in the aorta, the vena cava, and the hepatic veins; he saw red blood-corpuscles in these areas that seemed to have penetrated the intima from the lumen of the vessel by direct diapedesis.

The following complications may occasionally lead to death: Large extravasations into the pleura or abdominal cavities, infarcts of the lung, purulent peritonitis, croupous diphtheric processes of the small intestine, pneumonia, necrosis of the intestine, peritonitis from perforation, gangrene of the colon with swelling of the mesenteric glands, and ecchymoses and ulcers of the descending colon.

In addition to the bacteriologic findings described under Etiology, the writer wishes to mention the following: Tizzoni and Giovannini succeeded in isolating a bacillus from a case of hemorrhagic purpura complicated by an impetigo contagiosa. They called this bacterium Bacillus hæmorrhagicus velenosus. It was found, together with the Staphylococcus pyogenes aureus, in those hemorrhagic areas of the skin that contained impetigo pustules; in addition it was found in the blood of the liver and of the veins; not, however, in the spleen and the kidneys. In the purely hemorrhagic foci of the skin and also in the kidneys the staphylococcus alone was found.

The Bacillus hæmorrhagicus velenosus is motile, 0.2 to 0.4 μ broad, 0.7 to 1.3 μ long, stains well with anilin dyes, but not by the Gram method. Spore formation has not been observed. The organism, on the contrary, is distinctly resistant to desiccation. The colonies show irregular outlines, resembling curled hair; and the medium is not liquefied.

In gelatin stab culture a granular growth is seen, and on agar a

growth similar to that on gelatin; older cultures have a peculiar penetrating odor. On potato culture a superficial growth of an indistinct character and a dark-yellowish discoloration of the point of inoculation are seen. The growth on bouillon shows a moderate clouding, and later a slimy consistence. The bacillus is pathogenic for dogs, rabbits, and guinea-pigs, but not for pigeons or mice. The bacilli multiply at the site of inoculation, causing local edema; later, fever, hemorrhagic inflammation of the kidneys, vomiting, bloody stools, and hemorrhages into the skin. On autopsy of the infected animals coagulation necrosis of the liver and kidney epithelium and a lack of coagulability of the blood are found, the spleen remaining normal. Cultures sterilized at 70° C. can produce albuminuria. Repeated injections of such cultures produce an immunity against subsequent infection.

Kolb[1] examined bacteriologically 5 cases of genuine idiopathic Werlhoff's disease. All these cases were of the fulminating type, 3 of which terminated fatally after a brief sickness; the other cases recovered.

Microscopic examinations, culture experiments, and inoculation of guinea-pigs, rabbits, and pigeons with blood taken from living purpura patients gave negative results. The bacteriologic examination of the dead bodies was successful. The following tissues and organs were examined: (*a*) Blood from the heart and the portal vein; (*b*) pieces of skin containing characteristic extravasations of blood; (*c*) of hemorrhagic parts of the lung; (*d*) of the liver; (*e*) of the spleen; (*f*) of the kidneys; (*g*) of hemorrhagic portions of the intestine; (*h*) lymph glands from the thoracic and abdominal cavities. In sections of the hardened liver, spleen, kidneys, and pieces of hemorrhagic skin stained with methylene-blue and according to the Gram-Weigert method round-ended bacilli were found, measuring approximately 1 to 2 μ in length and 0.8 μ in width. These bacilli were found to be particularly numerous in the spleen, arranged in heaps within the little blood- and lymph-vessels or within the interstitial tissues; not so numerously in the latter as in the former nor so closely congregated. Here and there long threads were seen, formed by the end-to-end conjunction of many individual bacilli; as a rule, only two were united, forming diplobacilli. In the kidneys the bacilli were found mainly in the glomeruli; not so plentifully, however, as in the spleen. It was also possible to demonstrate the bacillus in sections from the liver and in hemorrhagic pieces from the skin; in the latter isolated bacilli were found even in the lower layers of the cutis. Sections through hemorrhagic glands were particularly instructive. In the fresh organs it was possible to demonstrate this species of bacterium.

The Bacillus hæmorrhagicus Kolb grows on gelatin; the adult colonies are round, with notched, serrated periphery; in the central parts of the colonies a furrowing is observed, while toward the periphery a more granular appearance is seen. Stab cultures form partly isolated, partly confluent colonies in the depth of the culture, and on

[1] *Arbeiten aus dem kaiserlichen Gesundheitsamte*, vol. vii., 1891.

the surface flat hyaline growths with ragged edges. Along the stab an extended configuration is formed, with indented and ragged margins, resembling leaves on a stem, of bluish-white color and a porcelain-like translucence. The bacillus of Kolb grows on agar and, a little more slowly, on blood-serum in the same manner as on gelatin. In potato culture a whitish, moist, shiny band is seen along the line of inoculation. A weak alkaline reaction is the most favorable for bouillon cultures; at the expiration of one day the solution becomes cloudy, and as the growth of the bacteria progresses a sediment is formed. In pure culture the bacillus is a short, oval, rather plump rod with rounded ends. Usually the bacilli occur in pairs. Individuals are from 0.8 to 1.5 μ long. By end-to-end approximation threads may form, attaining in pure culture a length of 30 μ. The bacillus is not motile and is a facultative anaërobe.

The bacillus of Kolb is fatal for mice; rabbits are susceptible; guinea-pigs are only rarely or not at all susceptible, and pigeons are unsusceptible. In susceptible animals the disease picture corresponds to human purpura hæmorrhagica. Cultures that contain no bacteria can produce the characteristic hemorrhagic spots in rabbits and death in mice.

Special Symptomatology.—The most conspicuous and characteristic symptom of this disease consists of the *hemorrhagic spots* that occur on a perfectly normal skin, unaccompanied by any inflammatory process. No hyperemia precedes their occurrence, so that we can say without any reservation that these hemorrhages arise from internal causes—in other words, are manifestations of the so-called hemorrhagic diathesis. The intensity and extent of the hemorrhagic efflorescences are no criteria for the gravity of the disease; at the same time experience teaches us that the small isolated petechiæ that disappear rapidly correspond to lighter forms; whereas the large, widely extended suggillations that persist for a long time and tend to recur correspond to the grave forms of the disease. All stages of transition are seen, from very light affections of the skin to the most serious lesions; the body may appear as if spattered with blood or covered with extravasations as large as an adult hand, and grading in color from violet to black. These may cover nearly the whole skin, leaving hardly any normal surface. Then, again, there may be deeply situated hematomata extending over wide surfaces and even penetrating the muscles; the skin over these blood-tumors shows all the colors of the rainbow, owing to the well-known changes that occur in extravasated blood-pigment. Finally stripe- and welt-like areas of discoloration may occur, particularly in the popliteal space, resembling the "vibices" of scurvy. They may assume almost any color, from dark blue to greenish yellow. It is of interest in passing to note the relation of the hemorrhagic efflorescences to the complications that are observed, particularly the lesions of the joints and the gastric disturbances.

