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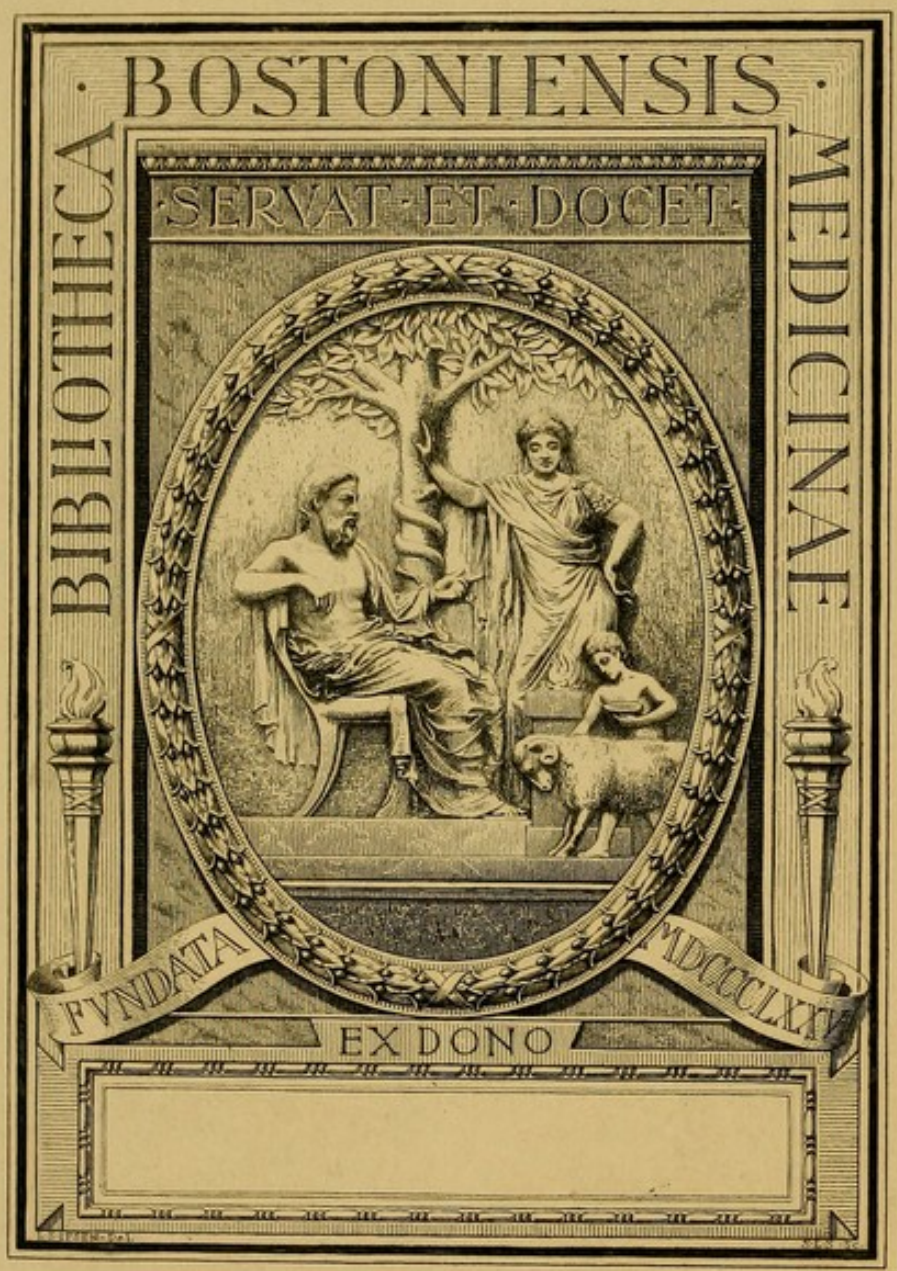

A TREATISE ON BRIGH'TS DISEASE AND DIABETES

TYSON

BY THE SAME AUTHOR

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A TREATISE ON

BRIGHT'S DISEASE

AND

DIABETES

WITH ESPECIAL REFERENCE TO

PATHOLOGY AND THERAPEUTICS

BY

JAMES TYSON, M.D.

PROFESSOR OF MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; ONE OF THE PHYSICIANS TO THE PENNSYLVANIA HOSPITAL; FELLOW OF THE COLLEGE OF PHYSICIANS OF PHILADELPHIA; MEMBER OF THE ASSOCIATION OF AMERICAN PHYSICIANS, ETC.

Second Edition, Illustrated

INCLUDING A SECTION ON THE

OCULAR CHANGES IN BRIGHT'S DISEASE AND IN DIABETES

BY

GEORGE E. DE SCHWEINITZ, M.D.

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PHILADELPHIA:
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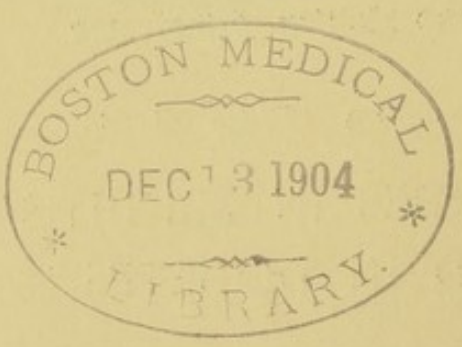

TO THE MEMORY

OF MY FRIEND AND COLLEAGUE

THE LATE WILLIAM PEPPER, M.D., LL.D.

PROVOST AND PROFESSOR OF MEDICINE

UNIVERSITY OF PENNSYLVANIA

PREFACE TO THE SECOND EDITION.

This book has been out of print many years. I have been unable to revise it earlier because of a pressure of what seemed more urgent demands on my time. As a consequence it has been in large part rewritten and much enlarged. To illustrate the text, I have added several original colored plates, representing the principal forms of Bright's disease drawn from cases in my own experience, now quite large, while a number of new drawings have been also added illustrating the histology of these forms. Moreover I have had the advantage of collaboration by my colleague, Professor George E. de Schweinitz, in the preparation of separate sections by him on the Ocular Manifestations of Bright's Disease and in Diabetes. These have also been illustrated by colored plates of eye grounds from his own cases.

I have added entirely new sections on acute interstitial nephritis and on the dietetic treatment of Bright's disease, a subject which is attracting much attention of late and with regard to which I think some erroneous views have become prevalent.

The unsettled state of the pathology and etiology of Diabetes makes the latter subject difficult to treat satisfactorily, but pains have been taken to present clearly the different conditions under which the symptoms arise, in order that they may be recognized and such conclusions drawn as to their origin as may be justified.

Under the dietetic treatment of Diabetes Mellitus I have included an analysis of some of the more usual foods, more particularly with regard to carbohydrate constituents, quite independent of the claims of the makers, in order that the physician may decide for himself which to select. These analyses were made most carefully by Dr. Daniel W. Fetterolf of the Chemical Department of the University of Pennsylvania and may be relied upon. It should be remembered, however, that there is generally some slight variation in the percent-

ages in different samples of the same food stuff when derived from wheat.

To the critical reader I would say that this book is a new edition and not a new work. Hence there will be found in it a good deal of matter from the first edition which it not new, but I believe little will be found that it not directly illustrative of the subjects treated.

Having always taken much interest in the history of the development of knowledge of disease, I have retained and added much bearing on that of Bright's disease. This may not interest some readers, but I know will be appreciated by others, while it adds a completeness which is always desirable.

I have also, somewhat contrary to modern methods, retained the section on the Histology of the Kidney, with which a good deal of pains was taken in the preparation of the first edition, feeling that a correct understanding of its diseases is facilitated by an accurate knowledge of its structure, and that this is most conveniently secured when both are bound under the same cover.

Acknowledgment is due my son, Dr. T. Mellor Tyson, for large assistance in various parts of the work.

PREFACE TO THE FIRST EDITION

It is quite usual for authors, in their prefaces, to give some reason for having written the book which they thus introduce,—in a word, to apologize for its appearance. In the present instance the existence of excellent treatises on both subjects covered by the title, makes it more than usually difficult to justify the appearance of another. The writer can only say that, for more than fifteen years, his thoughts, his studies, and his practical work have all been in the direction suggested by these subjects, and that during that time material has passed under his observation which ought at least, if properly used, to have resulted in an experience which should be useful to others. Whether this has been the case or not, must be left to the decision of those who may first read or examine the work.

In carrying out his object, the author has necessarily, in order to insure completeness, availed himself of the work of others, as well as his own, endeavoring, however, in all instances, to give credit where credit is due, and if he has omitted any proper acknowledgment it has been entirely unintentional. In the section on the "Histology of the Kidney," while he has used the illustrations of other writers, he has also added a number of original drawings, from the careful pencil of Dr. George C. Piersol. It is thought they will add to the accurate knowledge of the subject.

The very wide difference in the nature and pathology of the two sets of diseases has not been overlooked in including them under the same cover; but when it is remembered that although diabetes is not a urinary disease, it is nevertheless a disease to a knowledge of which a study of the urine is indispensable, and that one who devotes himself to the latter must inevitably be brought into frequent and intimate contact with diabetes, it is but natural that the consideration of the two conditions should be united.

1506 Spruce Street, April 1, 1881.

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ANATOMY OF THE KIDNEY.

THE kidneys, enveloped each in its capsule and covered with peritoneum, lie in the lumbar region in front of the quadratus lumborum muscle, one on each side of the vertebral column, towards which its concave edge is turned. They extend from about the eleventh dorsal vertebra to the upper border of the third lumbar. The right lies generally a little lower than the left, with its upper end in contact with the under surface of the liver, and behind the ascending colon. The left organ is in contact by its upper anterior surface with the under surface of the stomach; below this, with the left extremity of the pancreas, and, in its lower part, by loose connective tissue with the descending colon. During inspiration each kidney is depressed by the diaphragm fully one half an inch.

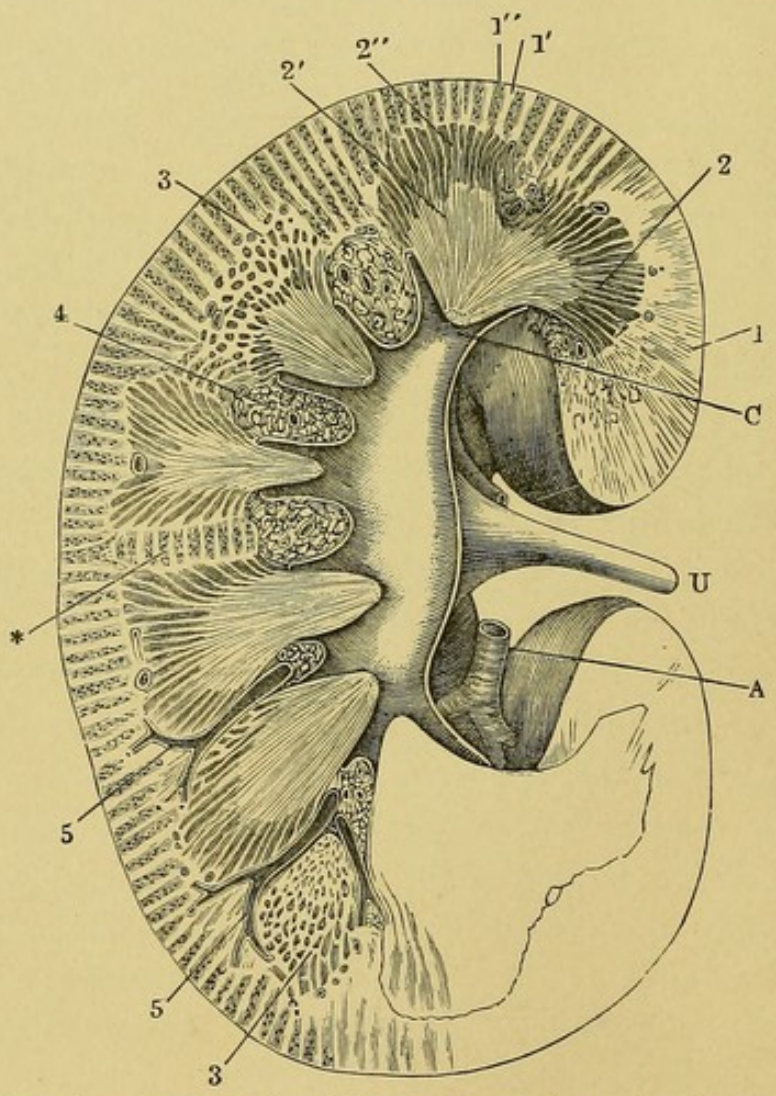
The few facts in the coarser anatomy of the kidney which it is necessary to recall with a view to a correct understanding of its diseases, are, before section of the organ, its size, weight, color, consistency, and the relation of its capsule to its substance; after section, the appearance of the cortex or convoluted portion, as contrasted with the pyramids of straight tubes in the medulla, and the relative area of each.

As to *size* and *weight,* the adult kidney is usually about 11 centimeters (4.4 inches) in length, 5 centimeters (2 inches) wide, and .75 centimeter (.3 inch) in thickness. It weighs in the male 113.5 to 170 grams (4 to 6 ounces); female, a little less, 113.5 to 156 grams (4 to $5\frac{1}{2}$ ounces). Its *color* in health is dark red, *surface* smooth, and in *consistence* it is usually firm and slightly elastic. The *capsule* is easily stripped off from the substance of the healthy organ, dragging none of the proper glandular structure with it.

On *section* of the kidney the *cortex* is found to be granular in appearance, and uniformly light-red in color. It varies somewhat

in width, but is usually 5 to 6 millimeters ($\frac{1}{5}$ to $\frac{1}{4}$ inch) wide, and in longitudinal section this granular substance is seen to dip down between the Malpighian pyramids of the medulla. The pyramids, 8 to 18 in number, are striated or fibrous in appearance, uniformly

FIG. 1.



Longitudinal section through the kidney, the pelvis of the kidney, and a number of renal calyces. A, branch of the renal artery; U, ureter; C, renal calyx; 1, cortex; 1′, medullary rays; 1″, labyrinth, or cortex proper; 2, medulla; 2′, papillary portion of medulla, or medulla proper; 2″, border layer of the medulla; 3, 3, transverse section through the axes of the tubules of the border layer; 4, fat of the renal sinus; 5, 5, arterial branches; * transversely coursing medullary rays.—After HENLE.

dark-red, and terminate in as many papillæ in the pelvis of the organ. The portions of cortical substance which dip down between the pyramids are known as the *Columns of Bertini.*

More important to a correct understanding of the pathology of

kidney diseases is a knowledge of the minute structure of the organ. Even the naked eye can discover further differences on the surface of a longitudinal section such as is presented in Fig. 1. These differences are rendered still more striking if the blood-vessels are injected with coloring matter. From each papilla as a center, radiate

FIG. 2.

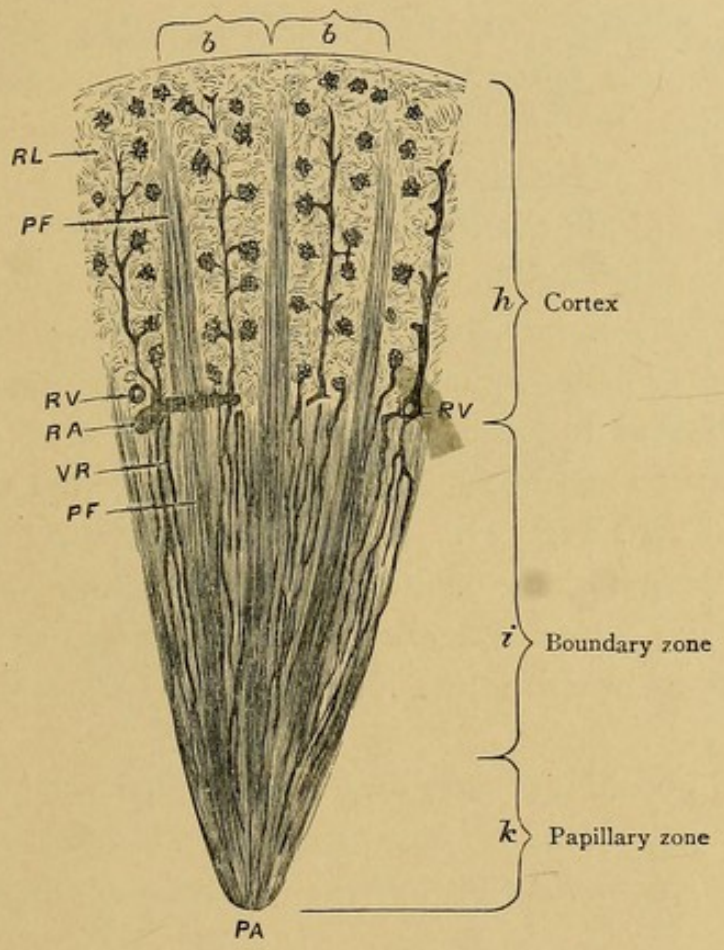


FIG. 3.

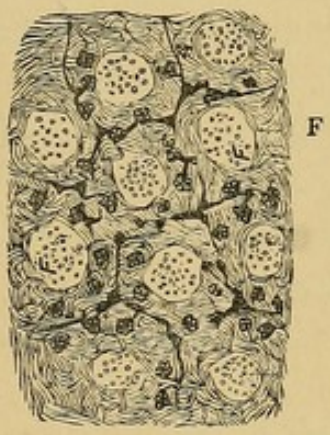


FIG. 2, Partially diagrammatic sketch of the structure of the kidney in longitudinal section, and, Fig. 3, Tangential section through the cortex; blood-vessels injected. After *Rindfleisch* and *Ludwig*, modified. *k*, papillary layer; *i*, boundary layer; *h*, cortex. The lighter striæ, *PF*, are bundles of uriniferous tubules, a part of which are seen prolonged into the cortex as medullary rays or pyramids of Ferrein. Between each two of these in the cortex is the *renal labyrinth*, or secreting portion proper of the kidney. *a*, *a*, *a*, embrace the bases of the renal lobules, which, in transverse section at Fig. 3, appear as polygonal figures. *RA*, a larger branch of the renal artery, which separates the medulla from the cortex; *RV*, lumen of a renal vein which takes up the interfascicular vessels; the latter appear in transverse sections on the surface as stellate figures; *VR*, straight vessels (*vasa recta*); *PA*, surface of a renal papilla.