Purpuric spots in the complicated forms are not different from the spots of an ordinary purpura. Occasionally the eruption begins

with a typical *urticaria* that gradually assumes a hemorrhagic character; later these eruptions dry in the same manner as in ordinary urticaria, the pustules collapsing and disappearing without leaving any trace. If the patients are carefully questioned, it will sometimes be found that they were sufferers from urticaria many years ago, long before purpura appeared. Occasionally, acute exanthemata precede the development of the petechiæ; sometimes the latter is complicated by an eruption of miliary vesicles. The alterations in the blood-pigment occurring within the hemorrhagic eruptions of the skin correspond to the changes observed after extravasation of blood from any cause.

The pictures seen in purpura are striking, mainly because such enormous suggillations occur, and because hemorrhagic extravasations of different age may so frequently be seen side by side. Such an appearance must be very confusing to one who is not experienced, particularly when very recent hemorrhages occur in or around an area that contains older extravasations of all shapes and colors. When these extravasations are reabsorbed pigment rarely remains behind, excepting in those cases where the extravasations were exceedingly large; even here the pigmentation disappears completely in time, so that after several weeks or months no trace of it is visible. This applies to naked-eye observation; microscopic examination, however, shows that the pigment masses deposited in the rete Malpighii persist for a long time, so that after months, or sometimes years, we may see that at one time large extravasations of blood had occurred into the skin.

In addition to the smaller hemorrhages, one occasionally sees in the skin evidence of deeply situated bleeding, such as hard, bluish, movable suggillations and infiltrations between the periosteum and the external skin; for instance, in the tibia, the scalp, etc. These hemorrhages may also be found in places where no bones are situated immediately under the skin. This form of extravasation is called *erythema nodosum;* it is particularly found in places where external pressure has been exerted for a considerable time, and is occasionally found in the course of purpura with or without affections of the joints. It exercises no influence on the course of the disease.

The most frequent location for the lesions of purpura is the legs, particularly the region of the malleoli and of the knee joints. Then in order of frequency come the abdomen, the back, and the upper extremities; least frequently, the face (particularly the eyelids) and the mucous membranes of the mouth.

It is necessary to emphasize in this place that in certain forms of true purpura the gums are occasionally affected, while, on the other hand, we know that cases of scurvy are reported in which the gums are not diseased. It would be very superficial to conclude that the latter are light cases of scurvy; the former, severe cases of purpura. The writer must here refer to the description of scurvy, and will in this place only impress the fact that hemorrhages from the gums may occasionally occur in the course of purpura, and that this disease may lead also to serious involvement of the gums, even resulting in fetor.

On the contrary, however, we never see the spongy softening and the ulcerative processes of the gums and the loosening of the teeth as they occur in scurvy.

The number of hemorrhagic eruptions [*i. e.*, the number of crops] that may occur in one case varies within wide boundaries, from 1 to 20; 4 attacks are probably the average.

The time relation of the skin hemorrhages to the other symptoms of the disease is variable; as a rule, the former are the primary symptom. In the case of children, according to v. Dusch, it is usually different, as frequent attacks of *intestinal disturbance* appear more frequently without a simultaneous eruption of blood-spots than with it. In the case of the joint affections of children this is less pronounced, particularly if an inflammatory extravasation has occurred into one or several joints. The joint lesions may persist for a long time, and several generations of purpuric spots may occur during this period.

It is very difficult to demonstrate the presence of such an *extravasation in a joint*—in children more so than in adults, in whom such an accident occurs in about 50 per cent. of all cases. Edema in the neighborhood of affected joints is found chiefly in adults.

The extravasation is rarely profuse, never grows purulent, and does not cause disturbances in the motility of the joint. The visible swelling is usually preceded by spontaneous pain in the joint or sensitiveness on pressure or motion; the joints of the lower extremity, of the foot and knee, are most frequently involved; next in order of frequency the joints of the wrist.

The differential diagnosis between purpura rheumatica and gonorrhœica may be very difficult, particularly if the patient deny the previous existence of a gonorrhea. The prognosis of the former is more favorable than that of the latter. Peliosis rheumatica is distinguished from typical acute inflammatory rheumatism by the general symptomatology of the disease, the different course of the fever, the absence of profuse sweating and of endocardial or pericardial complications; in addition the symptoms about the joints are less severe, although this statement must be taken with some reserve.

The causal relation between the affections of the joints and the hemorrhagic manifestations is not clear except in the case of hemorrhages into the joint. The only explanation that can be proffered is that the hemorrhagic diathesis usually becomes manifest in the serous membranes. We know from analogy with other diseases of the joints that serous membranes are in some way related to the joints, and that both these tissues frequently become affected simultaneously.

While it is true that in simple and hemorrhagic purpura, as well as in scurvy and erythema nodosum, the joints of the knee and of the feet are the most intensely involved, there is reason to doubt the correctness of Scheby-Buch's assumption that those joints are involved because they have to carry the weight of the body.

The writer thinks that the preferable view of this matter is to recur to the anatomic identity of the joint and serous cavities, and to content

ourselves with the assumption that hemorrhages into both these tissues occur as a result of the hemorrhagic diathesis. Of the *intestinal symptoms*, very distressing colics are the most characteristic manifestations in the severe and complicated forms of this disease; they resemble very much the colics of chronic lead intoxication. Patients locate the pain in the umbilical region, and state that from there it radiates in various directions. Although on autopsy hemorrhagic infiltration of the intestine with ulceration has been found in different parts, v. Dusch warns against attaching undue importance to the statement of patients: "I vomited blood," or "I passed a tarry, bloody stool." He believes that such occurrences offer but little conclusive proof of bleeding in the stomach or bowel, because of the fact that, particularly in small children or in patients who are asleep or unconscious and who are lying on the back, blood may pour into the stomach from the nose in considerable quantities, and that this may be vomited or passed from the bowel. The writer thinks that an explanation of this kind is far-fetched and very artificial, nor does he doubt that where violent colic exists enterorrhagia really occurs. He is strengthened in this view by the observation that the colics frequently decrease in severity after profuse hemorrhage from the bowels.

Concerning the *febrile disturbances* sometimes associated with hemorrhages, we know but little. Fever may precede or accompany hemorrhages or fail to appear at all. It will not be possible to gain a clear insight into these relations until we have a more solid etiologic basis for this disease. It seems remarkable to the writer that very high degrees of temperature (40° C.) are not influenced in the least by profuse hemorrhages from internal organs (kidneys, lungs, intestines). In a case observed by Kaltenbach, an intermittent type of fever existed for a long time, the temperature running as high as 39° C., and declining by lysis; this case was not uncomplicated, however. Sudden rise in temperature is always suspicious and usually points to some complication.