FIG. 3.—Polygonal appearance of the lobuli when cut transversely. *F*, transverse sections of the straight tubes forming the pyramids of Ferrein.

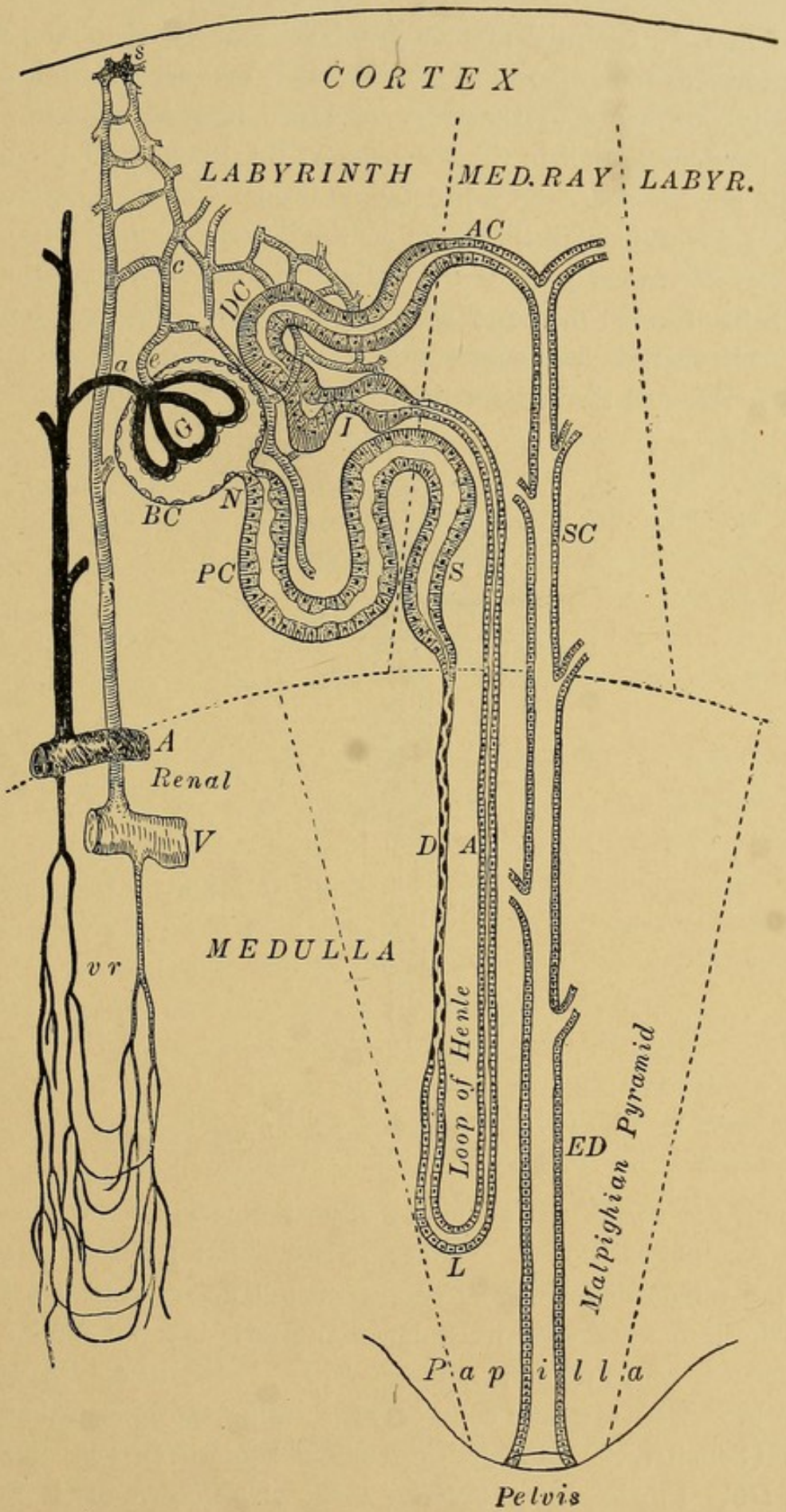
the excreting tubules, which appear as dark-red striæ in the natural organ. For a short distance they remain in contact, forming a continuous surface, known as the *papillary portion* of the medulla (Ludwig), or the *medulla proper* (Henle). This is represented at 2′, Fig. 1, and at *k*, Fig. 2. As they proceed towards the periphery, the striæ become separated into bands of nearly equal width, between which are collections of other striæ. These in an injected kidney exhibit the color of the injecting fluid, but in an uninjected organ, though lighter in hue or less opaque, are scarcely distinguishable from the bundles of straight tubes with which they alternate, unless they happen to be naturally injected with blood. These striæ are, therefore, blood-vessels, and the portion of the medulla which is thus made up of alternate bands of blood-vessels and straight tubules is called the *boundary layer*, or *marginal layer* of the medulla (2″, Fig. 1, and *i*, Fig. 2). Close examination, especially with a low magnifying power, enables us to trace into the cortex almost to its border the bundles of striæ or straight tubes which come from the papillæ (1′, Fig. 1, and *PF*, Fig. 2). In this situation they are called *medullary rays*, or pyramids of Ferrein. Alternating with these medullary rays in the cortex is a *granular* portion, yellowish-red in the uninjected organ, which is the *renal labyrinth*, or *cortex proper*.

The further study of the minute structure is best facilitated by a separate consideration of the *tubules, blood-vessels,* and *connective tissue* elements, and the *lymphatic* and *nervous* elements which accompany them.

I. *The Uriniferous Tubules.*

These, with the blood-vessels, make up the great bulk of the organ. They may be studied from their beginnings in the cortex, or backwards as it were, from their terminations in the discharging-tubes on the papillæ. Selecting the former, the little granules visible to the naked eye in the labyrinth are the beginnings of the uriniferous tubules. These are spherical dilatations, .15 to .2 mm. ($\frac{1}{160}$ to $\frac{1}{125}$ inch) in diameter, formed of basement membrane lined by a mosaic of pavement epithelium. They are the so-called *Bowman* or *Malpighian capsules, BC*, Fig. 4, and are continuous, by a neck-like

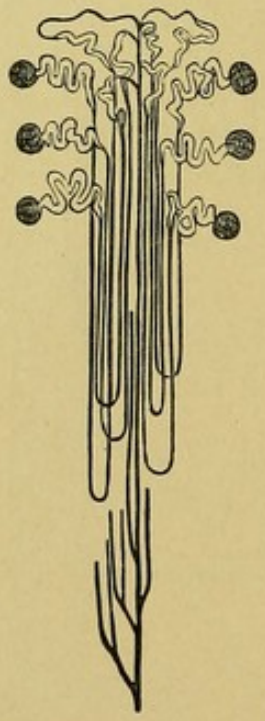
FIG. 4.



Diagrammatic representation of the course of the urinary tubules and of blood-vessels. For convenience the medulla is represented as greatly shortened. —After PIERSOL.

constriction, *N*, with the first or *proximal* convoluted tubule, which winds towards the adjacent medullary ray; reaching which, it passes vertically downward as the *wavy* or *spiral tube* of Schachowa, *S*. These portions are all in the cortex. At the junction of the cortex and the border layer, the spiral tubule becomes suddenly narrower, and dips down through this layer, as the *descending limb* of Henle's loop, the narrowest part of the entire uriniferous tubule, the loop itself being formed in the papillary layer. Just before reaching the loop itself the tubule becomes slightly wider, obtaining a diameter which is retained throughout the loop and the ascending limb. On

FIG. 5.



Diagrammatic exposition of the method in which the uriniferous tubes unite to form the tubes of the primitive cones.—After LUDWIG.

reaching the cortex the ascending limb reënters the medullary ray as its second constituent. Sooner or later, after reëntering the cortex, the tubule dips away from the medullary ray and passes into the labyrinth as a tube irregular in outline, breadth, and course, whence it is called the *irregular tubule, I*. Fairly in the labyrinth, it again becomes wider and convoluted, forming the intermediary segment (Schaltstück) of Schweigger-Seidel, or *distal convoluted* tubule, *DC*. Finally, by an *archlike* turn, whose convexity is towards

the circumference of the kidney, it passes back towards the medullary ray as a narrower "arched part" of the collecting-tube, which, uniting with other similar tubules, forms the "straight part" of the collecting-tube in the cortex. The collecting-tube passes down, still as a straight tube, though growing gradually wider, through the boundary layer. In the papillary layer it becomes the large collecting-tube, or tube of Bellini, which, uniting with others, forms the "ducts" or "discharging-tubes" which open on the papilla.

After the collecting-tube is formed it receives, just below its summit, a few additional canals, and then passes singly down to the papillary part of the medulla. Its diameter in the medullary ray is between .04 mm. ($\frac{1}{625}$ inch) and .08 mm. ($\frac{1}{312}$ inch) in the adult, and in the child .008 ($\frac{1}{3125}$ inch) and .05 mm. ($\frac{1}{500}$ inch), the narrowest canals being in the center of the ray. Having reached the papillary portion, the collecting-tubes unite by twos; first those of a single medullary ray, forming the principal or excreting tubes; then these unite with other excreting-tubes to form the papillary ducts, of which fifteen to twenty open on the surface of each papilla into the pelvis of the kidney.

Dr. George H. Rose, in an able graduation thesis *On the Arrangement of the Uriniferous Tubules,* presented to the Medical Faculty of the University of Pennsylvania, in March, 1879, concluded, first, that a certain number of the tubuli uriniferi do not go to form loops of Henle; and that the medullary rays are made up of the convoluted tubes which do not form loops, as well as of collecting-tubes and ascending and descending limbs of Henle.[1]

Thus the *labyrinth* contains: (1) Malpighian bodies each composed of glomerule, *G,* and capsule, (2) constricted necks of tubules, *N,* (3) proximal convoluted tubules, *PC,* (4) irregular tubules, *I,* (5) distal convoluted tubules, *DC,* (6) arched collecting-tubes, *AC.*

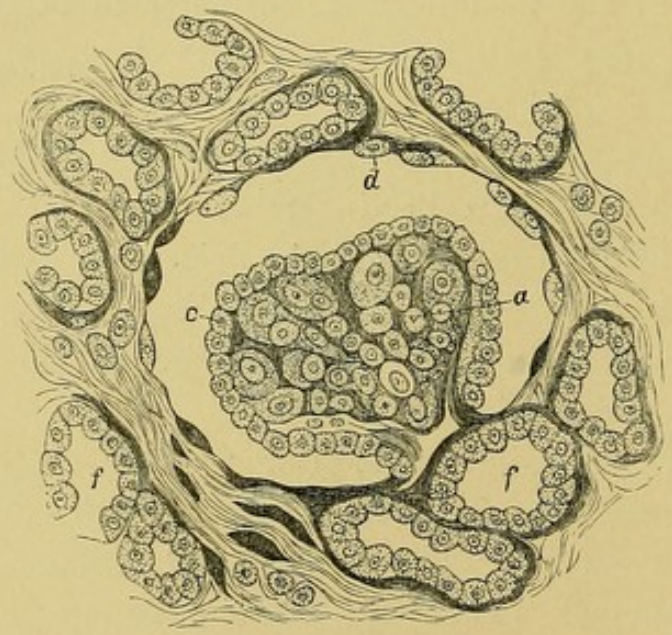
The *medullary ray* contains: (1) Spiral tubules, *S,* (2) ascending limbs of Henle's loops, *A,* (3) straight collecting tubules, *SC.*

The *medulla* contains: (1) Descending limbs of Henle's loops, *D,* (2) the loops, (3) ascending limbs of the loops, *A,* (4) collecting-tubules of all sizes.

[1] Dr. Rose's studies were made with extreme care upon macerated preparations of the kidney. They were many times repeated, and his thesis received the award of a prize.

Structure of the Uriniferous Tubules.—The Malpighian capsule is composed only of the basement membrane and mosaic of epithelial squams to which allusion has already been made. The cells, as seen in nitrate of silver preparations, are relatively large, although not uniform in size, and are provided with round and oval nuclei. The nuclei are arranged in groups of from two to ten. The group nuclei are round, about .01 mm. ($\frac{1}{2500}$ inch) in diameter, and, though flat, project slightly into the cavity of the capsule (*d*, Fig. 6). Each is surrounded by an amount of protoplasm, which is smaller the greater

FIG. 6.



Section through cortical substance of a human fetal kidney. *a*, glomerulus; *c*, epithelium covering the glomerulus; *d*, flattened epithelium lining Bowman's capsule; *f*, urinary tubules in section.—After KLEIN and NOBLE SMITH.

the number of nuclei in a group, whence the varying size of the cells. In the young kidney these cells are less flattened, and the nuclei project still further into the cavity of the capsule, as is seen in Fig. 6.

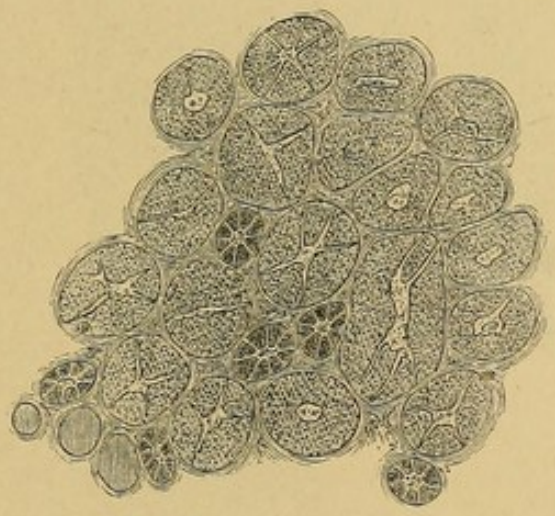
The capsules thus formed surround the capillary ball or glomerulus presently to be described, forming with it the Malpighian *corpuscle*. The latter is encircled by a few concentric layers of connective tissue, most numerous about those nearest the medulla.

This single layer of cells lining the capsule, which is comparable to an endothelium rather than an epithelium, extends into the neck of the capsule, whence onward to the papillary portion of the me-

dulla the uriniferous tubule is composed of a basement membrane lined with an epithelium. The basement membrane contains an occasional nucleus, and in nitrate of silver preparations the convoluted tubules may be imperfectly divided into endothelial plates like the walls of blood and lymph vessels similarly treated; but the membrane is otherwise quite glass-like, affording, when the epithelium is washed out, one of the most satisfactory and typical examples of a homogeneous membrane.

The *epithelium* below the neck varies greatly, although it is everywhere single-layered and nucleated. The nucleus alone, of the various cells is quite uniform, being round, sharply defined, and

FIG. 7.



Section through the cortex of a fresh kidney, showing cloudy epithelium. The spheroidal nuclei are concealed. In the wider tubules irregular, in the narrower, regular fissures divide the epithelial mass.—After LUDWIG.

slightly granular. On the other hand, in the *proximal convoluted* part of the tubule, the protoplasm of the adjacent cells is not differentiated, but each cell *fuses,* as it were, into its neighbor, so that the lining of the tubes, especially when acted upon by acetic acid, presents the appearance of a continuous *nucleated protoplasm* rather than of a number of separate nucleated cells. At intervals may be observed, however, more especially if the tubules have been injected, certain clefts or fissures where the cell bodies are not thus completely fused. These are well shown in Fig. 7, from Ludwig. Of importance in connection with the study of diseases of the tubules is the fact that, in this portion, the epithelium is but loosely attached to the basement membrane, and may even be pressed out in the shape

of a solid epithelial cylinder, or left as such by retraction of the basement membrane. The protoplasm of the cells in this situation is more or less "cloudy" in health, from the presence of a number of dark granules of albuminous composition, and even of some minute fat-globules. These serve to render the nucleus more or less obscure, while the addition of acetic acid, dissolving the albuminous granules, renders it again distinct.

R. Heidenhain[1] adds to the structures as above described an additional element, the effect of which is, as he says, to make the

FIG. 8. FIG. 9. FIG. 10.

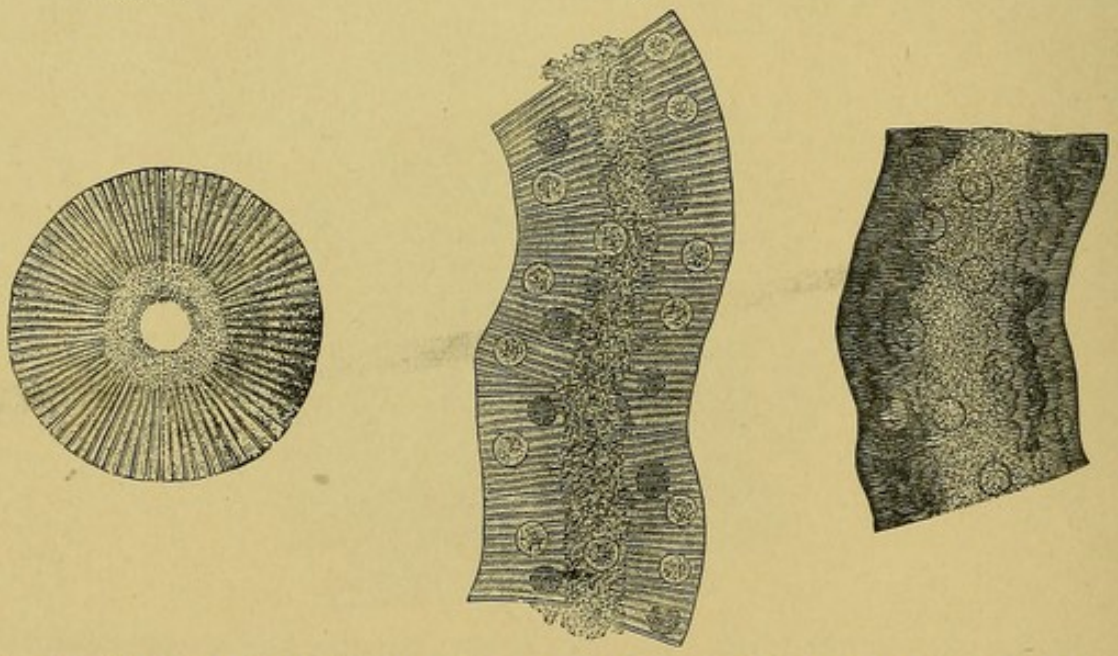


FIG. 8.—Transverse section through a convoluted tubule of a fresh dog's kidney, without the addition of any fluid. Magnified 500 diameters.—After HEIDENHAIN.