Hemorrhage from internal organs is rare. In addition to epistaxis, which is also rare, hematuria occasionally occurs as a result of the recent hemorrhagic nephritis. The urine contains a scanty number of blood-casts and unchanged or washed-out red blood-corpuscles; a large quantity of real albumin is always present. In addition to the hemorrhagic form of nephritis, we sometimes observe in the course of the disease, or immediately following it, a form of nephritis with much albumin and no hemorrhagic constituents; as a rule, this form of nephritis is cured, but in rare cases it leads to edema, uremia, and death. Occasionally albuminuria does not appear until several months after the disappearance of all the symptoms of purpura, and at a time when everyone has forgotten that purpura ever existed. This form of albuminuria, which runs its course without the passage of any corpuscular elements into the urine, is very obstinate, and it is doubtful whether it can ever be completely cured.

Hemorrhages from the *lungs*, after we carefully exclude all those

cases in which pulmonary phthisis may be suspected, hardly ever occur; if bloody sputum be expectorated, we should always suspect the bronchi as the source of the blood.

Retinal hemorrhages are rare. They do occur, however, in this disease; but, owing to their small extent and their peripheral situation, rarely lead to disturbances of vision. In isolated cases meningeal and cerebral hemorrhages have produced epileptiform seizures and paralyses.

Very little is to be said in regard to the consistence of the *spleen*. In isolated cases a distinct swelling of the organ has been demonstrated, the spleen extending as a soft, palpable tumor from 1 to 2 fingers below the costal arch. In other cases, even including one of purpura fulminans, no swelling of the organ has occurred during the whole course of the disease.

In conclusion we must briefly discuss the constitution of the blood. The writer will refer to the pure forms of the disease only, and these at the acme. He will not consider the findings in those cases reduced by anemia. In these, of course, the patients, owing to the impoverishment of the blood, show oligocythemia and leukocytosis.

In most cases of pure hemorrhagic purpura the majority of authors have found a slight decrease in the red and an increase in the white corpuscles. Ajello found a reduction in the reds to 2,500,000 to 3,000,000, and the specific gravity of the blood to be 1043. It is also stated that the erythrocytes show a particular tendency to regenerate rapidly; they exhibit no morphologic abnormalities. Spietschka, in protracted hemorrhages, found nucleated red blood-cells with polychromatophile protoplasm. In 2 cases of purpura hæmorrhagica he instituted continuous examinations of the blood, with enumeration of the corpuscles, estimation of the hemoglobin, and examination of specimens stained with gentian violet and aurantia. The findings were those of secondary anemia.

According to the writer's own numerous investigations, the hemoglobin is frequently more reduced than would correspond to the absolute decrease in the number of red blood-corpuscles.

Silbermann, in a case of Henoch's purpura, found most of the red blood-corpuscles normal; some contained a little less hemoglobin than normal; others again were mere shadows. The leukocytes were numerous and rapidly broken up; the blood-plates greatly increased. In order to determine whether any functional injury of the red blood-corpuscles, whose form was intact, had occurred, fresh mounts were examined according to the method of Maragliano: First, by sealing the preparation with paraffin; second, by heating; third, by compression; and fourth, by mixing with a 0.6 per cent. salt solution. This examination gave the following results:

In the fresh blood enclosed in paraffin, normal erythrocytes and a great many leukocytes are seen; two hours later numerous shadows are seen in the same specimen, many partially discolored red disks and a few microcytes; the white blood-corpuscles are in great part disintegrated and are replaced by small granular, whitish-gray masses. Five

hours afterward only a few blood-corpuscles are seen; the majority have become disintegrated. In the fresh undiluted blood the red blood-corpuscles are fragmented by slight pressure on the cover-slip; the same occurs if the blood be heated to 30° C. In normal salt solution a large number of the red blood-corpuscles are immediately dissolved; the white ones, too, rapidly disintegrate and form glassy lumps.

Examinations of the blood of this patient during health showed results diametrically opposed to those seen during his attacks. In the normal blood no shadows, no increase in leukocytes, and no blood-plates were noticeable. When the blood was examined under the same conditions as above, the red disks showed a normal resistance to these agencies—that is, they neither became discolored in great numbers nor disintegrated.

The writer has also examined the blood of various kinds of purpura for a great many years, and has never been able to arrive at uniform results; as a rule, no deviations from the normal were determinable. In other cases the phenomena observed in the anemic blood were very marked; he considers secondary anemic changes the only ones found in this affection. Thus, the chief abnormalities that he has been able to observe are a microcytosis, poikilocytosis, a great number of pessary forms, a disproportionate decrease of the hemoglobin, an increase of the blood-plates, and a correspondingly increased formation of rouleaux; occasionally an increase of the leukocytes, a tendency to disintegrate on the part of the white cells, and isolated nucleated red blood-corpuscles. The number of leukocytes varies within wide boundaries. The numerous pessary forms, particularly well marked in specimens stained with eosin, are only a sign of depletion in the individual erythrocytes; consequently we must not be surprised to find the total hemoglobin greatly reduced without a corresponding reduction in the number of red blood-corpuscles.

Treatment.—Prophylaxis.—In view of the spontaneous occurrence of purpura, prophylaxis, of course, is impossible. The frequent occurrence of relapses should warn those who have had one attack to beware of external injuries that might reduce their vitality; as, for instance, catching cold. It is said that a change of location has occasionally been followed by favorable results.

General Treatment.—The patient, even if no fever exist, should be kept in bed as long as possible; the more conscientiously this is carried out, the greater the protection against relapses. The patient should be instructed to move about as little as possible. The more cases of this disease the writer sees, the more he is impressed with the benefits to be derived from rest in bed. It is also essential to convince the patient of the necessity of rest, so that he will assist himself voluntarily and with good grace, and not just because the physician has so ordered. Particular attention should be given to measures preventive of slight injury to the patient's body; folds in the bed-sheets should be carefully avoided; the bed-covering should be light; the sick-room cool. Mental excitement and psychic disturbances are to be strictly avoided.

Nourishment should be plain; all food should be administered cool. Coffee, strong tea, and spirituous liquors should be restricted except in the case of collapse. The best food is milk, or somatose (made by Beyer's Anilin Dye Factory in Elberfeld) dissolved in milk. The writer can recommend Mrs. Hedwig Heyl's book on *Sick-diet*, Hable, Berlin, 1889, for all directions for the preparation of appropriate food for the sick.

A supervision of the stools is necessary in order that hemorrhages may be discovered. In cases of constipation, laxatives (ricinus, tamarind, and rheum) or enemata should be given.

Special Treatment.—Owing to Werlhoff's authoritative statements we still give sulphuric acid in the form of acidum Halleri. Werlhoff considered this as a specific. In addition he recommends decoctum corticis chinæ (8–10 : 200), one tablespoonful every two hours. Basing on the pathology of the disease, ergot, acetate of lead, oil of turpentine, and the sesquichlorid of iron are indicated. In very obstinate cases with frequent relapses, the writer has employed arsenic in the form of Fowler's solution, and with good results, especially when combined with carbonated or salt baths. He can recommend this form of medication, particularly in those cases where all other measures have been unsuccessful.

Henoch employs secale as follows:

℞. Extract. secal. cornut., 2.5;
Aqu. destill., 150.0.—M.
Sig.—Teaspoonful every three hours for children; tablespoonful for adults.

Liquor ferri sesquichlorati should be administered thrice daily in the dose of 1 to 5 drops.

The following medication proved successful:

Ext. hydrastis canadensis, 20 to 30 drops every two to three hours.

In peliosis rheumatica the administration of salicylic acid and of antipyrin should be tried.

℞. Sol. natr. salicylic (8 : 200).
Sig.—Tablespoonful every two to three hours.

Antipyrin is given as a powder three times a day in doses of 0.3 to 0.5 gm., or in solution.

In epistaxis the patient should be instructed to lie upon his back with the head low; cold applications should be made to the nape of the neck, and the application of chlorid of iron to the bleeding surface attempted. Drawing cold water, to which a few drops of this preparation have been added, into the nose frequently acts as a styptic. In addition we must consider packing the nostrils as an emergency measure. Hemorrhages from the stomach and the intestine should be treated by ice, opium, and the ice-bag; hemorrhages from the kidneys, by tannin, acetate of lead, or solutions of iron.

In collapse, analeptics and excitants (wine, coffee with cognac, champagne, camphor, ether) are recommended. Application of heat by warm bandages or hot sand-bags may also become necessary. Infusion of physiologic salt solution may be considered.

During convalescence a strengthening diet is to be administered. A trip to the seashore or the mountains and life in the country are to be recommended. Of drugs, iron is the best. The urine should be examined for a long time after the disease has run its course, as frequently, either immediately following it or even weeks or months after its termination, albuminuria is found. This condition is frequently cured by a strengthening diet and warm baths; in other cases it progresses and gradually merges into chronic nephritis. In regard to the treatment of the latter, the writer must refer to the sections on this condition. He might add here that even in this condition he has seen good results follow cold sea-bathing (particularly in the North Sea) in subjects who were well nourished and strong.

LITERATURE.

Complete account of the early literature will be found in:
Hoffmann, *Lehrbuch der constitutionellen Krankh.*, Stuttgart, 1893.
Immermann, *v. Ziemssen's Sammelwerk*, Leipzig, 1879.
Henoch, *Vorlesungen über Kinderkrankh.*, 2d ed.
Among recent literature the following are mentioned:
Maragliano, "Ueber die Resistenz der rothen Blutkörper," *Berlin. klin. Woch.*, 1887.
Green, "Clinical Remarks on Purpura," *Med. Times and Gaz.*, 1883.
du Castel, "Des diverses espèces de Purpura," *Thèse*, Paris, 1883.
Mackenzie, "On the Nature of Purpura," *Brit. Med. Jour.*, 1883.
Ed. Krauss, "Ueber Purpura," *Inaug. Diss.*, Heidelberg, 1883.
v. Dusch, "Ueber Purpura." *Deutsch. med. Woch.*, 1889.
O. Silbermann, "Klinische und experimentelle Beobachtung über Purpura," *Festschrift f. Henoch.*
v. Dusch and Hoche, "Die Henoch'sche Purpura," *ibid.*
v. Kogerer, "Zur Entstehung der Hauthämorrhagien," *Zeits. f. klin. Med.*, vol. x.
Leloir, "Contribution à l'étude des Purpures." *Ann. de Derm. et de Syph.*, 1884.
Ceci, *Arch. f. exper. Path.*, vol. xiii.
Reher, *ibid.*, vol. xix.
Petrone, *Rivista Clin.*, 1887.
Demme, *Fortschr. der Med.*, 1888.
Le Gendre-Gimard, *L'union méd.*, 1888.
Simon-Legrain, *Rev. méd. de l'Est.*, 1889.
Jones, *Med. Press and Circular*, 1889.
Letzerich, "Ueber Purpura haem.," *Monographie*, Leipzig, 1889.
Letzerich, *Zeits. f. klin. Med.*, vol. xviii.
Tizzoni and Giovannini, *Zeigler's Beiträge*, vol. vi.
M. Litten, *Charitié-Ann.*, vol. iii., Jahrgang, 1878.
M. Litten, *Zeits. f. klin. Med.*, vol. ii.
M. Litten, *Dermatologische Zeit. by Lassar*, vol. i, Nos. 4 and 6.
M. Litten, *Deutsch. med. Woch.*, 1896.
Bristowe, *Med. Times*, 1885.
Hirschsprung, *Hospitals Tidende*, 1886.
Scheby-Buch, *Deutsch. Arch. f. klin. Med.*, vol. xiv.
Mathieu, *Arch. gén. de méd.*, Sept., 1883.
Gimard, *ibid.*, 1883.
Stroganow, *Virchow's Archiv*, vol. lxiii.
Hayem, *Revue scientifique*, 1883.
Jardet, *Progrès méd.*, 1884.
Kretschy, *Wien. med. Presse*, 1878.
Arragon, *Arch. de Phys.*, 3. S., ii, 7, p. 352.
v. Recklinghausen, *Handb. der allg. Path.*, 1883.

H. Neumann, *Arch. f. Kinderheilk.*, vols. xii. and xiii.
Lockwood, *N. Y. Med. Rec.*, 1890.
Spietschka, *Arch. f. Dermatol.*, 1890.
Billings, *Johns Hopkins Hosp. Bull.*, May, 1893.
Lebreton, *Mercredi méd.*, 1893.
Bobrizki, *Russkaja Medizini*, 1889, No. 16.
Grósz, *Arch. f. Kinderheilk.*, vol. xviii.
Steffen, *Jahrb. f Kinderheilk.*, 37, i.
Grawitz, *Klin. Path des Blutes*, Berlin, 1896.
Ajello Salvatore, *Rif. med.*, 1894.
Albertoni, *Policlinico*, 1895.
Babes, *Deutsch. med. Woch.*, 1893.
Barlow, *Med.-Chi. Trans.*, London, 1883, and *Centralbl. f. inn. Med.*, 1895.
Bouchut, *Gaz. des. hôp.*, 1878.
Denys, *Centralbl. f. allg. Path.*, 1893.
Marfan, "La maladie de Werlhoff," *Médec. mod.*, 1895.
Ralfe, *Lancet*, 1877.
Reinert, *Münch. med. Woch.*, 1895.
Uskow, *Centralbl. f. die med. Wissenschaft*, 1878.
Widal and Thérèse, *Centralbl. f. allg. Path.*, 1894.
Wjeruschki, *Wratsch*, 1889.