FIG. 9.—Section of a convoluted tubule of a dog's kidney, ammonium chromate preparation. Magnified 440 diameters.—After HEIDENHAIN.

FIG. 10.—Surface view of a convoluted tubule. Same amplification.—After HEIDENHAIN.

epithelial cell of the convoluted tubules a very complicated organized structure. According to him the protoplasm is further differentiated into a large number of delicate cylindrical structures, or "rodlets" (Stäbchen), which rest their peripheral ends on the basement membrane. The rodlets envelop, "like a mantle," the nuclei, which

[1] R. Heidenhain, Mikroskopische Beiträge zur Anatomie und Physiologie der Nieren, in Max Schultze's Archiv für Mikroskopische Anatomie, Bd. X., 1874, s. 1.

are placed at regular intervals, surrounded by a considerable remnant of undifferentiated protoplasm. According to Heidenhain the minute granules, formerly described as present in the matrix of the cells, are nothing but the ends of the transversely cut rodlets.

Figs. 8, 9, and 10, from Heidenhain's paper, exhibit the appearances described.

Dr. Klein, of London, substantially confirms the observations of Heidenhain, but says these rods or fibrils, when looked at from the

FIG. 11. FIG. 12. FIG. 13. FIG. 13*a*.

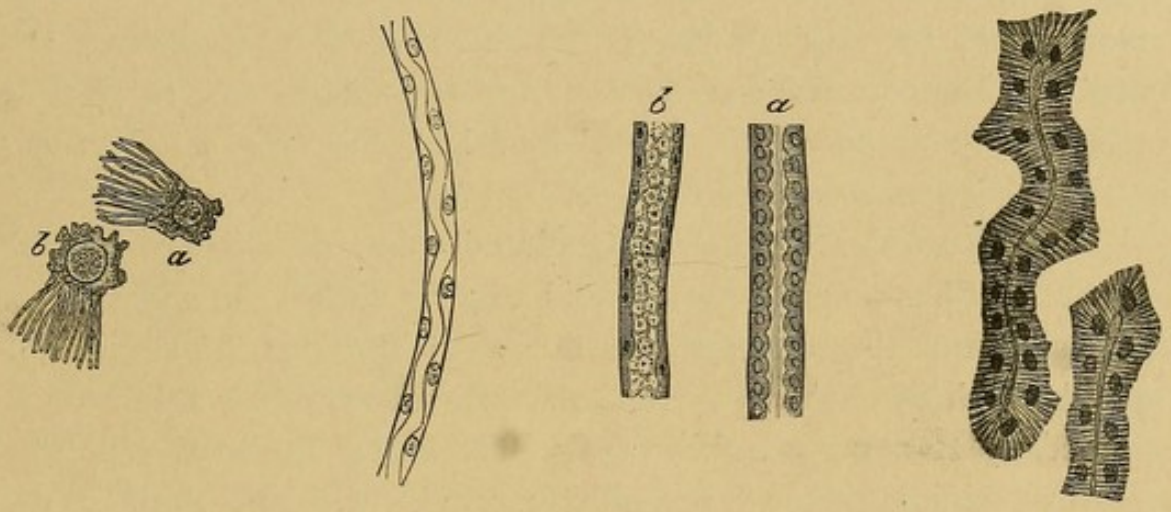


FIG. 11.—Isolated cells and rodlets from the rat's kidney. Same treatment and amplification.—After HEIDENHAIN.

FIG. 12.—An isolated fragment of a descending limb, showing the clear, delicate epithelium, with alternate projections caused by the nucleus.—After LUDWIG.

FIG. 13.—*a*, a portion of a convoluted tubule; *b*, of an ascending limb of Henle's loop, according to Heidenhain. The ascending limb has the greater lumen. Klein confirms Heidenhain in all essential particulars, but says, also, that, in the narrower part of the ascending limb, about the middle of the boundary layer, "many cells appear possessed of short processes and are more or less imbricated, a fact already known to Steudener."

FIG. 13*a*.—Irregular tubule from the cortex of the kidney of a dog.—After KLEIN.

surface, are clearly connected into a network, so that they are more probably "septa of a honeycombed network seen in profile." H. B. Millard has also demonstrated these in morbid cells of the kidney.

The epithelium of the *spiral tubule* is similar to that of the proximal convoluted tubule, composed of low columnar cells with granular protoplasm but less distinct striation.

In the *narrow descending limb of Henle's loop* is found a single layer of epithelium, the cells of which are characterized by a transparent protoplasm and oval nucleus, which projects into the lumen of the tubule at alternate points, as shown in Fig. 12. The resemblance of these tubules to capillary blood-vessels is very marked, especially in transverse section; but the nuclei are more numerous than in a capillary, and the tubule has, further, a *membrana propria* outside the layer of cell-plates.

Just before reaching the loop, still in the descending limb the tube becomes wider and the epithelium polyhedral, characterized by flattened nuclei and faint striations. The lumen is here distinct but narrow. The remainder of the loop and ascending limb are similar.

The *irregular tubule,* as figured by Klein, Fig. 13*a,* is a striking object. He describes it as follows:

"It is situated among the convoluted tubes of all parts of the labyrinth; it has a very irregular and angular outline; in some places three and four times as thick as in others, and then of almost the same breadth as a convoluted tubule. But this greater thickness is due merely to a greater thickness of the lining epithelial cells, the lumen remaining everywhere a narrow canal. The cells show, in the profile view, exceedingly thick rods of a bright, homogeneous aspect, more distinct than in any other section of the urinary tubule. The cells are very angular and, in many places, imbricated; but in this, as in the former cases, this imbrication is due to the irregular outline of the tube and the great variation in height of the adjacent cells. Each cell possesses an oval or angular nucleus next the lumen."

In the intermediary portions the epithelium reassumes the appearance of that of the convoluted segment of the tubule; and here, again, Heidenhain and Klein reintroduce the rodlets, or, rather, their ends, as the cause of the faintly granular appearance.

In the *distal* convoluted tubes the epithelium is like that of the proximal, but the cells are more nearly cubical; they are sharply defined, rather broader at the base, which is seated on the wall of the tubule, while their truncated apices are directed towards its lumen.

In the next portion, the *arched collecting tubule,* is found a lining of low cuboidal cells, which with slight changes become the epithe-

lium of the *straight collecting tubules*. In the *medulla* the cells of the *collecting tubes* are again columnar and retain this form with increasing distinctness in the remainder of their course. The large ducts of the *papillæ*, known as the *excretory* ducts or *tubes* of *Bellini* are lined by beautifully distinct columnar cells of large size. They contain oval nuclei situated somewhat nearer their basal attachment. In the papillary ducts a basement membrane can no longer be differentiated from the connective tissue around it, and the cells rest upon the connective tissue alone.

Anatomical Peculiarities of the Glomerulus or Malpighian Tuft; its Epithelial Covering, etc.—It is now generally conceded that, in addition to the mosaic of epithelium which lines the Malpighian capsule, the glomerulus itself is covered with a layer of epithelial cells, but all observers are not agreed as to its exact arrangement. According to some it simply covers the surface, bridging the space between the capillaries and the lobules which compose the glomerulus. Others consider that it also dips down between the capillary loops. The studies of Heidenhain[1] and of Langhans,[2] lead them to accept the latter view, while Schweigger-Seidel[3] and Von Seng[4] adopt the former. The cells are for the most part well defined, but differ somewhat according as they cover the surface of the glomerulus or dip down between the capillary loops. In the former instance they are thin vaulted plates, whose concave surface rests upon the convexity of the capillary loop and is moulded to it. The shape of the cells also varies somewhat, according as they cover one or more capillary loops. In the latter instance the under surface of the cell is divided by projecting edges into several concave areas for the reception of the individual capillary loops. The edges unite at the center, at which is the nucleus, which itself is conical in shape. At this situation—the seat of the nucleus—the external or upper surface

[1] Heidenhain, Archiv für Mikrosk. Anatomie, B. X., 1874, p. 3.

[2] Langhans, Ueber die Veränderungen der Glomeruli bei der Nephritis nebst einigen Bemerkungen über die Entstehung der Fibrincylinder, Virchow's Archiv, 76 Bd., erstes Heft, April, 1879, p. 85.

[3] Schweigger-Seidel, Die Nieren, Halle, 1865, p. 76.

[4] Victor von Seng, Ein Beitrag zur Lehre von den Malpighischen Körperchen der Menschlichen Nieren, Wiener Sitzungsberichte, LXIV., 13 April, 1871.

is frequently depressed, so that the lateral extensions of the cell assume a pterygoid appearance. Other cells are concave on both surfaces, an effect probably due to their being insinuated between two capillary loops.

The nuclei measured by Langhans are oval, .01–.014 mm. ($\frac{1}{2500}$–$\frac{1}{1786}$ in.) long and .006–.01 mm. ($\frac{1}{4168}$–$\frac{1}{2500}$ in.) wide, and somewhat flattened. The cells themselves reach .025 mm. ($\frac{1}{1000}$ in.) in diameter at a maximum. In some instances the line of junction between neighboring cells is not demonstrable, so that the covering of the glomerulus appears as a homogeneous nucleated plate. The cells and nuclei are much more easily demonstrable in the fetal kidney, in which they are more cubical, as seen in Fig. 6, from Klein's Atlas; undergoing a change after birth which is compared by Schweigger-Seidel to the post-fetal transformation of the alveolar epithelium of the lung. The epithelial covering of the glomerule is continuous with the epithelial lining of the capsule, as is well shown in Fig. 6.

According to Axel Key the capillary blood-vessels of the lobules of the glomerules are held together by a homogeneous connective tissue containing flattened stellate and nucleated connective tissue corpuscles. But Langhans was unable to convince himself of the presence of connective tissue, except the adventitia of the vas afferens, which extends only until the vessel begins to break up into capillaries.

The capillaries of the glomerule or Malpighian tuft, like all capillaries, are provided with nuclei, which in common with all the cellular elements named are subject to pathological change.

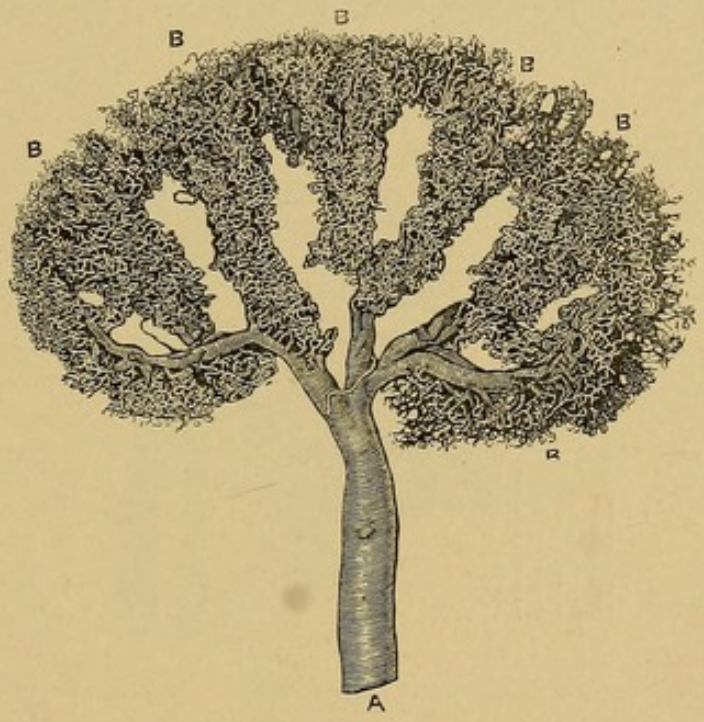
There are no Malpighian corpuscles in that part of the cortex immediately bordering the capsule, nor in that bordering the boundary layers, that is, in the most external and most internal portions.

II. *The Blood-vessels of the Kidney.*

The renal artery, before it enters the substance of the organ, breaks up into two or three branches, which penetrate the capsule at the border of the pelvis of the kidney, and, after further rapid subdivision, radiate directly to the upper part of the marginal layer of the medulla. From branches arching more or less irregularly along

this border ascend and descend vertical branches. The ascending arteries pass into the labyrinth midway between two medullary rays, and are called interlobular or interfascicular arteries. From them pass off, laterally, numerous smaller branches called afferent,—*vasa afferentia,*—each one of which promptly perforates the nearest Malpighian capsule at a point opposite to the constricted neck of the

FIG. 14.



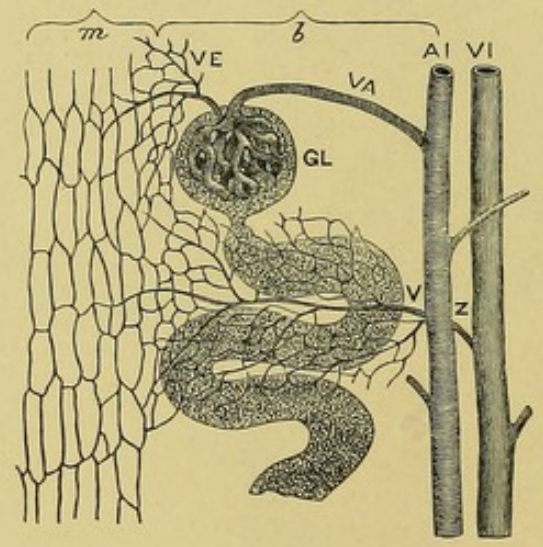
Distribution of the larger blood-vessels of the kidney. Engraved from a photograph of an injected and macerated preparation by Hyrtl in the Museum of the College of Physicians, Philadelphia. *A,* the artery. *B, B, B, B* correspond to the distinct lobar divisions of the kidney, to each one of which the branches of an artery are distributed, which again unite to form the area of the cortex. The open spaces correspond to the areas of the straight tubules or pyramids, which containing comparatively few blood-vessels were washed away in the maceration. The vertical interlobular arteries alluded to in the text are not seen, because the kidney is shown entire and not in hemi-section.

latter. The vas afferens, according to the measurements of Thoma,[1] is .014 to .02 mm. ($\frac{1}{1\,7\,\frac{1}{5}}$ to $\frac{1}{2\,5\,0}$ inch) in diameter. Having perforated the capsule, it immediately splits up, forming a capillary ball—the *Malpighian tuft* or *glomerule.* The capillary vessels of this ball reunite within the capsule to form a vessel,—the *vas efferens,* —which perforates the capsule outwards at the same point at which

[1] Thoma, Zur Kenntniss der Circulationstörung in den Nieren bei chronischer interstitieller Nephritis, Virchow's Archiv, Bd. 71, 1877, s. 65.

the vas afferens enters, and slightly exceeds the latter in diameter. The efferent vessel proceeds towards the nearest medullary ray, and becomes a second time capillary. The resulting network embraces partly the straight tubules of the medullary ray, and partly the tortuous tubules, and, in the extreme periphery of the cortex, to which the medullary rays do not extend, the tortuous tubules only. To these capillaries are added others, derived from a few minute branches given off by the afferent vessels before they reach the Mal-

FIG. 15.



Diagrammatic representation of the blood-vessels in the cortex of the kidney. *m*, region of the medullary ray; *b*, region of the tortuous portion of the tubules; AI, interlobular artery; VI, interlobular vein; VA, vas afferens glomeruli; VE, vas efferens; GL, Malpighian capsule containing in its interior the capillary ball known as the glomerule, or Malpighian tuft; VZ, venous twig of the interlobular vein.—After LUDWIG.

pighian capsule. A few only of the *vasa efferentia* lying adjacent to the medulla do not thus divide, but distribute their branches in a manner presently to be described. With these exceptions, the capillaries from all the neighboring efferent vessels communicate with each other, and the whole cortex becomes interpenetrated, as is well shown in Figs. 15 and 17. The meshes of the resulting network surrounding the convoluted tubules are small and nearly round, while those embracing the medullary rays are larger and wider. According to Ludwig, the vessels are not closely applied to the tubules, but lacuniform spaces, frequently filled with fluid, intervene between the two. The terminal branches of the interlobular arteries reach the capsule of the kidney.

That part of the network which surrounds the medullary rays is continuous with the capillary system of the medulla, but the blood from the cortical plexus is, for the most part, collected by a system

FIG. 16.