INDEX.

Ashton's Practice of Gynecology

The Practice of Gynecology. By W. EASTERLY ASHTON, M. D., LL.D., Professor of Gynecology in the Medico-Chirurgical College, Philadelphia. Handsome octavo volume of 1079 pages, containing 1046 original line drawings. Cloth, 27s. 6d. net.

JUST ISSUED—THOROUGHLY ORIGINAL

Dr. Ashton's Practice of Gynecology is a new departure in medical text-book making. The author takes up each procedure necessary to gynecologic work step by step, the student being led from one step to another, just as in studying any non-medical subject, the minutest detail being explained in language that cannot fail to be understood even at first reading. Nothing is left to be taken for granted, the author not only telling his readers in every instance what should be done, but also precisely how to do it. A distinctly original feature of the book is the illustrations, numbering over one thousand line drawings made especially under the author's personal supervision from actual apparatus, living models, and dissections on the cadaver. These line drawings show in detail the procedures and operations without obscuring their purpose by unnecessary and unimportant anatomic surroundings, thus enabling the student to see at a glance the exact method employed. All the methods, tests, etc., discussed have been carefully verified by the author so as to assure their value and accuracy. Definite and precise instructions are given as to how to preserve specimens of morbid tissue and secretions, and how to deliver them in good condition to the pathologist. That part of the book dealing with antiseptic technic shows great care, the author here describing only those methods which he employs in his own practice, in order that the student may have a clear and definite conception of the subject, and not have his mind confused by a description of the technic of other surgeons. Especial attention has been given to the consideration of visceral injuries, no other work on gynecology or general surgery discussing this important subject with the same amount of detail. The operations of end-to-end and lateral intestinal anastomosis are given step by step, and the operative manipulations profusely illustrated.

Hirst's Diseases of Women

A Text-Book of Diseases of Women. By BARTON COOKE HIRST, M. D., Professor of Obstetrics, University of Pennsylvania; Gynecologist to the Howard, the Orthopedic, and the Philadelphia Hospitals. Handsome octavo of 683 pages, with 655 entirely original illustrations, many in colors. Beautifully bound in cloth, 21s. net.

WITH 655 ORIGINAL ILLUSTRATIONS—RECENTLY ISSUED

This new book of Dr. Hirst's is on the same lines as his "Text-Book of Obstetrics." As diagnosis and treatment are of the greatest importance in considering diseases of women, particular attention has been devoted to these divisions. To this end, also, the work has been magnificently illuminated with 655 illustrations, for the most part original photographs and water-colors of actual clinical cases accumulated during the past fifteen years. The palliative treatment, as well as the radical operative, is fully described, enabling the general practitioner to treat many of his own patients without referring them to a specialist. An entire section is devoted to a full description of all modern gynecologic operations, illuminated and elucidated by numerous photographs. The author's extensive experience renders this work of unusual value.

OPINIONS OF THE MEDICAL PRESS

Medical Record, New York

"Its merits can be appreciated only by a careful perusal. . . . Nearly one hundred pages are devoted to technic, this chapter being in some respects superior to the descriptions in many other text- boks."

Boston Medical and Surgical Journal

"The author has given special attention to diagnosis and treatment throughout the book, and has produced a practical treatise which should be of the greatest value to the student, the general practitioner, and the specialist."

Medical News, New York

"Office treatment is given a due amount of consideration, so that the work will be as useful to the non-operator as to the specialist."

Hirst's Text-Book of Obstetrics

Third Edition, Thoroughly Revised and Enlarged

A Text-Book of Obstetrics. By BARTON COOKE HIRST, M.D., Professor of Obstetrics in the University of Pennsylvania. Handsome octavo, 873 pages, with 704 illustrations, 36 of them in colors. Beautifully bound in cloth, 21s. net.

MANY BEAUTIFUL ILLUSTRATIONS, 36 IN COLORS

Immediately on its publication this work took its place as the leading text-book on the subject. Both in this country and abroad it is recognized as the most satisfactorily written and clearly illustrated work on obstetrics in the language. The illustrations form one of the features of the book. These are numerous and are works of art, most of them being original. In this edition the book has been thoroughly revised. New matter has been added to almost every chapter, notably those treating of Diagnosis of Pregnancy, the Pathology of Pregnancy, the Pathology of Labor, and Obstetric Operations. More than fifty new illustrations, including three colored plates, have been introduced.

OPINIONS OF THE MEDICAL PRESS

British Medical Journal

"The popularity of American text-books in this country is one of the features of recent years. The popularity is probably chiefly due to the great superiority of their illustrations over those of the English text-books. The illustrations in Dr. Hirst's volume are far more numerous and far better executed, and therefore more instructive, than those commonly found in the works of writers on obstetrics in our own country."

Bulletin of Johns Hopkins Hospital

"The work is an admirable one in every sense of the word, concisely but comprehensively written."

The Medical Record, New York

"The illustrations are numerous and are works of art, many of them appearing for the first time. The author's style, though condensed, is singularly clear, so that it is never necessary to re-read a sentence in order to grasp the meaning. As a true model of what a modern text-book on obstetrics should be, we feel justified in affirming that Dr. Hirst's book is without a rival."

Webster's Text-Book of Obstetrics

A Text-Book of Obstetrics. By J. CLARENCE WEBSTER, M. D. (EDIN.), F. R. C. P. E., Professor of Obstetrics and Gynecology in Rush Medical College, in Affiliation with the University of Chicago; Obstetrician and Gynecologist to the Presbyterian Hospital, Chicago. Handsome octavo volume of 767 pages, beautifully illustrated, including many in colors. Beautifully bound in cloth, 21s. net.

RECENTLY ISSUED—BEAUTIFULLY ILLUSTRATED

This entirely new work is written for the student of obstetrics as well as for the active practitioner. The anatomic changes accompanying pregnancy, labor, and the puerperium are described more fully and lucidly than in any other text-book on the subject. The exposition of these sections is based mainly upon studies of frozen specimens, in which department the author has had a larger experience than any other worker. Unusual consideration is given to embryologic and physiologic data of importance in their relation to obstetrics. Great care was taken in the selection of the illustrations, aiming to meet the varied requirements of both the undergraduate and the practising physician. The book expresses the most advanced thought of the day.

OPINIONS OF THE MEDICAL PRESS

Medical Record, New York

"The author's remarks on asepsis and antisepsis are admirable, the chapter on eclampsia is full of good material, and . . . the book can be cordially recommended as a safe guide."