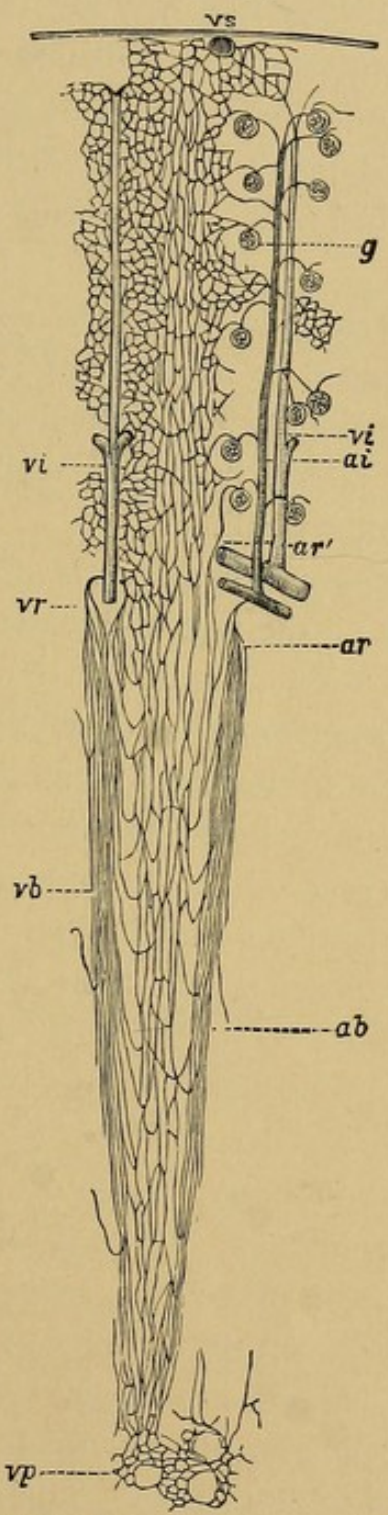


Diagram of the circulation in the kidney. *vs*, stellate veins; *g*, glomerule; *vi*, interlobular veins; *ai*, interlobular artery; *ar'*, elongated efferent vessels sometimes called arteriæ rectæ; *ar*, descending arteriæ rectæ; *vr*, vena recta; *vb*, venous branches; *ab*, arterial branches; *vp*, venous plexus.—After LUDWIG.

of veins (*vi,* Fig. 16) corresponding to the interlobular arteries. Some of these, at least, begin on the surface of the kidney by the union of a number of minute veins from the external layers of the cortex, which unite in a radial manner, so that the resulting vessels are called stellate veins (see Fig. 16, *vs*). Thence they descend, each vein in company with an interlobular artery, towards the marginal layer of the medulla, receiving numerous branches from the capillaries of the cortical plexus above described. The interlobular veins which do not begin in the stellate veins of the periphery begin in the labyrinth.

The interlobular arteries, with the glomeruli and their afferent branches, may be compared to a bunch of ripe currants, the interlobular vessel corresponding to the vertical stem of the raceme, the afferent vessels to the lateral branches, while the currant itself is the red glomerus or capillary ball.

The Vasa Recta and the Blood-vessels of the Medulla.—It was stated on p. 32 that not all the vasa efferentia split up into the capillary system described, but that a certain number lying adjacent to the medulla distribute their branches differently, sending them down directly into the medulla, in the shape of straight vessels, comparable in their distribution to the drooping branches of the willow-tree, which are called *vasa recta.* But although straight *vessels,* they are *not arteries,* though sometimes called *arteriolæ,* since they are without circular muscular fiber-cells in their walls. They are simply elongated efferent vessels (see Fig. 16, *ar'*). These contribute, however, but a small proportion to the vasa recta. The majority, which are true arteries, are derived from the same arching branches which give off the interlobular vessels at the upper edge of the marginal layer of the medulla, but pass in the opposite direction. The straight vessels from these two sources, passing downwards, enter first the spaces between the bundles of tubules in the marginal layer of the medulla, dividing and subdividing in a brush-like manner (Fig. 16, *ar* and *ab*) until they finally become capillary, and embrace the tubules in wide meshes. The number of trunks of the straight vessels progressively diminishes as the tubules become closer and the papillæ are approached, until the latter are reached, when but one or two remain to form a plexus of capillaries on the papillæ

themselves. The capillaries reunite to form veinlets, corresponding to the straight arterioles, and these veins accompany the arterioles in the fissures between the bundles of tubules, reuniting to form larger trunks, which finally empty into vessels at the border of the cortex, corresponding with those which give off the straight arterioles (see Fig. 16, *vb* and *vr*).

The system of the vasa recta is one of great importance in the circulation of the organ. It has been remarked that the capillary system at the border of the cortex is in communication with that of the medulla; but it is evident also that the vasa recta, derived from the same branches as the interlobular arteries, admit of the transit of a large amount of the blood of the kidney through a coarse-meshed capillary plexus without its passing through the complex system of the labyrinth. This is an important provision, which doubtless tends to preserve the integrity of the kidney in congestions, or when a large amount of blood is driven through it. Under these circumstances a short cut is, as it were, provided for the blood out of the organ, and the more delicate vessels of the labyrinth are protected from rupture.

We are indebted to Virchow and McDonnel for the discovery of the vasa recta, and to Virchow, Ludwig, and Beale for our present accurate knowledge of their arrangement.

III. *The Connective Tissue of the Kidney.*

From a pathological standpoint the connective tissue of the kidney becomes one of the most important of its elementary structures. All anatomists and renal pathologists, however, are not agreed upon its quantity and importance.

While none deny its presence in the medullary portion of the kidney there is still a difference of opinion as to its existence in the cortex. Goodsir, in 1842, described the connective tissue framework or matrix of the kidney in the cortex, as well as the medulla, as though it were as distinct from the vascular and tubular structures of the organ as the beams and rafters of a house are distinct from the materials between them.[1] Von Wittich,[2] in Germany, first con-

[1] Rosenstein gives Bowman the credit of first describing the connective tissue in the medulla and Goodsir in the cortex.

[2] Von Wittich, Beiträge zur Anatomie der gesunden und Kranken Niere, Virchow's Archiv für Patholog. Anatomie, Bd. 3, 1849, s. 142.

tested this view, claiming that the intervals between the tubules are occupied only by capillary vessels, and that there is no connective tissue in the cortex. In this he was for a time sustained by German histologists generally. Arnold Beer,[1] in 1859, reasserted the importance, from an anatomical point of view, of the connective tissue as a stroma or framework for the support of the tubules and vessels. Henle,[2] in 1864, asserted that demonstrable quantities of connective tissue are only found in the apices of the pyramids, where they occupy the intervals between the tubules. According to Henle it is a substance which in the fresh condition is clear and transparent, and it is only after the long-continued action of chromic acid and chromate of potash solutions that delicate fibers appear, containing round and elliptic nuclei. Further inwards, towards the cortex (boundary layer of the medulla), the nuclei become less numerous, and finally disappear altogether, leaving between the tubules only delicate layers of a finely fibrillated tissue, which cannot be considered an artificial product, because the fibrillæ are often arranged circularly around the tubules. In the cortex the tubules and vessels are so closely intercalated that we can, as a rule, only speak of a cement substance rather than an intertubular and intervascular substance. "*True* connective tissue," says Henle, "is found in the cortex and medulla only in the immediate neighborhood of the blood-vessels."

The late Sir George Johnson and Lionel S. Beale, of England, also assert that the connective tissue is of minimum importance, that it has no share in the anatomy of the organ, and therefore, none in the pathology. Dr. Beale says: "1. In the cortical portion of the kidney there is no evidence of the existence of a fibro-cellular matrix distinct from the walls of the tubules and capillaries. 2. The fibrous appearance observed in those sections of the kidney which have been immersed in water is fallacious, and is due to a crumpled, creased, and collapsed state of the membranous walls of the secreting-tubes and capillary vessels. 3. A small quantity of transparent material is to

[1] Arnold Beer, Die Bindesubstanz der menschlichen Niere im gesunden und krankhaften Zustände. Berlin, 1859.

[2] Henle, J., Handbuch der Systematischen Anatomie des Menschen. Zweiter Band, zweite Lieferung, Harn und Geschlechtsaparat. Braunschweig, 1864.

[3] Beale, Kidney Diseases and Urinary Deposits. Philadelphia, 1869, p. 23.

be demonstrated between the walls of the tubes and the capillaries in health, and not even this can be detected at an early period of development."

Dr. Johnson says:[1] "The so-called matrix has no existence apart from the basement membrane and capillaries. The convolutions of the tubes and the network of capillaries mutually support each other. No connective or supporting tissue is required; and, as Dr. Beale well remarked, the intervention of any such tissue would tend to increase the distance between the secreting cells and the blood, and so render the gland less fitted for the discharge of its function." . . . "If there be any connecting medium it is a homogeneous and structureless element."

Modern histology has solved the problem consistently with all observations. It is true that there is no distinct framework or "supporting" structure of connective tissue for the tubules and vessels of the cortex, for they require none. At the same time, we know that no blood-vessel of any size penetrates a gland without carrying with it its adventitia, and although this diminishes with the growing fineness of the subdivisions of the artery, it is scarcely possible to draw the line where the cells of the connective tissue sheath entirely disappear. The interlobular arteries described are doubtless accompanied by such cells. Further, the researches of Ludwig, Kölliker, and Schweigger-Seidel have shown that the connective tissue of the cortex and of the marginal layer of the medulla is not of the fibrillar kind, but of the reticular or purely cellular variety; very delicate, soft, and scanty, as this kind of connective tissue usually is, winding its spindle and reticular cells in sparse numbers between the tubules and blood-vessels, yet sufficiently numerous to permit an isolated cell to be seen in almost any slide prepared from the fresh organ. These small isolated fusiform cells are described both by Ludwig and Schweigger-Seidel as being placed with their longer axes transverse to the direction of the convoluted tubules.

These two sources, therefore, the reticular connective tissue of the cortex and the adventitia of the blood-vessels, while they do not afford a matrix or framework, still furnish connective tissue cells in sufficient numbers to become the focus of an overgrowth. Further,

[1] George Johnson, Lectures on Bright's Disease. New York, 1874, p. 7.

in the case of the Malpighian bodies, no one who is in the habit of examining kidney sections under the microscope can have failed to see that they are surrounded by a capsule *of fibrillar* connective tissue, especially in the region of the medulla. This is a fact of great importance, because, in the case of diseased organs, it becomes necessary to distinguish such capsule from a pathological overgrowth of the same tissue.

As we recede from the boundary layer of the medulla towards the apices of the cones—the papillæ, the proportion of fibrous connective tissue increases until it becomes quite abundant in the latter region, surrounding the tubuli in a concentric manner.

As has been said, it is even claimed by Axel Key that a reticular connective tissue formed of stellate cells is found uniting the capillaries and capillary lobules of which the glomerule is composed.

The Capsule of the Kidney.—The kidney is surrounded by a firm capsule, composed mostly of fibrillar connective tissue imperfectly laminated. In health it is feebly adherent by a looser and more delicate layer, to the cortex of the organ, whence it is stripped with facility, the only attachments being a few filaments of connective tissue, and some small blood-vessels which pass from one to the other. In certain diseased states, especially where the connective tissue is involved, this adhesion is more intimate, so that it is impossible to strip off the capsule without dragging more or less of the secreting structure of the kidney with it; and in descriptions of post-mortem conditions, we constantly read that the capsule stripped off easily or was closely adherent, etc. Eberth described a plexus of unstriped muscular fiber-cells under the capsule of the kidney in man.

The blood-supply of the capsule is derived partly from those branches of the interlobular arteries which do not proceed as afferent vessels to the Malpighian bodies, and partly from branches of the phrenic, lumbar, and supra-renal arteries. These form a large-meshed capillary system, whence the blood is collected by corresponding veins, including the stellate veins of the cortex.

IV. *The Lymphatic Vessels of the Kidney.*

The more accurate knowledge of modern times as to the lymphatic system in general, only partially includes that of the kidneys, although the researches of Ludwig and Zawarykin[1] have furnished some facts of importance. From them we learn: (1) That the capsule of the kidney is provided with well-defined lymphatics possessing even valves. They ramify in the deeper layers of the capsule and are known as the *superficial* system of renal lymphatics; (2) that similar larger trunks issue from the hilus of the organ along with the artery and vein; and (3) that the spaces between the tubules and vessels of the cortex are of the nature of lymphatic spaces, constituting the *deeper lymphatic channels* of the kidney. These spaces are less numerous in the medullary rays, and still less in the medulla. These observers have also shown that communication exists between the lymphatics of the capsule and those of the cortex, and between the latter and the lymphatics of the hilus, but the exact paths of such communication are not determined.

V. *The Nerves of the Kidney.*

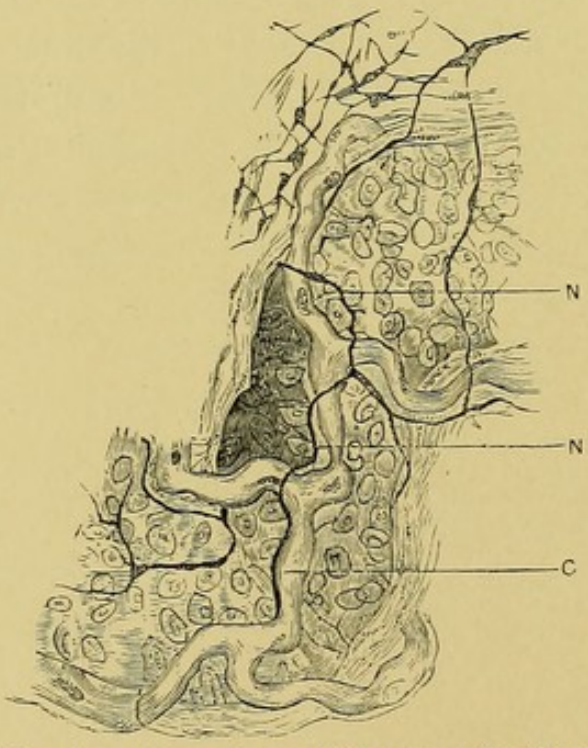
While the nerves of the kidney doubtless play a most important rôle in its physiology, they are less demonstrably influenced by its pathological states than any other of the elementary tissues composing it. They consist of ganglia and nerves running thereto and are derived chiefly from splanchnic nerves and pre-lumbar ganglia of the sympathetic system, and it is probably for this reason that, except in the case of acute Bright's disease and of impacted calculus, pain is a rare symptom in renal diseases, although this is contrary to popular opinion, which ascribes almost all pain in the back to kidney disease.

The renal nerves enter with the vessels at the hilum and are distributed to the arteries and the convoluted tubules of the organ. Among the earliest contributors to our knowledge of this subject was Professor Lionel S. Beale, of London. Beale early described nerves, pale and dark-bordered (medullated), distributed to the

[1] C. Ludwig mit Zawarykin, Wiener Akademische Sitzungberichte, Bd. XLVIII.

secreting-tubes and capillaries as well as the arteries; connected with the nerve-bundles are numerous ganglia and ganglion-cells similar to those found in connection with the ramifications of the sympathetic generally in mammalia.[1] I have myself,[2] following Dr. Beale's methods, sought to demonstrate these cells in connection with nerve fibers in the pig's kidney. Dr. Beale said further, that these "nuclei," so numerous on the nerves of the kidney, as well as on all the peripheral nerve-fibers of various tissues of mammalia, have been hitherto included among the connective tissue corpuscles of the

FIG. 17.



A part of a convoluted portion of a uriniferous tube from the newt's kidney, showing capillary vessels and nerve fibers, and the thickened basement membrane continuous in structure with the connective tissue. × 215. (After BEALE.) The finer dark lines, N, represent the nerve fibrils with nuclear thickenings. C, capillary blood-vessels.

matrix. He considers that the nerve-fibers distributed to the walls of the uriniferous tubules constitute an *afferent* system capable of influencing through the nerve-centers the *efferent* fibers distributed to the arteries, the caliber of which they govern, and thus regulate the amount of blood flowing through the capillaries. The ganglia

[1] Beale, Kidney Diseases and Urinary Deposits, 1869, p. 15.
[2] American Journal of the Medical Sciences, October, 1869.

within the kidney are connected by nerve-fibers with those external to the organ, and with the spinal nerve-fibers, and through these with the great nervous centers. And thus is explained the well-known influence of the emotions over the secretion of urine.

Recent researches by aid of the most refined methods add very little to the results obtained by Beale whose studies have been almost ignored. Thus Henry J. Berkley,[1] after a careful study of the histology of the nerves of the kidney by these methods, concludes as follows:

"The renal nerves enter with the vessels at the hilum, and with their multifarious ramifications and ganglionic enlargements form a not inconsiderable portion of the kidney's entire substance. From the vascular nerves—which we may call the primary ones—come secondary divisions, distributed throughout all the cortical and medullary-cortical regions in the form of a vast open network. The glomeruli are surrounded by a wide-meshed plexus of fibers having terminal end-knobs approximated closely to the Bowman capsule, but no finer nerves can be seen penetrating that membrane; and end-terminations within the capsule upon the convoluted vessels, either in the form of knobs, or in the finer pointed terminations cannot be discovered. Fibers pass off singly and separately from the vascular nerves, and are distributed on the convoluted tubes, not only with end terminations in the form of the well-known globular ending, but also in fine delicate threads that penetrate the membrana propria of tube and presumably enter the cement substance between the epithelial cells; and the function of these divisions to the *tubuli contorti* is probably one concerning the urinary secretion. Lastly, that ganglionic enlargements occur widely, but that strictly speaking no nerve cells provided with nucleus, body, and protoplasmic arms, are to be found; and that all renal nerves belong to the sympathetic system."

VI. *Minute Appearance of the Kidney as Seen in Transverse and Longitudinal Sections.*

For a proper study of the minute changes in a kidney, healthy or diseased, sections should be made in two directions: (1) longi-

[1] The Intrinsic Nerves of the Kidney—A Histological Study, Bulletin of the Johns Hopkins Hospital, Vol. IV., 1893, p. 1.

tudinally, or in the direction from the cortex to the papillæ; (2) transversely to this direction. In this manner the relation of the elementary tissues which make up the organ is preserved, and the changes in them may be studied understandingly. From cuts in the first direction one picture only is obtained, which may extend from

FIG. 18.