Buffalo Medical Journal

"As a practical text-book on obstetrics for both student and practitioner, there is left very little to be desired, it being as near perfection as any compact work that has been published."

Dublin Journal of Medical Science

"Both to the student . . . and to the practitioner who requires the latest opinion on any point of practice, Dr. Webster's book will be of the greatest value."

GET THE BEST

Dorland's

THE NEW STANDARD

Illustrated Dictionary

Third Revised Edition—Recently Issued

Dorland's Illustrated Medical Dictionary. A new and complete dictionary of the terms used in Medicine, Surgery, Dentistry, Pharmacy, Chemistry, and kindred branches; with over 100 new and elaborate tables and many handsome illustrations. By W. A. NEWMAN DORLAND, M. D., Editor of "Dorland's Pocket Medical Dictionary." Large octavo, nearly 800 pages, bound in full flexible leather. Price, 19s. net; with thumb index, 21s. net.

Gives a Maximum Amount of Matter in a Minimum Space, and at the Lowest Possible Cost

THREE EDITIONS IN THREE YEARS—WITH 1500 NEW TERMS

The immediate success of this work is due to the special features that distinguish it from other books of its kind. It gives a maximum of matter in a minimum space and at the lowest possible cost. Though it is practically unabridged, yet by the use of thin bible paper and flexible morocco binding it is only 1¾ inches thick. The result is a truly luxurious specimen of book-making. In this new edition the book has been thoroughly revised, and upward of fifteen hundred new terms that have appeared in recent medical literature have been added, thus bringing the book absolutely up to date. The book contains hundreds of terms not to be found in any other dictionary, over 100 original tables, and many handsome illustrations, a number in colors.

PERSONAL OPINIONS

Howard A. Kelly, M. D.,

Professor of Gynecology, Johns Hopkins University, Baltimore.

"Dr. Dorland's dictionary is admirable. It is so well gotten up and of such convenient size. No errors have been found in my use of it."

Roswell Park, M. D.,

Professor of Principles and Practice of Surgery and of Clinical Surgery, University of Buffalo.

"I must acknowledge my astonishment at seeing how much he has condensed within relatively small space. I find nothing to criticize, very much to commend, and was interested in finding some of the new words which are not in other recent dictionaries."

Norris and Dickinson's Text-Book of Obstetrics

Second Edition, Thoroughly Revised and Enlarged

A Text-Book of Obstetrics. In two volumes. Edited by RICHARD C. NORRIS, M.D., Assistant Professor of Obstetrics in the University of Pennsylvania; Art Editor, Robert L. Dickinson, M.D., Assistant Obstetrician, Long Island College Hospital, N. Y. Two handsome octavo volumes of about 600 pages each; nearly 900 illustrations, including 49 colored and half-tone plates. Per volume: Cloth, 17s. 6d. net.

RECENTLY ISSUED—IN TWO VOLUMES

Since the appearance of the first edition of this work many important advances have been made in the science and art of obstetrics. The results of bacteriologic and of chemicobiologic research as applied to the pathology of midwifery ; the wider range of the surgery of pregnancy, labor, and of the puerperal period, embrace new problems in obstetrics. In this new edition, therefore, a thorough and critical revision was required, some of the chapters being entirely rewritten, and others brought up to date by careful scrutiny. A number of new illustrations have been added, and some that appeared in the first edition have been replaced by others of greater excellence. By reason of these extensive additions the new edition has been presented in two volumes, in order to facilitate ease in handling. The price, however, remains unchanged.

PERSONAL AND PRESS OPINIONS

Alex. J. C. Skene, M. D.,

Late Professor of Gynecology, Long Island College Hospital, Brooklyn.

"Permit me to say that 'A Text-Book of Obstetrics' is the most magnificent medical work that I have ever seen. I congratulate you and thank you for this superb work, which alone is sufficient to place you first in the ranks of medical publishers."

Matthew D. Mann, M. D.,

Professor of Obstetrics and Gynecology in the University of Buffalo.

"I like it exceedingly and have recommended the first volume as a text-book for our sophomore class. It is certainly a most excellent work. I know of none better."

British Medical Journal

"This is the most sumptuously illustrated work on midwifery that has yet appeared. In the number, the excellence, and the beauty of production of the illustrations it far surpasses every other work upon the subject."

Penrose's Diseases of Women

Third Revised Edition

A Text-Book of Diseases of Women. By CHARLES B. PENROSE, M. D., PH. D., formerly Professor of Gynecology in the University of Pennsylvania; Surgeon to the Gynecean Hospital, Philadelphia. Octavo volume of 529 pages, with 217 fine original illustrations. Cloth, 16s. net.

THREE EDITIONS IN AS MANY YEARS

Regularly every year a new edition of this excellent text-book is called for, and it appears to be in as great favor with physicians as with students. Indeed, this book has taken its place as the ideal work for the general practitioner. The author presents the best teaching of modern gynecology, untrammeled by antiquated ideas and methods. In every case the most modern and progressive technique is adopted, and the main points are made clear by excellent illustrations. The new edition has been carefully revised, much new matter has been added, and a number of new original illustrations have been introduced. In its revised form this volume continues to be an admirable exposition of the present status of gynecologic practice.

PERSONAL AND PRESS OPINIONS

Howard A. Kelly, M. D.,

Professor of Gynecology and Obstetrics, Johns Hopkins University, Baltimore.

"I shall value very highly the copy of Penrose's 'Diseases of Women' received. I have already recommended it to my class as THE BEST book."

E. E. Montgomery, M. D.,

Professor of Gynecology, Jefferson Medical College, Philadelphia.

"The copy of 'A Text-Book of Diseases of Women' by Penrose received to-day. I have looked over it and admire it very much. I have no doubt it will have a large sale, as it justly merits."

Bristol Medico-Chirurgical Journal

"This is an excellent work which goes straight to the mark. . . . The book may be taken as a trustworthy exposition of modern gynecology."

Garrigues' Diseases of Women

Third Edition, Thoroughly Revised

A Text-Book of Diseases of Women. By HENRY J. GARRIGUES, A. M., M. D., Gynecologist to St. Mark's Hospital and to the German Dispensary, New York City. Handsome octavo, 756 pages, with 367 engravings and colored plates. Beautifully bound in cloth, 18s. net.

INCLUDING EMBRYOLOGY AND ANATOMY OF THE GENITALIA

The first two editions of this work met with a most appreciative reception by the medical profession both in this country and abroad. In this edition the entire work has been carefully and thoroughly revised, and considerable new matter added, bringing the work precisely down to date. Many new illustrations have been introduced, thus greatly increasing the value of the book both as a text-book and book of reference. In fact, the illustrations form a complete atlas of the embryology and anatomy of the female genitalia, besides portraying most accurately numerous pathologic conditions and the various steps in the gynecologic operations detailed. The work is, throughout, practical, theoretical discussions being carefully avoided.

PERSONAL AND PRESS OPINIONS

Thas. A. Reamy, M. D.

Professor of Clinical Gynecology, Medical College of Ohio.

"One of the best text-books for students and practitioners which has been published in the English language; it is condensed, clear, and comprehensive. The profound learning and great clinical experience of the distinguished author find expression in this book in a most attractive and instructive form."

Bache Emmet, M. D.

Professor of Gynecology in the New York Post-Graduate Medical School.

"I think that the profession at large owes you gratitude for having given to the medical world so valuable a treatise. I shall certainly put it forward to my classes as one of the best guides with which I am familiar, not only with which to study, but for constant consultations."

American Journal of the Medical Sciences

"It reflects the large experience of the author, both as a clinician and a teacher, and comprehends much not ordinarily found in text-books on gynecology. The book is one of the most complete treatises on gynecology that we have, dealing broadly with all phases of the subject."

Saunders' Year-Book

Saunders' Year-Book of Medicine and Surgery. A Yearly Digest of Scientific Progress and Authoritative Opinion in all branches of Medicine and Surgery. Arranged with critical editorial comments by eminent specialists, under the editorial supervision of GEORGE M. GOULD, M. D. Vol. I., *General Medicine;* Vol. II., *General Surgery:* Per volume: Cloth, 13s. net.

JUST READY—ISSUE OF 1905

The contents of these volumes, critically selected from leading journals, monographs, and text-books, is much more than a compilation of data. The extracts are carefully edited and commented upon by eminent specialists, the reader thus obtaining also the invaluable annotations and criticisms of the editors.

The Lancet, London

"It is much more than a mere compilation of abstracts for, as each section is entrusted to experienced and able contributors, the reader has the advantage of certain critical commentaries and expositions . . . proceeding from writers fully qualified to perform these tasks."

Barton and Wells' Medical Thesaurus

A Thesaurus of Medical Words and Phrases. By WILFRED M. BARTON, M. D., Assistant to Professor of Materia Medica and Therapeutics, Georgetown University, Washington, D. C.; and WALTER A. WELLS, M. D., Demonstrator of Laryngology, Georgetown University, Washington, D. C. 12 moof 534 pages. Flexible leather, 12s. net; with thumb index, 14s. net.

A UNIQUE WORK—RECENTLY ISSUED

This work is just the opposite of a dictionary: when the idea or meaning is in the mind, it endeavors to supply the word or phrase to express that idea. Its value is evident.

Boston Medical and Surgical Journal

"We can easily see the value of such a book, and can certainly recommend it to our readers."

Baldy's Text-Book of Gynecology

Second Edition, Thoroughly Revised

A Text-Book of Gynecology: MEDICAL AND SURGICAL. By 10 eminent Gynecologists. Edited by J. MONTGOMERY BALDY, M. D., Professor of Gynecology in the Philadelphia Polyclinic. Handsome imperial octavo volume of 718 pages, with 341 illustrations in the text, and 38 colored and half-tone plates. Beautifully bound in cloth, 25s. net.

MEDICAL AND SURGICAL

This volume is thoroughly practical in its teachings, and is intended to be a working text-book for physicians and students. Many of the most important subjects are considered from an entirely new standpoint, and are grouped together in a manner somewhat foreign to the accepted custom. In the revised edition of this book much new material has been added and some of the old eliminated or modified. More than forty of the old illustrations have been replaced by new ones. The portions devoted to plastic work have been so greatly improved as to be practically new. Hysterectomy, both abdominal and vaginal, has been rewritten, and all the descriptions of operative procedures have been carefully revised and fully illustrated.

OPINIONS OF THE MEDICAL PRESS

The Lancet, London

"Contains a large amount of information upon special points in the technique of gynecological operations which is not to be found in the ordinary text-book of gynecology."

British Medical Journal

"The nature of the text may be judged from its authorship; the distinguished authorities who have compiled this publication have done their work well. This addition to medical literature deserves favorable comment."

Boston Medical and Surgical Journal

"The most complete exponent of gynecology which we have. No subject seems to have been neglected . . . and the gynecologist and surgeon, and the general practitioner who has any desire to practise diseases of women, will find it of practical value. In the matter of illustrations and plates the book surpasses anything we have seen."

Dorland's Modern Obstetrics

Modern Obstetrics: General and Operative. By W. A. NEWMAN DORLAND, A. M., M. D., Assistant Demonstrator of Obstetrics, University of Pennsylvania; Associate in Gynecology in the Philadelphia Polyclinic. Handsome octavo volume of 797 pages, with 201 illustrations. Cloth, 17s. net.

Second Edition, Revised and Greatly Enlarged

In this edition the book has been entirely rewritten and very greatly enlarged. Among the new subjects introduced are the surgical treatment of puerperal sepsis, infant mortality, placental transmission of diseases, serum-therapy of puerperal sepsis, etc. By new illustrations the text has been elucidated, and the subject presented in a most instructive and acceptable form.

Quarterly Medical Journal, Sheffield

"We have read Dr. Dorland's manual with a great deal of pleasure. It appears to be the work of one of the younger members of the American profession, who is a scientific teacher and an earnest student. . . . The illustrations are good and to the point."

Davis' Obstetric and Gynecologic Nursing

Obstetric and Gynecologic Nursing. By EDWARD P. DAVIS, A. M., M. D., Professor of Obstetrics in the Jefferson Medical College and Philadelphia Polyclinic; Obstetrician and Gynecologist, Philadelphia Hospital. 12mo of 400 pages, illustrated. Buckram, 8s. net.

JUST ISSUED—SECOND REVISED EDITION

Obstetric nursing demands some knowledge of natural pregnancy, and gynecologic nursing, really a branch of surgical nursing, requires special instruction and training. This volume presents this information in the most convenient form. This second edition has been very carefully revised throughout, bringing the subject down to date.

The Lancet, London

"Not only nurses, but even newly qualified medical men, would learn a great deal by a perusal of this book. It is written in a clear and pleasant style, and is a work we can recommend."

Schäffer and Edgar's Labor and Operative Obstetrics

Atlas and Epitome of Labor and Operative Obstetrics. By DR. O. SCHÄFFER, of Heidelberg. *From the Fifth Revised and Enlarged German Edition.* Edited, with additions, by J. CLIFTON EDGAR, M. D., Professor of Obstetrics and Clinical Midwifery, Cornell University Medical School, New York. With 14 lithographic plates in colors, 139 other illustrations, and 111 pages of text. Cloth, 9s. net. *In Saunders' Hand-Atlas Series.*

This book presents the act of parturition and the various obstetric operations in a series of easily understood illustrations, accompanied by a text treating the subject from a practical standpoint. The author has added many accurate representations of manipulations and conditions never before clearly illustrated.