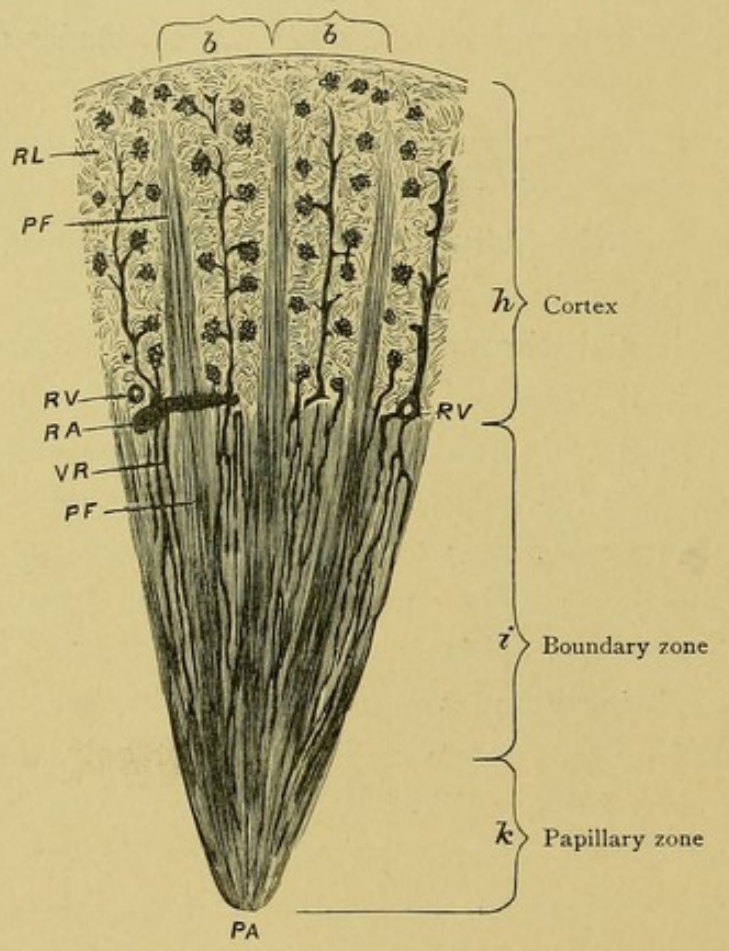


FIG. 19.

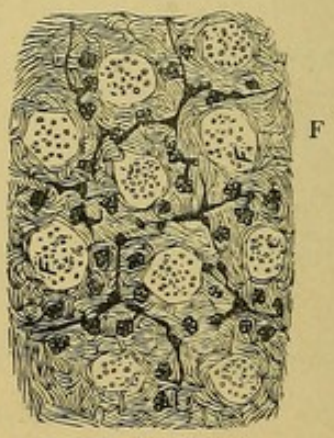
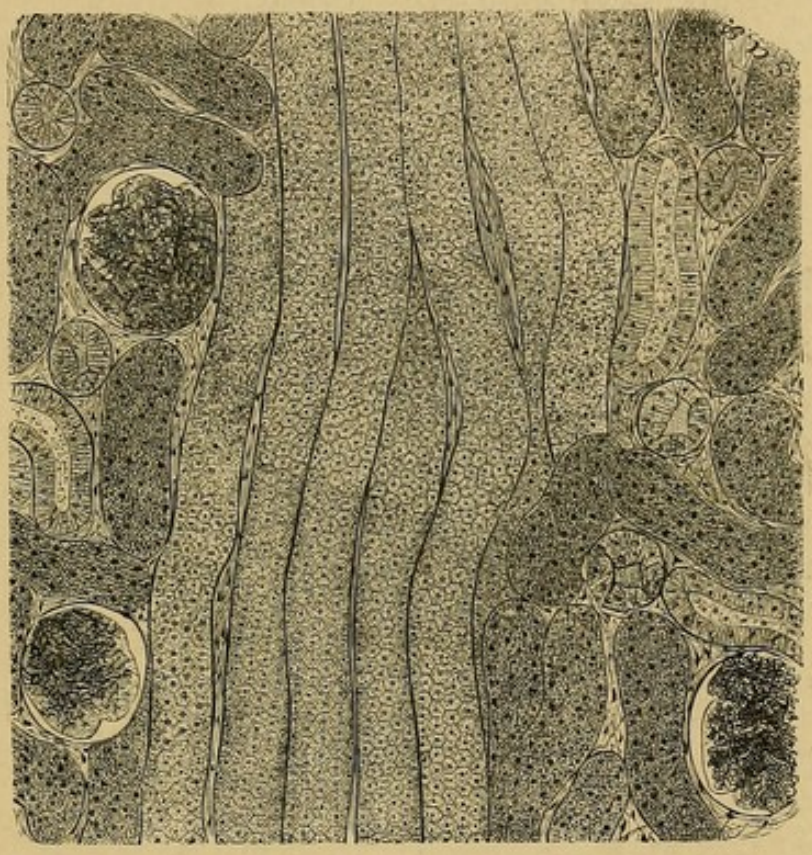


FIG. 18.—Partially diagrammatic sketch of the structure of the kidney in longitudinal section, and Fig. 19, Tangential section through the cortex; blood-vessels injected. After *Rindfleisch* and *Ludwig*, modified. *k*, papillary layer; *i*, boundary layer; *h*, cortex. The lighter striæ, *PF*, are bundles of uriniferous tubules, a part of which are seen prolonged into the cortex as medullary rays or pyramids of Ferrein. Between each two of these in the cortex is the *renal labyrinth*, or secreting portion proper of the kidney. *b*, *b*, embrace the bases of the renal lobules, which, in transverse section at Fig. 19, appear as polygonal figures. *RA*, a larger branch of the renal artery, which separates the medulla from the cortex; *RV*, lumen of a renal vein which takes up the interfascicular vessels; the latter appear in transverse sections on the surface as stellate figures; *VR*, straight vessels (*vasa recta*); *PA*, surface of a renal papilla.

FIG. 19.—Polygonal appearance of the lobuli when cut transversely. *F*, transverse sections of the straight tubes forming the pyramids of Ferrein.

the cortex to the papillæ. Transverse cuts present a different picture, according as they are made through the cortex, or at different situations in a medullary cone—near the cortex, between it and the papilla, or at the papilla itself. It will be found that in the various forms of Bright's disease the cortex alone is generally involved, so

FIG. 20.



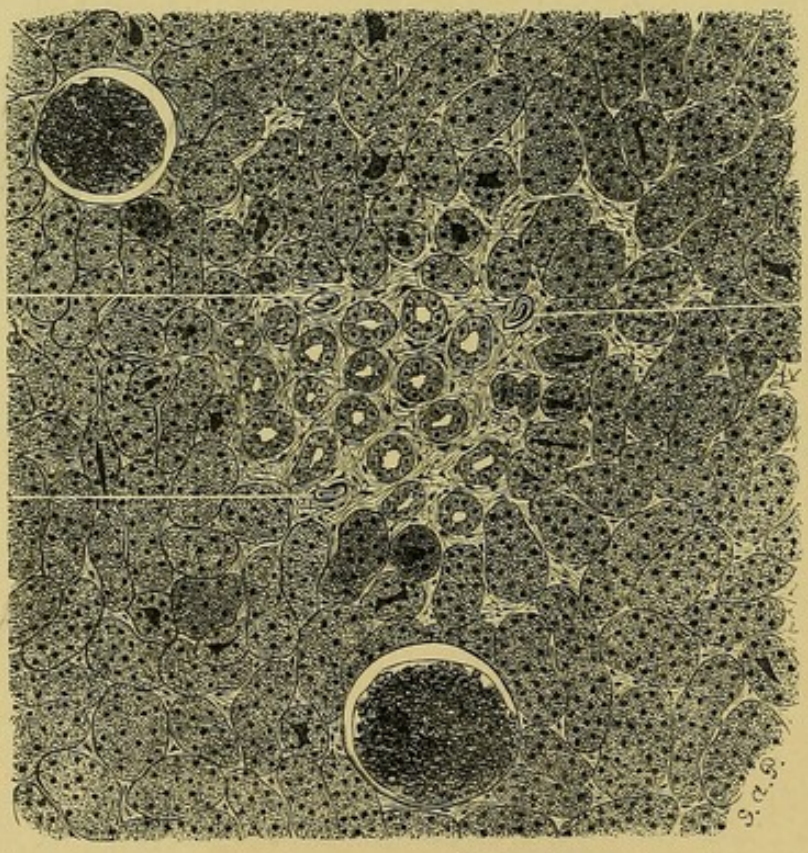
Longitudinal section through the cortex. Tubules forming medullary ray in center, showing faintly outlines of epithelial cells. Malpighian bodies among sections of convoluted tubules. In several places these have been laid open, exposing the lumen of the tubule. The nuclei are seen imbedded in the dark granular protoplasm lining the tubules. The striated appearance of the cells is also well shown. Certain tubules are also transversely cut. × 160.

that for the study of these conditions it is necessary only to make sections through this portion. It is especially desirable that the normal picture should be familiar, in order that the abnormal may be understood.

Fig. 19 will give an idea of the appearance, under a low power, of a longitudinal section of an injected kidney. Fig. 20, however, presents the picture of a portion of the cortex under a higher power, which is necessary for a correct appreciation of structure.

21 In Fig. 20 is seen the appearance which is presented under a low power in a transverse section through the cortex, a short distance below the capsule, of the same kidney from which Fig. 19 20 represents a longitudinal cut. It also affords a correct notion of the lobular structure which the kidney really possesses, but which would not be suspected without the microscope. The renal lobules are seen to be polygonal figures, of which the sides are formed by the branches of the interlobular vessels already described. The center is occupied by the straight tubes of the pyramids of Ferrein

FIG. 21.

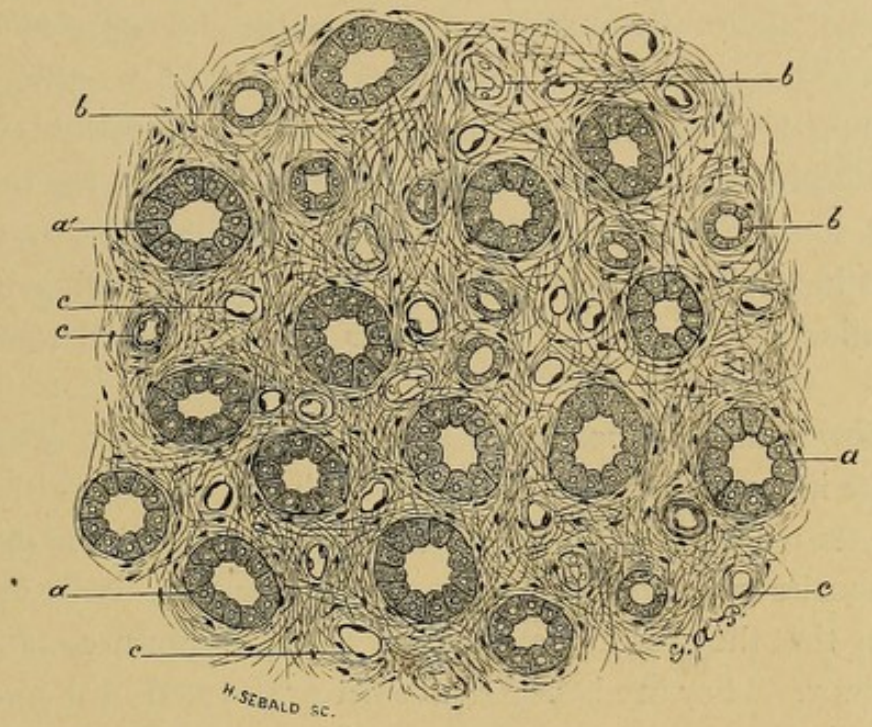


Tangential section through the cortex. Collecting tubes in center cut transversely. Two Malpighian bodies. Numerous sections of tubules, some in transverse section showing dark lumen of tubuli. Sections of several vessels, V, are seen near the central collecting tubes. × 150.

(medullary rays), and between these and the border is the labyrinth, which is the seat of the most important lesions of interstitial and parenchymatous nephritis. A section immediately at the surface, just under the capsule, would not give precisely the same picture, for it will be remembered that the medullary rays do not extend quite to the surface of the kidney. A section at this most superficial posi-

tion would show only convoluted tubules and their intermediary portions. Not even Malpighian bodies would be here seen. In the longitudinal section, shown at Fig. 19, the brackets indicate the boundaries of the lobules. Figs. 21 and 22 show, much enlarged,

FIG. 22.



Transverse section through papillary portion of a medullary cone. *a*, Collecting tubes in transverse section separated by connective-tissue fibers and cells. *b*, Portions of loops. *c*, Blood-vessels. × 150.

the appearance of transverse and longitudinal sections in the cortex. Fig. 23 a transverse section through the papillary portion of the medulla, showing the relatively large proportion of connective tissue between the collecting tubes in this situation.

VI. *Nature of the Act of Secretion of Urine.*

It is commonly known that two widely different views exist as to the nature of the act of secretion of urine. According to the much older view of Bowman, it is partly physical and partly vital. According to the later theory of Ludwig and his school it is a purely physical act. Ludwig claimed that all the constituents of the urine are separated in very dilute solution by a pure act of filtration from

the capillaries of the glomerulus into its capsule; and that in the convoluted tubules there occurs merely an aqueous reabsorption resulting in a concentration of the fluid. Professor Küss[1] goes so far as to claim that the filtered product is really the *serum of the blood,* whence in health the *albumin,* as well as some of the water, is reabsorbed in the convoluted tubules; and Küss explicitly asserts that "the epithelium of the uriniferous tubes simply absorbs, but does not secrete."

According to Bowman, on the other hand, the filtrate separated in the Malpighian capsule is almost pure water. In it may be dissolved some of the inorganic salts of the urine; but the most important ingredients, the organic nitrogenous,—including urea, uric acid, creatin, creatinin,—and extractives are added in the convoluted tubes.

It is now generally conceded that these organic constituents, as well as the inorganic, exist preformed in the blood; and although the experiments made many years ago by Oppler,[2] Perls,[3] and Zalesky[4] led to opposite conclusions, they lack confirmation, and now few, if any, claim that the urea and extractives are manufactured, so to speak, in the kidney. They are believed to exist preformed in the blood, and are selected therefrom by the cells of the convoluted tubules.

A priori there are two important reasons why we should expect that the proper gland-cells of the kidney should have some more highly specialized function than that of aqueous reabsorption: (1) They possess the anatomical peculiarities of glandular epithelium whose function everywhere else in the economy is an elaborating one. (2) When, as the result of disease, the tubules are stripped of epithelium, urea and allied toxic substances are retained and uremia results. The experiments of R. Heidenhain, confirmed by those of Adami, have reaffirmed the older view. The indigo sulphate of sodium (indigo-carmine) is a substance which, when injected into

[1] Küss, A Course of Lectures on Physiology (second edition). Translated by Dr. Amory, Boston, 1875, pp. 465–467.

[2] Oppler, Beiträge zur Lehre d. Urämie, Virchow's Archiv, Vol. XXI., p. 260, 1861.

[3] Perls, Beiträge zur Lehre d. Urämie, Konigsberg Med. Jahrb., Vol. IV., p. 56, 1864.

[4] Zalesky, Untersuch. über d. Urämischen Process, Tubingen, 1865.

the blood of animals, is promptly separated by the kidneys and appears in the urine. Heidenhain injected this substance, and after appropriate intervals, removed the kidneys and examined them microscopically. In no instance did he find any of the indigo-carmine in the Malpighian capsules; but the cells of the convoluted tubules and the ascending loop of Henle were filled with it, as was also the lumen of the tubes if the animal was killed sufficiently long after the injection. Similar experiments with urate of sodium showed that this substance is secreted in precisely the same situation.[1]

With these facts before us it no longer seems reasonable to deny a direct selective action on the part of the cells of the convoluted tubules, and I accept, therefore, as the correct view of the nature of the urinary secretion, that the water of the urine is filtered out in the Malpighian capsule, the condition favorable to such filtration being supplied by the increased blood-pressure which exists in the glomerulus. In this water may be dissolved some of the inorganic constituents of the urine, but the most important nitrogenous principles, the true effete and poisonous matters which it is the office of the kidney to remove, are separated by the agency of the cloudy cells lining the convoluted tubules, the ascending limb of Henle's loop, and the intermediary segment of Schweigger-Seidel. From these cells they are pushed out into the lumen of the tube by the *vis a tergo* of additional secretion, and dissolved by the water which comes down from the Malpighian capsule, thus producing the urine, which is gathered up by the collecting and excreting tubes, by which it is emptied into the pelvis of the kidney at the papillæ.

[1] For the details of these interesting experiments the reader is referred to the paper of J. Heidenhain in Max Schultze's Archiv, Vol. X., 1874, p. 1; also to his paper, Versuche über den Vorgang der Harnabsonderung, in Pflüger's Archiv, Vol. IX., p. 1, 1874. Good abstracts are also found in Foster's Physiology, p. 277 (first edition), 1877, and in Charcot's Treatise on Bright's Disease, translated by Millard, 1878. See also J. G. Adami, On the Function of the Glomerule of the Kidney, The Practitioner, London, 1888.

SECTION II.

TESTING FOR ALBUMIN.—ALBUMINURIA, ITS SOURCES AND MECHANISM OF ITS PRODUCTION.

TESTING for albumin lies at the bottom of all diagnosis in Bright's disease, and there is no form of kidney affection in the investigation of which we dare omit to determine the presence or absence of albumin. Further, I am confident that even at the present day small amounts of albumin are not unfrequently overlooked in hasty examinations. Hence it cannot be out of place to discuss briefly this matter. It may be mentioned in passing that albumin was first discovered in urine by Cotugno in 1770.[1]

When large quantities of albumin are present in urine, its detection is most easy. The addition of from 5 to 30 drops of acid—nitric and acetic are commonly used—to half an ounce of urine in a test-tube, will promptly precipitate the albumin, if much is present. Or, if the urine is acid in its reaction, the albumin is as promptly thrown down by boiling; and if, after boiling, a few drops of acid are added, the solution of any phosphates precipitated by the heat is secured; while any albumin which may have remained in solution because the original urine was alkaline when boiled, will be thrown down. It should not be overlooked that, unless a considerable amount is present, albumin is not precipitated by heat from an alkaline urine.

But it is the small amounts of albumin which escape attention, and it is to these that I would especially direct attention. Under ordinary circumstances, by far the most distinctive test for small quantities of albumin is that form of the nitric acid test known as Heller's, to be presently described. It is, however, less delicate than the ordinary heat and acid test applied in the manner to be described.

Many who have often tested urine for albumin by the ordinary heat and acid test, will have observed that after boiling the clear urine, and adding a few drops of nitric acid, the resulting fluid will

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

be apparently clear; but upon setting aside the urine thus treated, for an hour or two, there will sometimes be found a small deposit. Supposing the urine before testing to have been *carefully filtered,* this deposit is either: (1) Acid urates; (2) uric acid; (3) nitrate of urea; or, (4) albumin. The *first* result from a partial decomposition of the neutral urates by the nitric acid added; the *second* by a further action of the acid upon the acid urates, and a resulting complete separation of the uric acid from the sodium, potassium, etc., with which it was combined; the *third* is found only when the urine happens to be highly concentrated and contains an unusual proportion of urea. The *second* and *third* have well-known forms of crystallization, by which they can be easily recognized under the microscope, but the acid urates and albumin are both amorphous and cannot therefore be thus distinguished. *All,* however, *except albumin,* disappear on the reapplication of heat. In all doubtful instances, urine which has been tried by heat and nitric acid *should be boiled again* after cooling and standing from an hour or two to six, and if the sediment is not dissolved by such heating it is albumin.

The method which on the whole I have found most satisfactory is as follows:

I. *The Heat Test.*—Unless *perfectly* clear the urine is first filtered. A portion of the filtered urine is then *boiled,* and carefully watched in a *suitable light* for detection of the least diminution in transparency. I say a *suitable* light, because it is not always a bright light that is desired. A diminished transparency might easily be overlooked in it, and it is generally desirable to shade the light a little with the hand or a book before the diminished transparency can be noticed, if the latter is slight. On the other hand, an insufficient light, such as that of a dark day, is altogether unsatisfactory. A drop or two of nitric acid is then added, and if any turbidity resulting from the action of the heat disappears, such turbidity is due to phosphates and not to albumin. A few drops more of acid should then be added. It is sometimes desirable to compare the tube and contained urine with another filled to the same depth with urine which has not been heated. If any degree of turbidity remains, it is caused by albumin, and the test may end here, although it is well to put the test-tube aside, in order that, after subsidence, the albumin may be approxi-

mately estimated. If, however, there is the least doubt about the presence of albumin, the tube must be set away, carefully protected from dust, for an hour or two, in order that any appreciable sediment may subside, and be subsequently again tried with heat.

II. *Heller's Contact Method With Nitric Acid.*—Another small test-tube is then filled to the depth of half an inch with colorless nitric acid. About as much urine is then allowed to fall gently upon it from a pipette, in the manner represented in the figure, while the point of junction of the two fluids is carefully watched for the white line of albumin. This is best seen by shading the tube by the hand or a pamphlet placed behind and slightly below the line of junction, so that the light may fall obliquely upon it. The gradual delivery of the urine from the tube is greatly facilitated by rotating the latter under the index finger, especially if the upper end of the tube is a little roughened. This secures such a gradual entrance of the air as permits the urine to descend very slowly without mixing with the acid below.

Precautions.—In concentrated urines of high specific gravity, a white band may make its appearance at the border between the two fluids, which is not albumin, but amorphous *acid urates,* resulting from the partial decomposition of the neutral urates and the precipitation of the more insoluble acid salt. But the behavior of the band thus produced is quite different from that of the albumin. Although sharply defined at first, the lower border stands at a slightly higher level than that of the albumin, while the upper edge soon ceases to be sharp and rises upward into the urine like a cloud, soon pervading the entire supernatant urine; whereas the albumin remains sharply defined at the line between the two fluids, until, in the course of several hours, if its quantity be small, it may be completely dissolved by the excess of acid present. *Further, the cloud of acid urates is promptly dissolved by the application of a moderate heat.* If, as sometimes happens in acute fevers, the urine is both concentrated and contains albumin, there may be two layers, an upper cloudy one of urates, and a lower sharply defined of albumin. It sometimes happens that the entire bulk of a test-tube of urine may sometimes be rendered cloudy by the addition of acid to be again dissipated by heat. But in chronic Bright's disease, at least, urine is

generally of low specific gravity, and the complication is not likely to occur.

When these precautions are observed in connection with the above double test, it is almost impossible to err as to the presence of albumin.

It sometimes happens, however, that, in consequence of age and putrescence, the urine has become alkaline, precipitated phosphates pervade the fluid, and it swarms with bacteria. As a consequence, it is so opaque that small quantities of albumin cannot be detected. Filtering does not mend this. The bacteria and finely divided phosphates pass through the minute openings of the filter with the filtrate. Under these circumstances it becomes necessary to clarify the urine. This may be done by boiling a portion of the urine with an *equal* bulk of officinal liquor potassæ, and filter. If still not quite clear, add a few drops of the "magnesian fluid,"[1] warm again, and filter. To the clear fluid thus obtained Heller's acid test may be applied, or, after careful acidulation, the *heat* test. In this manner very small quantities of albumin may be recognized in urine which would not otherwise permit its detection.

To Indicate the Quantity of Albumin in a given Specimen of Urine.—In practice it is scarcely possible to apply the only exact quantitative method of estimating albumin, by coagulation, filtration, drying, and weighing, because of the time it necessarily occupies. The method by Esbach's albumometer is only partially satisfactory because the results by it are not constant.

For practical purposes it is sufficient to compare from day to day the bulk of precipitated albumin with that of the urine tested. For this purpose it is convenient to have a test-tube graduated, by which the estimation is facilitated. In writing or speaking, this should be referred to as one half, one fourth, or one tenth the bulk of urine tested, as it may happen to be. A very careless habit of speaking of these proportions as *percentages* should be avoided. Thus, when the albumin in a given specimen of urine equals one fourth its bulk, it is often carelessly said that there is 25 per cent. of albumin. Now

[1] The *magnesian fluid* is made by dissolving magnesium sulphate and pure ammonium chlorid, each *one* part, in *eight* parts of distilled water, and adding one part of liquor ammoniæ.

when we remember that the serum of the blood does not contain more than 5 per cent. of albumin, and the most highly charged albuminous urines rarely contain more than 2 per cent., the absurdity of this mode of expression is evident. Only when the albumin is coagulated, dried, and weighed, and the weight compared with that of the urine when it is taken, should we speak of percentage; otherwise the proportion of bulk is referred to, and it should be clearly indicated.

Seat of Transudation of Albumin in the Albuminuria of Renal Disease.

It is commonly believed that when urine is albuminous, the albumin transudes along with the water into the Malpighian capsule, although there has never been any absolute demonstration that this is the case. Experiments of Heidenhain, with a view to settling the question, led to negative results, and until some positive demonstration is afforded to the contrary we may accept on theoretical grounds the view usually held. These lie in the fact that in the first place there is a physiological constriction at the orifice of the efferent vessel by which the blood leaves the glomerulus. This is of course increased under pathological conditions when there is hyperemia of the second capillary network, producing swelling and overgrowth of the cells of the convoluted tubules, which compress the blood-vessels of the rete, and further resist the egress of the blood from the glomerulus. Under these circumstances we have an increased pressure under which albumin will transude, although its osmotic equivalent is very low, and under normal conditions it will not pass out. This well-known property of albumin is a sufficient reason against the view of Küss, already alluded to, page 46, that under normal conditions the transudate into the Malpighian capsule is the serum of the blood, whence the albumin is reabsorbed by the cells of the convoluted tubules.

Albuminuria from other Sources than the Parenchyma of the Kidney. The So-called False Albuminuria.—It is well known that albumin may enter the urine from other sources than the secreting substance of the kidney. The pelvis of the organ, the ureters, the bladder, and the urethra, and in the female, the vagina and uterus also, are these sources. In all of them except the uterus it

is almost invariably the serum of *pus* formed during inflammation of their mucous surfaces which furnishes the albumin. The presence of pus-corpuscles, therefore, in sufficient number in the urine is usually sufficient to explain the source of such albumin, usually also small in quantity. It must not be overlooked, however, that the two sources, the kidney itself and the mucous surfaces, referred to, may unite, in which event careful microscopic examination would sooner or later discover tube-casts, while the quantity of albumin would be larger than could be caused by pus alone.

Carl Bartels[1] mentions copious albuminuria, with an inconsiderable sediment of pus, after the free use of cantharides internally and externally, as a form of albuminuria to be distinguished from that of Bright's disease; but it seems to me the condition thus resulting ought to be regarded as the first stage of acute Bright's disease or parenchymatous nephritis.

Menstrual and *lochial blood* need only be referred to as sources of albumin in the urine, hardly likely to be overlooked by any physician; while *hemorrhage* from any one of the mucous surfaces referred to, as well as the kidney itself, would be a source of albuminuria.

It is usually comparatively easy to determine whether a hemorrhage has its source in the kidney or the mucous membranes above mentioned. In the former, coagula are never present, but the blood entering the pelvis of the kidney, slowly and intimately mixed with the urine, imparts to it when acid in reaction a *smoky hue* which is very characteristic. The coloring matter of the corpuscles is mostly dissolved out by the urine which it thus tinges, and on standing the stroma of the corpuscles sinks to the bottom in the shape of a brownish sediment. The microscope reveals these corpuscles shrunken, almost colorless, and often crenated. I have said that the smoky hue is present only in acid urine. When the latter is alkalized, either by spontaneous or artificial change in reaction, it assumes a brighter red hue, the degree of which depends upon the quantity of blood. The same cause, acidity, produces the smoky hue of blood which is vomited, and mixed with gastric juice. When blood comes

[1] Bartels, Carl, article on Diseases of the Kidney, in Ziemssen's Cyclopedia of Medicine, Vol. XV., p. 31, New York, 1877.

from the pelvis of the kidney or the ureter in any quantity, coagula, which are moulds of the ureter, are sometimes found, the descent of which is often attended with severe pain.

Another source of albuminous urine, though not likely to cause error, should be mentioned, and that is the so-called *chylous urine,* or *chyluria,* in which, in consequence of some as yet imperfectly understood communication between the lymphatic system and the urinary tracts, chyle enters the urine and imparts more or less of its physical and chemical characters. These are a milk-white appearance, due to the presence of fat in a molecular state of division, and a large amount of albumin. The disease is one of tropical countries usually, but I have met two cases in this latitude.

The Immediate Cause of the Transudation of Renal Albumin.—It has already been intimated that obstruction to the onward movement of the blood is the immediate agency which forces albumin, an otherwise non-osmotic substance, through the walls of the capillary blood-vessels. It was at one time claimed that a peculiar state of the albumin of the blood in disease facilitated its transit, but the exhaustive experiments of Stockvis[1] some time ago refuted this view. The required obstruction is produced by any cause which sufficiently resists the movement of the blood through the kidneys, whether that cause resides in the organ itself or the venous system beyond it, whence the albuminuria which so often attends extreme valvular disease of the heart.

It is equally certain, however, that the transudation is facilitated by changes in the capillary walls. In the first place it is conceivable that some change in the texture of the membranous wall takes place analogous to such as occurs in a filtering membrane through which a fluid is forced by pressure, an increase in the size of the apertures or pores of the membrane if we so choose to term them. On the other hand, the experiments of Cohnheim upon inflammation[2] have shown that among its phenomena is a free transudation of albumin accompanying the wandering out of the colorless corpuscles of the blood. This element of increased albumin exudation would be found only

[1] Stockvis, Recherches Expérimentales sur les Conditions Pathogéniques de l'Albuminurie, in Journal de Médecine de Bruxelle, vols. 44, 45, 1867.

[2] Cohnheim, Ueber Entzündung, Virchow's Archiv, Bd. 40, S. 77.

in the more acute inflammatory conditions of the kidney, and accounts for the larger amount of albumin in these as compared with the more chronic processes where pressure is the sole agent. The transudate of albumin takes place, not only from the glomerulus into its uriniferous tubule, but also into the interstices of the organ outside of the tubules, wherever the colorless corpuscles wander, furnishing there a pabulum for the overgrowth of the intertubular and intervascular connective tissue, always sooner or later present.

It is possible, also, that pathological changes in the cellular lining of the uriniferous tubules may facilitate the transudation of albumin. But the quantity of this source must be very small, and the fact remains that intravascular pressure, aided by alterations in the capillary walls, is the chief immediate cause of albuminuria, at least in acute renal disease. In chronic albuminuria another important condition operates in facilitating the transudation of albumin. This is the *hydremic state* of the blood, which is itself a consequence of albuminuria.

One other source of renal albumin requires to be alluded to. It is the albumin which appears in the urine in grave cases of infectious diseases, such as typhoid fever, smallpox, scarlatina, etc. The albuminuria of diphtheria and scarlatina, due to intercurrent parenchymatous nephritis, is of course not intended. The albuminuria alluded to is not usually large, and disappears with the decline of the disease. erhardt[1] first suggested that this albumin represented the disintegration of numerous red blood-disks, and the observations of Obermüller[2] were confirmatory. It seems quite unnecessary to adduce such or any explanation which goes back of the acknowledged fact that all of the infectious diseases may become complicated with a nephritis, the milder degrees of which, manifested by cloudy swelling, are attended by a correspondingly small albuminuria. It may, however, be worth while to mention in passing the explanation of Carl Bartels, who agrees with Gerhardt that in subjects of acute fever, whose temperature stands persistently above 40° C. (104° F.),

[1] Gerhardt, Ueber die Eiweisstoffe des Harns, in Deutsches Archiv für klin. Med., Bd. 5, S. 213.

[2] Obermüller, Beiträge zur Chemie des Eiweissharns, Inaug. Dissertat. Würzburg, 1873.

albumin passes into the urine. He holds that the properties of the filtering membrane are changed by the high temperature, that the surface of the filter is enlarged, and its pores must of necessity become more roomy.[1] Finally, he concludes that febrile albuminuria is akin to the overflow of albumin into the urine which follows section of the vasomotor nerves of the kidney, the excessive heat of the body acting in the same way as such section.

[1] Bartels, op. citat., p. 53.

SECTION III.

CASTS OF THE URINIFEROUS TUBULES—THEIR NATURE AND CLINICAL SIGNIFICANCE.

A SO-CALLED "urinary cast" or "tube-cast" or "cylinder" is a mould of a uriniferous tubule. To this all are agreed. But beyond this, opinions differ not a little as to its exact mode of origin, composition, and significance. I retain the term "cast," in common with most English physicians, in preference to that of "cylinder," because it conveys the idea of what is meant with sufficient preciseness, while it implies nothing more. The adjective "fibrinous" I also discard as conveying an erroneous impression as to the composition of many tube-casts, although it is true that some are fibrinous.

Casts may be studied as a sediment in the urine or *in situ* in the uriniferous tubules where they are formed. They are characterized by differences in appearance and structure, as the result of which they are variously named. Thus there are hyaline casts, epithelial casts, pus-casts, blood-casts, oil-casts or fatty casts, waxy casts, cylindroids or mucus-casts and granular casts. Of the latter there are three subdivisions,—*slightly* granular, *pale* or moderately granular, and *dark* granular casts. As to the material of which casts are composed different views are held. I will first present my own, because it will enable me at the same time and in the briefest manner to describe the several varieties.

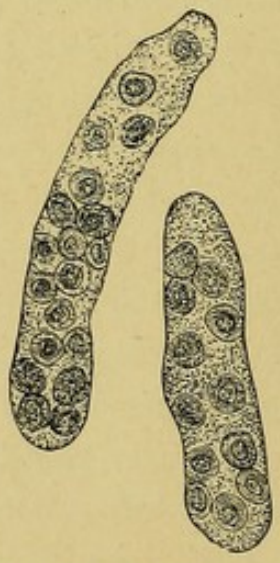
In the first place, all casts are not of the same composition. Thus, what are known as *blood-casts* are made up of coagulated fibrin and blood-corpuscles, the latter being entangled in the coagulum precisely as they are in a clot formed out of the body. The blood, by transudation or because of rupture of the capillaries of the Malpighian tuft, trickles down into the tubule, where it coagulates, forming a mould of the tube, and, after contraction, slips out into the pelvis of the kidney, whence it passes by the usual channel into the bladder. Blood-casts are represented in Fig. 23.

Second, the term *epithelial cast* (Fig. 24) is applied to any cast to which epithelial cells are attached, be they few or many. In the latter case, the entire mould is often made up of closely-packed desquamated cells, which may be cemented by their own adhesive properties or by a small quantity of fibrin from simultaneously transuded blood; for blood-casts and epithelial casts constantly accompany each other. When the epithelial casts are unassociated with blood, and the cells and their fragments—often their nuclei only—are few, the cells are separated by intervals, at times quite regular, of a hyaline material, to which they may be attached, or in which they may be imbedded. It is the nature of this hyaline material which is the subject of dis-

FIG. 23.

Blood-casts.—After WHITAKER.

FIG. 24.