American Medicine

"The method of presenting obstetric operations is admirable. The drawings, representing original work, have the commendable merit of illustrating instead of confusing. It would be difficult to find one hundred pages in better form or containing more practical points for students or practitioners."

Schäffer and Edgar's Obstetric Diagnosis and Treatment

Atlas and Epitome of Obstetric Diagnosis and Treatment. By DR. O. SCHÄFFER, of Heidelberg. *From the Second Revised German Edition.* Edited, with additions, by J. CLIFTON EDGAR, M. D., Professor of Obstetrics and Clinical Midwifery, Cornell University Medical School, N. Y. With 122 colored figures on 56 plates, 38 text-cuts, and 315 pages of text. Cloth, 13s. net. *In Saunders' Hand-Atlas Series.*

This book treats particularly of obstetric operations, and, besides the wealth of beautiful lithographic illustrations, contains an extensive text of great value. This text deals with the practical, clinical side of the subject. The symptomatology and diagnosis are discussed with all necessary fullness, and the indications for treatment are definite and complete.

New York Medical Journal

"The illustrations are admirably executed, as they are in all of these atlases, and the text can safely be commended, not only as elucidatory of the plates, but as expounding the scientific midwifery of to-day."

Schäffer and Norris' Gynecology

Atlas and Epitome of Gynecology. By DR. O. SCHÄFFER, of Heidelberg. *From the Second Revised and Enlarged German Edition.* Edited, with additions, by RICHARD C. NORRIS, A. M., M. D., Gynecologist to Methodist Episcopal and Philadelphia Hospitals. With 207 colored figures on 90 plates, 65 text-cuts, and 308 pages of text. Cloth, 15s. net. *In Saunders' Hand-Atlas Series.*

The value of this atlas to the medical student and to the general practitioner will be found not only in the concise explanatory text, but especially in the illustrations. The large number of colored plates, reproducing the appearance of fresh specimens, give an accurate mental picture and a knowledge of the changes induced by disease of the pelvic organs that cannot be obtained from mere description.

American Journal of the Medical Sciences

"Of the illustrations it is difficult to speak in too high terms of approval. They are so clear and true to nature that the accompanying explanations are almost superfluous. We commend it most earnestly."

Galbraith's Four Epochs of Woman's Life

Second Revised Edition—Recently Issued

The Four Epochs of Woman's Life: A STUDY IN HYGIENE. By ANNA M. GALBRAITH, M. D., Fellow of the New York Academy of Medicine, etc. With an Introductory Note by JOHN H. MUSSER, M. D., Professor of Clinical Medicine, University of Pennsylvania. 12mo of 247 pages. Cloth, 6s. 6d. net.

MAIDENHOOD, MARRIAGE, MATERNITY, MENOPAUSE

In this instructive work are stated, in a modest, pleasing, and conclusive manner, those truths of which every woman should have a thorough knowledge. Written, as it is, for the laity, the subject is discussed in language readily grasped even by those most unfamiliar with medical subjects.

Birmingham Medical Review, England

"We do not as a rule care for medical books written for the instruction of the public. But we must admit that the advice in Dr. Galbraith's work is in the main wise and wholesome."

Schäffer and Webster's Operative Gynecology

Atlas and Epitome of Operative Gynecology. By DR. O. SCHAFFER, of Heidelberg. Edited, with additions, by J. CLARENCE WEBSTER, M.D. (Edin.), F.R.C.P.E., Professor of Obstetrics and Gynecology in Rush Medical College, in affiliation with the University of Chicago. 42 colored lithographic plates, many text-cuts, a number in colors, and 138 pages of text. *In Saunders' Hand-Atlas Series.* Cloth, 13s. net.

JUST READY

Much patient endeavor has been expended by the author, the artist, and the lithographer in the preparation of the plates of this atlas. They are based on hundreds of photographs taken from nature, and illustrate most faithfully the various surgical situations. Dr. Schaffer has made a specialty of demonstrating by illustrations.

Medical Record, New York

"The volume should prove most helpful to students and others in grasping details usually to be acquired only in the amphitheater itself."

De Lee's Obstetrics for Nurses

Obstetrics for Nurses. By JOSEPH B. DE LEE, M.D., Professor of Obstetrics in the Northwestern University Medical School; Lecturer in the Nurses' Training Schools of Mercy, Wesley, Provident, Cook County, and Chicago Lying-In Hospitals. 12mo volume of 460 pages, fully illustrated. Cloth, 12s net.

JUST ISSUED

While Dr. De Lee has written his work especially for nurses, yet the practitioner will find it useful and instructive, since the duties of a nurse often devolve upon him in the early years of his practice. The illustrations are nearly all original, and represent photographs taken from actual scenes. The text is the result of the author's eight years' experience in lecturing to the nurses of five different training schools.

J. Clifton Edgar, M. D.,

Professor of Obstetrics and Clinical Midwifery, Cornell University, New York.

"It is far and away the best that has come to my notice, and I shall take great pleasure in recommending it to my nurses, and students as well."

Dorland's Pocket Dictionary

Fourth Revised Edition—Recently Issued

DORLAND'S POCKET MEDICAL DICTIONARY. Edited by W. A. NEWMAN DORLAND, A.M., M.D., Assistant Obstetrician to the Hospital of the University of Pennsylvania; Fellow of the American Academy of Medicine. Over 550 pages. Full leather, limp, with gold edges. 5s. net; with patent thumb index, 6s. net.

James W. Holland, M.D.,

Professor of Medical Chemistry and Toxicology, and Dean, Jefferson Medical College, Philadelphia.

"I am struck at once with admiration at the compact size and attractive exterior. I can recommend it to our students without reserve."

Long's Syllabus of Gynecology

A SYLLABUS OF GYNECOLOGY, arranged in conformity with "A Text-Book of Gynecology." By J. W. LONG, M.D., Emeritus Professor of Diseases of Women and Children, Medical College of Virginia, etc. Cloth, interleaved, 4s. net.

Brooklyn Medical Journal

"The book is certainly an admirable *résumé* of what every gynecological student and practitioner should know, and will prove of value."

Boislinière's Obstetric Accidents, Emergencies, *and* Operations

OBSTETRIC ACCIDENTS, EMERGENCIES, AND OPERATIONS. By the late L. CH. BOISLINIÈRE, M.D., Emeritus Professor of Obstetrics, St. Louis Medical College; Consulting Physician, St. Louis Female Hospital. 381 pages, illustrated. Cloth, 8s. net.

British Medical Journal

"It is clearly and concisely written, and is evidently the work of a teacher and practitioner of large experience. Its merit lies in the judgment which comes from experience."