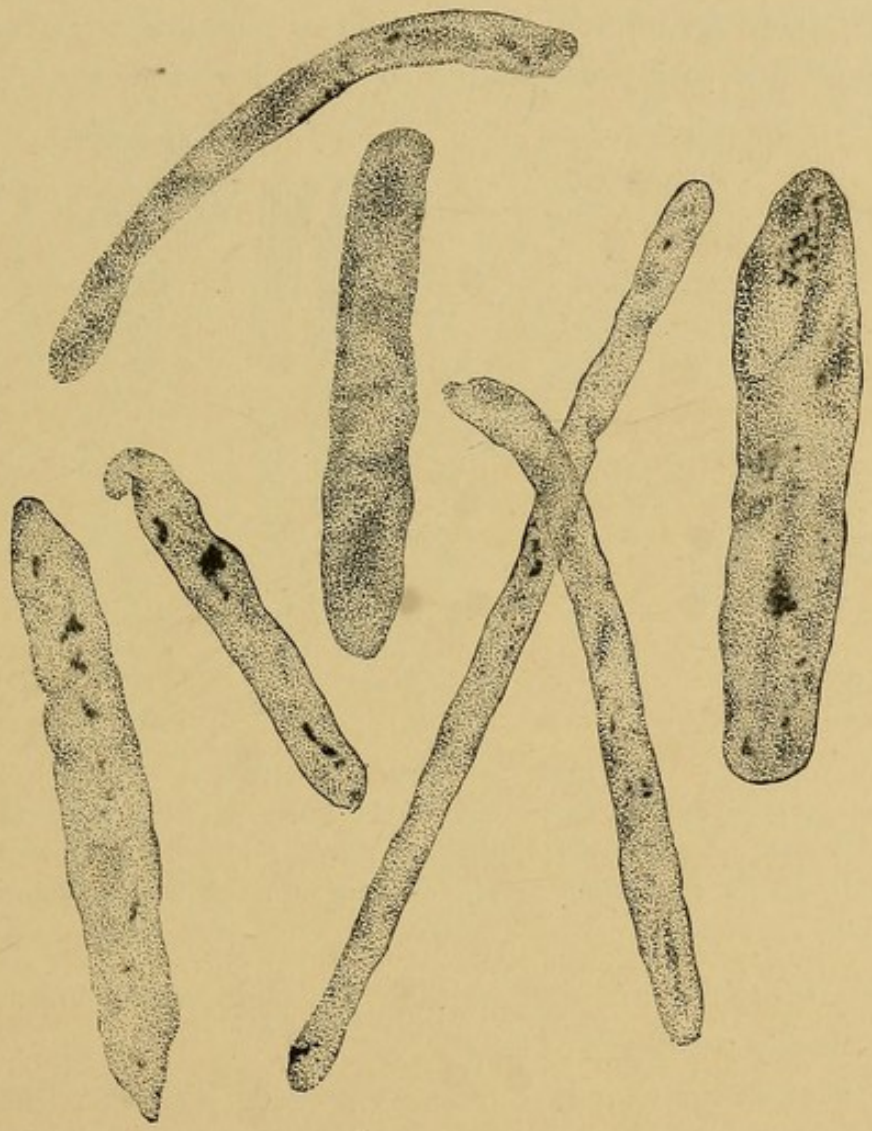


Epithelial casts. × 200.

pute. It seems most reasonable to consider it an exudate from the blood of a fibrinous or an albuminoid substance, coagulating after transudation into the tubules, entangling there, as does fibrin, whatever substances may be in the tubule, and occluding it for the time being. That it is true fibrin coagulated is not unlikely, the fibrinogen being furnished by the blood-plasma, the fibrino-plastin by the blood-corpuscles. Where there is hemorrhage into the tubules, both conditions of coagulation are abundantly present and blood-casts are also formed. It is true, the chemical properties of casts have been investigated by Axel Key and also by Rovida, who assert them to be altogether different from those of fibrin. But, that the hyaline material

is in many instances some sort of exudate rather than a result of a metamorphosis of cells, is sustained by the fact that the hyaline is the only shape of cast formed in the slightest derangements of the kidney, as when there is a mere transitory congestion of the organ, and where there is no alteration of the epithelium whatever. The

FIG. 25.



Granular casts. × 225.

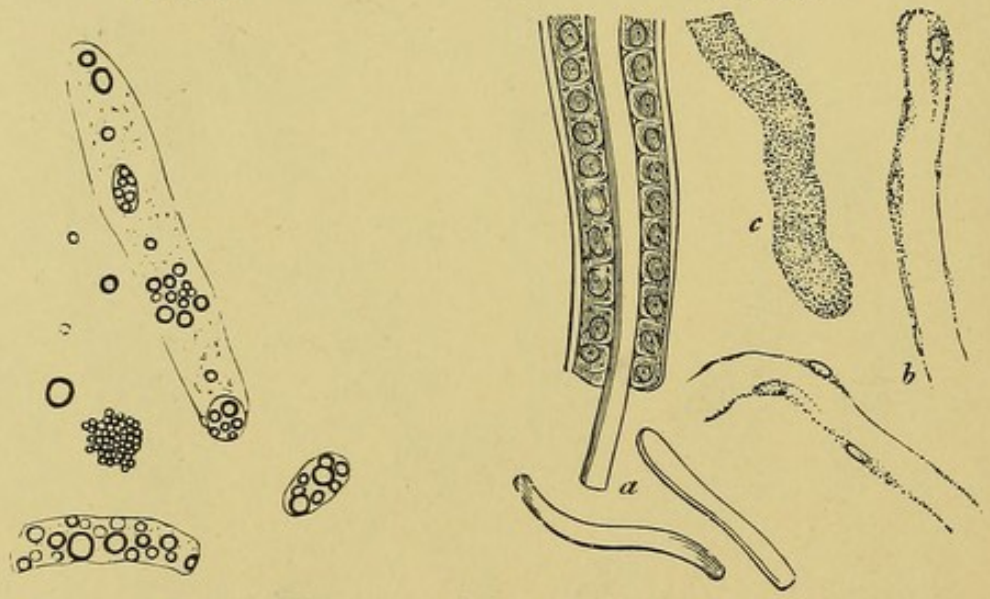
same objection holds to the basic substance being a secretion of the cells lining the tubules.

Third, the *pus-cast* is formed when pus-cells have wandered out into the tubules and unite to form a mould of the tubule.

Fourth, the three forms of *granular cast* have probably different modes of origin. In the case of the *dark granular cast* the cells have

undergone complete disintegration, and the products of this form a closely packed, dark, granular mass. If many red blood-disks happen to be in the tubule and share the breaking up, a yellowish tinge is communicated to this form of cast. In other instances the granular matter is less abundant, and a *pale* granular cast is the result, and when only a few granules are present the cast is *slightly granular*. The granules here are less easily accounted for. They may result from a similar disintegration of cells fewer in number, or they may be due to a precipitation of granules from the albuminous

FIG. 26. FIG. 27.



Oil casts and fatty epithelium.

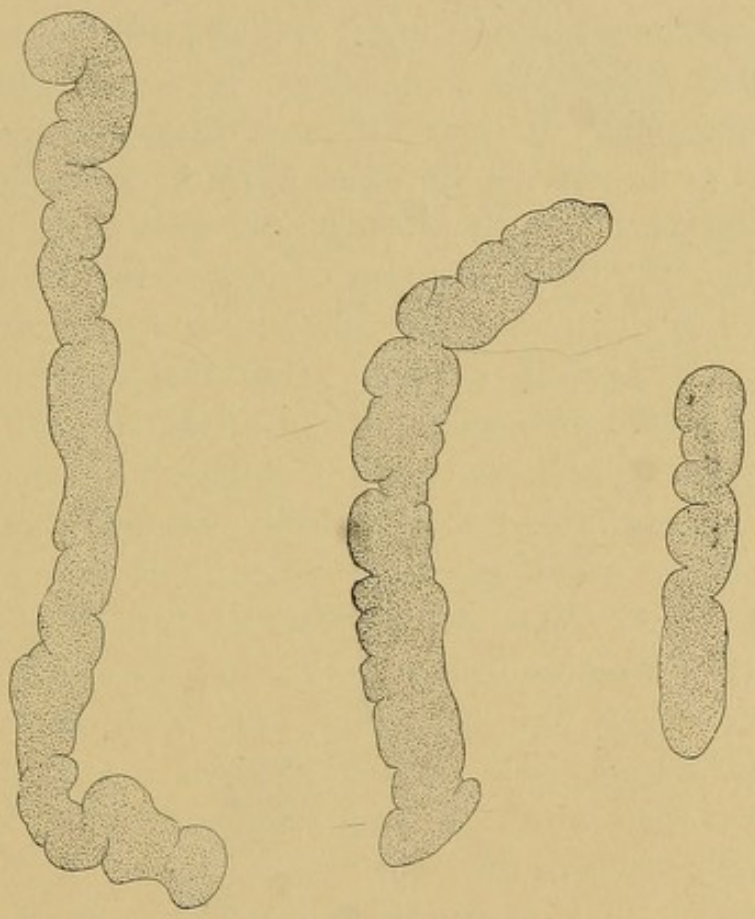
Pale granular and hyaline casts, one of the latter of small diameter, protruding from a tubule in which the epithelium remains intact. A cast of the same tubule bereft of its epithelium would evidently be of larger diameter.—After RINDFLEISCH.

substance of the hyaline cast, similar to that which occurs in the so-called cloudy swelling of cells.

Fifth, the *oil-cast* is a like product. Here the cells have undergone a fatty degeneration, some having completely broken up into fatty globules, while other cells retain their continuity and shape, forming *granular fatty* cells (compound granule-cells) and other forms of fatty cells. The oil-drops and fatty cells are seldom so abundant that they form a closely packed mass constituting the cast, but they are more or less separated by the hyaline basis referred to. Fatty casts in urine are apt to be accompanied by free oil-drops and free fatty cells, as seen in Fig. 27.

Sixth, *hyaline casts* are the simplest form of cast. They are delicate, structureless, or almost so, and composed of the transparent substance already referred to. They are of different width, even when produced in the same tube, according as the cast is formed when the tubule is bereft of its epithelium or the latter remains adherent. This will be understood by examining Fig. 28. In the former case a hyaline cast of "large" diameter is produced, in the

FIG. 28.



Hyaline casts. × 225.

latter one of "small" diameter. The range of width thus produced is from .025 mm. to .05 mm. ($\frac{1}{1000}$ to $\frac{1}{500}$ of an inch). Hyaline casts are sometimes so delicate and transparent as to be scarcely visible, and require care in illuminating the field of view of the microscope to bring them out distinctly. They are also often characterized by peculiar indentations or partial fractures, as shown in Fig. 29. Hyaline casts occur in all forms of renal disease.

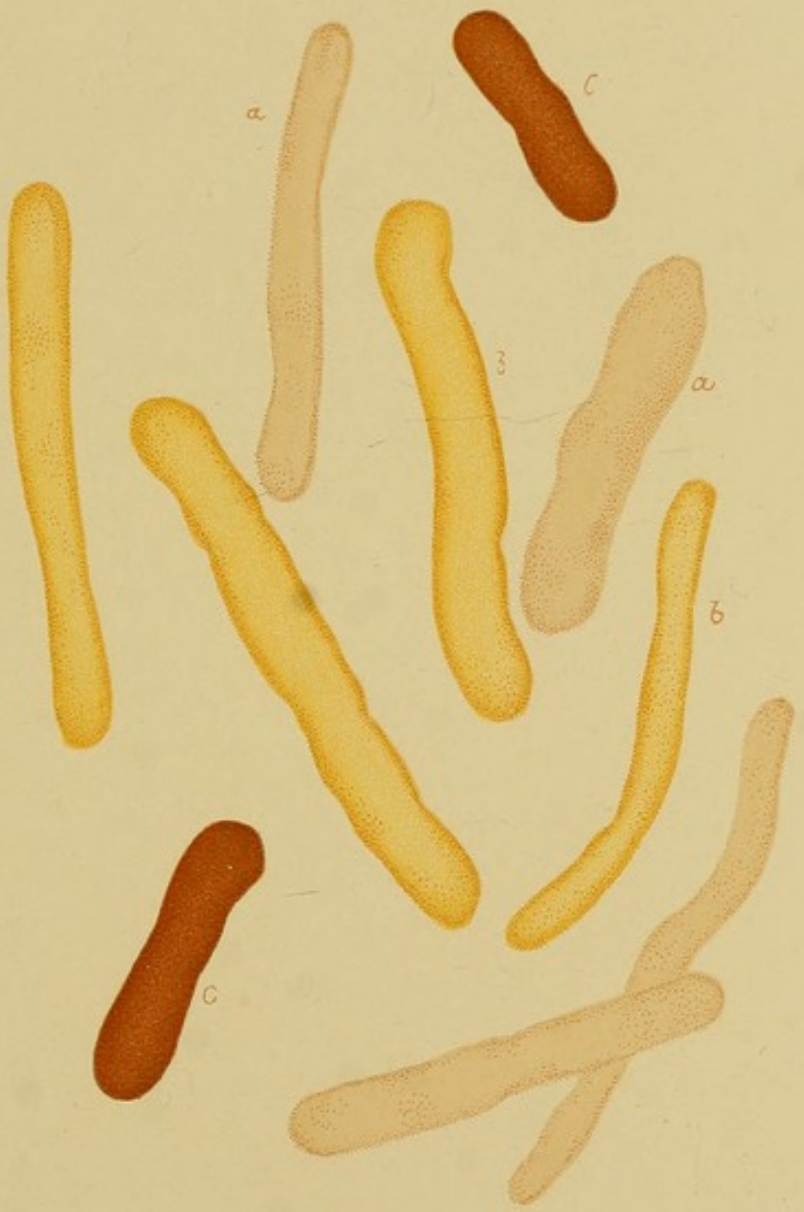
Seventh, *waxy casts* are also hyaline, but more solid and glistening in appearance, more highly refracting, and apt to present a

yellowish tinge. From their supposed resemblance to molten wax, they have been called "waxy," but they bear no essential relation to the so-called "waxy" or lardaceous or amyloid kidney, by all of which terms it is known. The material of which they are composed has, at least, different refracting properties from that of the ordinary hyaline cast, and probably originates differently. It will be seen, presently, that it is this form of cast with regard to which there is most unanimity in ascribing it to a fusion and hyaline transformation of desquamated epithelium, or of other cells within the tubules. The same objections which lie in the way of admitting such an origin of the simple hyaline casts do not exist here, and it is not unlikely that they thus arise. It is uncertain, however, whether the transformation is or is not the so-called waxy or amyloid transformation, the presence of which in the blood-vessels, tubules, and cells of the kidney constitutes the form of kidney disease known under that name. For these waxy casts do not, as a rule, strike the iodin reaction of the amyloid change. That they do occasionally, is attested by the dark mahogany-red tint of the two casts pictured in the colored plate opposite, a result I obtained, however, only after many times carefully and systematically treating these casts with iodin. The more usual coloration by iodin is that of the yellow casts shown in the same plate. Bartels[1] has obtained the same reaction in two instances, and suggests that the age of the material forming the cast may have something to do with the transformation into true amyloid material. And Rindfleisch[2] also said that he was convinced that casts which are long retained in the urinary tubules, especially in the bends of the looped tubes, undergo a glassy swelling, and assume the micro-chemical characters of amyloid substance, striking the iodin reaction, even in kidneys which are not otherwise amyloid. That they are not always the altered epithelium of the tubes is evident, for the reason assigned by Rindfleisch; in the first place the epithelium is seen well preserved between the casts and the basement membrane, and in the second, it is only in the highest degrees of the amyloid degeneration of the kidney that the cells are involved.

[1] Bartels, in Ziemssen's Cyclopedia of Medicine, Vol. XV., p. 90.

[2] Rindfleisch, Patholog. Histol., New Syd. Soc. Transl., Vol. II., 1872, p. 144; fifth German edition, 1878, p. 443; sixth German edition, 1886, p. 534.

PLATE I



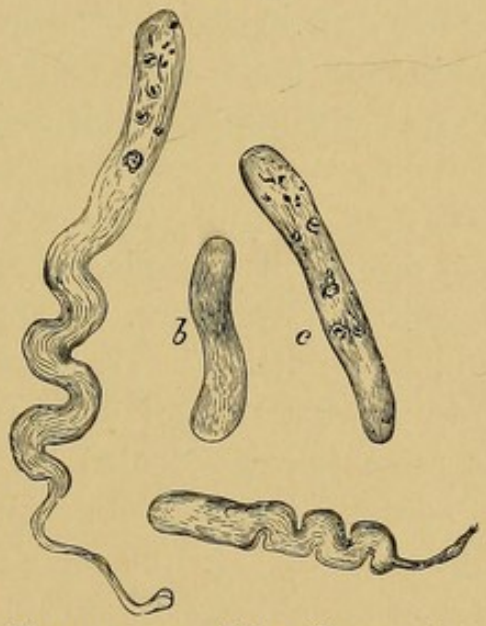
WAXY CASTS TREATED WITH IODINE

Again, waxy casts are found in all forms of acute and chronic renal disease, in chronic interstitial nephritis more rarely.

Finally, there are cylindroids or *mucus-casts*. These are transparent, sometimes delicately fibrillated bodies doubtless also moulded in the uriniferous tubules and composed of a mucoid material, probably a secretion of the epithelial lining of the tubules. They are at times so like a hyaline tube cast that it is not easy to distinguish between them. The cylindroid is commonly longer and often branching, the successive branches becoming gradually smaller in diameter, and often terminating in a pointed or spiral ending . They are well shown in the annexed figure.

They are associated with irritation of the urinary passages and often with urine of high specific gravity and acid reaction. There

FIG. 29.



Mucus casts. (After STENGEL.)

may be a trace of albumin in the same urine or none at all. They are probably formed in the branching tube of the medulla.

Cylindroids were incidentally described by Rayer[1] as far back as 1851, also by Lehman, Frerichs, L. Mayer, Wyss, and Obermeier, especially in association with cholera and relapsing fever, but were more accurately described by Thomas[2] in connection with scarlet fever. He considered that in part at least they are formed in the uriniferous tubules.

[1] Mem. de la Societe de Biol., 1851, Pl. III., figs. 3–4.
[2] Archiv d. Heilkunde, 1870, XI.

In addition to cylindroids there are often found in acid urine of high specific gravity threads or bands of fibrillated material commonly regarded as composed of precipitated mucin, which are not to be confounded with mucus-casts, although they may be of the same composition.

Dimensions of Casts.—Casts may attain the unusual length of one mm., when they are usually hyaline, or they may be broken into fragments so small that it is only by comparing their appearance with larger undoubted casts that their nature can be recognized. Their diameter varies with that of the tubule in which they are formed, say from $\frac{1}{2500}$ to $\frac{1}{500}$ inch or .01 mm. to .05 mm.

Views as to the Nature and Formation of Tube-casts.

Dr. A. Burkhart, in a successful prize essay[1] presented to the medical faculty of Tübingen, in 1871, furnishes an interesting historical sketch of the study of casts, from the time of their discovery to the date of his essay. Although Simon is their reputed discoverer, several observers had previously published descriptions of objects found in urine, which were evidently casts. The first of these was Vigla, who, in a paper on the microscopic constituents of urine, published in a journal called *l'Expérience,* in 1837, spoke of "finely granular longish albuminous plates." He gave no further description, and did not state in what kind of urine they were found. In 1838 Donné, in the same journal, denied the occurrence of these albuminous plates. To this Vigla replied that he had observed them in the urine of Bright's disease. In the same year, 1838, Rayer, in his treatise on diseases of the kidneys, described certain membranous, irregularly shaped, finely granular, white or yellow lamellæ, as occurring in albuminous urine but said nothing of their composition. The first unmistakable description of these bodies was given by Nasse, of Marburg, in a notice published in Schmidt's *Jahrbuch,* in 1838, of Donné's plates of urinary sediments, and more clearly in a paper by him on the microscopical constituents of the urine in Bright's disease, published in 1843.[2] Simon first described casts as constit-

[1] Burkhart, A., Die Harncylinder mit besonderer Berücksichtigung ihrer diagnostischen Bedeutung. Gekrönte Preisschrift. Mit Einer Tafel. Berlin, 1874.

[2] Nasse, Medizinischen Correspondenzblatt rhenischer und westphalischer Aerzte, No. 8, s. 121, 1843.

uents of urine in Bright's disease in his work on practical chemistry, in 1842.

Henle was the first to study casts *in situ* after he had previously examined them in the urine of a case of Bright's disease. This he did in 1844,[1] and then asserted their *fibrinous* composition, whence the term "fibrinous" cast still in use. From this time forward numerous communications appeared, and by 1845 the presence of casts in the urine of Bright's disease was an acknowledged fact.[2] In this year Scherer published Heller's theory, according to which casts were the result of congestion and exudation of liquor sanguinis.

To pass to more modern observers, Traube also held that casts are composed of fibrin, which is caused to exude by a high degree of intravascular pressure.

The late Sir George Johnson[3] said: "The basis of all renal tube-casts is the fibrin within the uriniferous tubules; but these casts assume various appearances, according to the nature of the products which they contain and the condition of the tubes in which they have been moulded."

Dr. Beale[4] says: "The transparent material probably consists of a peculiar modification of an albuminous matter possessing somewhat the same characters as the walls of some epithelial cells, the elastic laminæ of the cornea, etc., but not condensed like these structures." This, according to him, is the basis substance, which, becoming solid, entangles epithelial cells, nuclei, granular matter, blood-corpuscles, or whatever may be in the tube at the time the effusion occurs; or which solidifies in the shape of a hyaline cast, if the tube be empty, or the epithelium so firmly adherent that the cast slips out without detaching it.

Dr. Dickinson[5] believes that, as a rule, fibrin forms the basis of all casts, but says "it sometimes happens that cylinders are found in the urine, which appear to consist entirely of compacted epithelial

[1] Henle, in Henle und Pfluger's Archiv, Band I., Heft I., s. 60, 1844. Henle, in Zeitschrift für rationelle Medizin, Bd. I., s. 68.

[2] See the work of Burkhart alluded to for a full historical sketch, more particularly of German authors.

[3] Johnson, Lectures on Bright's Disease, New York, 1874.

[4] Beale, Kidney Diseases and Urinary Deposits, Philadelphia, 1869, p. 339.

[5] Dickinson, W. Howship, On the Pathology and Treatment of Albuminuria, 2d edition, London, 1877, p. 19.

cells, or of epithelial cells held together by fibrin so small in amount as to be barely perceptible."

Sir Grainger Stewart[1] held that tube-casts are composed of coagulated fibrin with altered epithelium and not unfrequently blood-corpuscles. Weissgerber and Perls[2] are among those who adhere to the view that casts are formed of exuded fibrin, while Robin, as early as 1855, protested against the use of the term "fibrinous" cast, as being erroneous.

Axel Key,[3] having shown that the chemical characters of casts were incompatible with a fibrinous composition, early claimed that at least the so-called "hyaline gelatinous" and "hyaline waxy" casts are composed of desquamated epithelium which has fused and degenerated into a hyaline mass, and that dark granular casts are also formed by an agglomeration of degenerated epithelial cells. O. Bayer[4] asserted that all varieties of casts originate in this melting together and transformation of cells. Schachowa,[5] in some experiments upon the artificial production of nephritis in dogs, by means of cantharides, obtained results which sustained the same conclusions. On the other hand Œdmansson[6] claimed that all casts originate as a *secretion from the epithelial cells* lining the tubules, and Œrtels[7] defends the same view.

Langhans[8] says that while many casts arise from a metamorphosis of cells contained in the uriniferous tubules, he is far from claiming that all casts originate in this manner. It is especially the waxy casts that are thus formed, while the pale homogeneous cylinders are a *kind of secretion from the epithelium*. According to Langhans, the cells which undergo conversion into waxy casts may be either the desquamated epithelium of the tubules,

[1] Stewart, Grainger, Bright's Disease, 2d edition, New York, 1871, p. 80.

[2] Weissgerber und Perls, Archiv für Experiment. Pathologie, Bd. VI., 1876.

[3] Key, Ernst Axel, Om. des k. Tubularafgjutningarnas olika former och bildning vid sjuckdomar i Njurarne; Med. Archiv, Stockholm, 1863, I., 233–277, 2 pl.

[4] O. Bayer, Ueber den Ursprung der sogennant. Fibrin-cylinder des Urins, Archiv für Heilkunde, 1868, s. 136.

[5] Schachowa, Untersuchungen über die Niere. Dissert., Bern, 1876.

[6] Œdmansson, quoted by Bartels, op. citat., p. 84.

[7] Œrtels, Experimentelle Untersuchungen über Diphtherie, Deutsches Archiv für Klin. Med., Bd. VIII, s. 292.

[8] Langhans, Theodore, Ueber die Veränderungen der Glomeruli bei der Nephritis nebst einigen Bemerkungen über die Entstehung der Fibrincylinder, Virchow's Archiv, Bd. 76, erstes Heft, 1879, 85.

lymph-corpuscles, or red blood-disks. In either event, first melting into each other, they break up into a finely granular mass, which subsequently undergoes a glass-like transformation. This begins at the periphery, and extends thence towards the center. A yellowish tinge and more highly refracting character result when the cells thus converted are red blood-disks.

Rovida,[1] whose observations on the nature of casts have been alluded to, makes but three varieties of casts,—the *colorless,* the *yellow hyaline,* and *epithelial,* and he considers the colorless and yellow hyaline a secretion from epithelial cells.

Bartels[2] (1870) admits three modes of origin for casts. First, that dark granular casts originate directly by an agglomeration of degenerated epithelial cells, by which agglomeration I infer also he forms epithelial casts, although he makes no direct statement to that effect. He insists, however, that in every case in which he has examined microscopically thin sections of diseased kidneys whose tubules were blocked by the dark granular casts, the tubules invariably exhibited an epithelial lining. He reconciles this fact with his view by admitting that the theory of Key and Bayer, that the epithelium thus shed is rapidly reproduced, may be correct. Secondly, he believes that the yellow (waxy) casts arise as a species of secretion from the epithelium. Third, Bartels holds that certain "homogeneous, transparent, lightly streaked, or faintly shaded varieties, or the forms which are so delicately stippled with the finest granules or minute oil-drops,—in a word, the casts which are most rightly called hyaline, are formed by a coagulation of the albumin and its derivatives secreted by the urine."

Charcot[3] (1878) denied that casts are fibrinous and considered that some (certain granular casts) are made up of broken-down epithelial cells, others (hyaline and some granular) of an albuminous substance, while epithelial casts are agglomerations of epithelial cells more or less altered.

E. Wagner[4] (1882) says neither clinical nor anatomical investiga-

[1] Rovida, Ueber das Wesen der Harncylinder, Moleschott's Untersuchungen zur Naturlehre des menschen und der Thiere, Bd. XI., s. 1.

[2] Bartels, op. citat., 84, 85, 86.

[3] Charcot, On Bright's Disease, translated by Millard. New York, 1878, p. 29 et seq.

[4] Morbus Brightii, Leipzig, p. 52.

tion has as yet furnished a satisfactory explanation of the formation of casts. He cites four theories of cast formation:

1. By secretion or increased functional activity of the renal epithelium. He asserts that Œdmansson and Rovida hold that all casts originate in this way; while Virchow, Axel Key, Burkhart, Aufrecht, Bartels, Senator, Cornil, Langhans and Litten hold it is chiefly hyaline casts that are thus formed. Wagner rejects this view, which he says is based partly on theoretical grounds and partly on a false interpretation of the unstainable hyaline spherical structures known as *boules proteiques* or plasma spheres found in the tubules of the kidney, and which are normal products.

2. Casts arise through metamorphosis and further fusion of renal epithelium. Wagner considers this view confirmed by numerous microscopic appearances noted in the human kidney.

3. Many casts at least arise from cells contained in the urinary tubules such as desquamated renal epithelium, lymph or red corpuscles. Wagner ascribes this view especially to Langhans.

4. Casts arise by coagulation of albuminoid bodies by a process analogous to the coagulation of fibrin. This oldest of all views announced originally by Henle is the one most generally entertained at the present day. The precise process, he says, is still unknown.

Rindfleisch[1] (1886) held that casts are made up of a transparent homogeneous coagulum composed of some modification of albumin, resembling perhaps most closely fibrinogen, on which may be deposited fine and coarse granular material, exfoliated epithelium, fat globules, granular fat-cells and blood corpuscles. He said further that he early favored the view that in some instances at least the epithelial cells may elaborate in their protoplasm a substance which they pour out into the lumen of the renal tubules, in other words that casts might also be a secretion of the renal cells.

Rindfleisch also held that the majority of casts are formed in the looped tubes of Henle, while the casts sometimes found *in situ* in sections of the cortex lie not in the convoluted tubules proper but in Schweigger-Seidel's segments or the collecting tubes which, according to Henle, penetrate the entire cortex, demarking the labyrinth.

[1] Edouard Rindfleisch, Lehrbuch der Pathologischen Gewebelehre, Sechste Auflage. Leipzig, 1886, s. 533–4.

According to Rindfleisch casts long remaining in situ may be converted into amyloid substance giving the amyloid reaction with iodin.

Henry B. Millard[1] (1892) regards casts as an albuminous exudate into the tubules from the surrounding capillaries plus the epithelium lining the tubules. The cells perish almost always completely, but sometimes partially in the process and by the appearance produced in their various stages and kind of degeneration contribute to the varieties of casts. Thus when the cells are converted into amyloid matter the product is the waxy cast. He considers it impossible for casts to form in tubules which have lost their epithelium and that when casts are found surrounded by epithelia it may be taken for granted that they have been carried into the place occupied from some other locality. "The epithelial and blood casts are simply hyaline casts with blood corpuscles or portions or entire epithelium adherent. The yellow are the result of imbibition of the coloring matter of the blood, while the waxy and fatty casts have undergone a waxy or fatty degeneration or rather the degeneration has taken place in the epithelia."

Waxy casts are especially characterized by their resistance to the action of acids and alkalis; hyaline casts, on the other hand, are rendered paler by the long-continued action of acetic acid while they are quickly dissolved by alkalis.

Siegmund Rosenstein[2] (1894) also divides casts into three principal varieties, *hyaline, waxy* and *epithelial*. Accepting Rovida's results that while the chemical reaction of casts corresponds with that of no known albuminous bodies it accords more closely with that of albumin; also that though the origin of all varieties is not known some owe their formation to secretory changes, and others to coagulation phenomena within the tubules. While there can be little doubt as to the mode of formation of epithelial casts and blood-casts opinions vary as to the origin of hyaline casts though the tendency of all explanations is to ascribe them to coagulation independent of epithelial change. This view is based on the fact that in sections of hardened kidneys casts are seen in tubules in which the epithelium is intact. The same thing is seen in kidneys in which artificial nephritis is produced by ligating their arteries and compressing

[1] Millard, Bright's Disease of the Kidneys, 3d edition. New York, 1892, pp. 97–98.

[2] Rosenstein, Nierenkrankheiten, vierte verbesserte Auflage. Berlin, 1894, p. 50.

them. Finally he alludes to Ribbert's ingenious experiments wherein, after causing casts to be produced, he injected carmin into the blood-vessel and found the casts unstained, while the epithelium of the tubules took the stain. Rosenstein has himself also been able to confirm the observations of Key and the experiments of Langhans as to the gradual conversion of epithelium *in situ*. He considers that the suggestion of Covine and Aufrecht that casts are secretion products is rendered likely by the experiments of Langhans, and the earlier observations of Virchow, who also described drops and spherules secreted by epithelium. Rosenstein has, however, never been able to see their union into casts and considers this mode of origin unlikely, while the exudation from the blood may be regarded as certain. The fibrinous composition of hyaline casts has been contested because of their homogeneousness and the total absence of fibrillated structure. So, too, they fail to respond to the staining characteristic of fibrin as practiced by Weigert and Rosenstein, although O. Israel and Paul Ernst claimed they do. Especially does the last assert the fibrin reaction for dried preparations obtained from urine and of sections through the cortex and claims that the more casts are formed in the medulla remote from the cortex the less do they present the fibrin reaction. O. Lubarsch[1] contests the distinctive character of Ernst's staining because there are numerous hyaline masses in various parts of the body which respond to Weigert's method which are not fibrin; and further that so-called fibrinous casts are stainable by stains which will not color fibrin. Lubarsch ascribes them not to an exudate from the blood, but to a secretion of the cell protoplasm. Th. Burmeister[2] showed that the true exudate which coagulates in the capsule of the glomerule after ligation of the renal vein does not respond to the Weigert stain.

Dr. H. Senator[3] divides casts into three principal varieties: (1) *Those composed completely or mainly of cells;* (2) *granular* casts; (3) *hyaline* or *amorphous* casts, either structureless or delicately striated. Between the three varieties are all possible transition forms including also such in which one part of the cast corresponds to one variety and another part to another. Besides are also frequently

[1] Centralblatt f. allg. Path. u. Path. Anat., Bd. IV., 1893.
[2] Virchow's Archiv, CXXXVII., p. 442, 1894.
[3] Die Erkrankungen der Nieren, Wien, 1896, p. 24.

found casts upon which are deposited bodies accidentally present in the urine, namely cells, crystals, microparasites, etc.

I. Cells of which casts are composed are mostly red blood corpuscles or epithelium from the uriniferous tubules. Casts are seldom formed of white blood cells alone, though such cells may be attached to other forms of casts. The epithelial casts arise by the agglomeration of exfoliated renal epithelial cells which become closely packed into a cylindrical mass in passing through narrow segments of tubules. The cells are more or less perfect or may present various stages of granular and fatty degeneration, sometimes swollen. The nuclei may be evident or indistinct. Blood-casts are made up of red blood corpuscles thus agglomerated and cemented by coagulated fibrin.

II. Granular casts Senator divides into coarse and fine granular. The granules are often highly refractive and their chemical behavior (a black stain by osmic acid) indicates that they are made up of the minutest fat drops (granular fatty casts); others again are made up of disintegrated albuminoid matter. "Doubtless," he says, "the various granular casts are in many instances made up of epithelium or epithelial casts in which the cells have undergone granular and fatty degeneration either before or after their desquamation." But hyaline casts may also probably in the lapse of time undergo a granular or fatty degeneration as does often albumin long retained within the body.

III. Amorphous or structureless casts Senator divides into *hyaline* and *waxy*. The former are also further divided into colloid, glassy and fibrinous casts.

Hyaline casts are pale and transparent, uniformly homogeneous or more rarely striated. Their transparency is often so great that they are not always easily recognized and are sometimes even overlooked or may be rendered visible only by accidental substances deposited upon their surface. They are better recognized when stained with weak tincture of iodin or other staining agencies. When treated with staining mixtures such as Ehrlich's they behave like coagulated albumin and they show also the other albumin reactions.

It is these casts, he says, the origin and nature of which is so much disputed. The oldest view is that they are made up of coagulated

fibrin such as the exuded fibrin characteristic of inflammation. In opposition to this, apart from other reasons, is the fact that these casts undoubtedly occur in conditions where inflammation is altogether out of the question, such as simple congestion of the kidney, simple amyloid degeneration, dyscrasic albuminuria, and finally in albuminuria of the new-born.

Senator also refers to Rovida's and O. Lubarsch's observations on Weigert staining and other properties of fibrin as already quoted in discussing Rosenstein's views.

Two possible sources for the albuminous substance of hyaline casts remain: The albumin of the blood serum and the epithelium of the renal tubes. As to the former there is the theory that albumin may transude from the blood-vessels into the capsules of the glomeruli or in the renal tubules, coagulate there and so form casts. Senator says he long ago showed such view to be untenable. There must at least be added an element which determines coagulation, because the urine itself is much more disposed to hinder coagulation than to favor it. This was shown by the studies of J. C. H. Lehmann and is confirmed by experiments and by clinical facts. Thus in chyluria, for example, where the urine contains albumin in a very coagulable state so that it coagulates simply when exposed to the air casts are never found. Even in a case of fibrinuria observed by Senator no casts were found. There is also the additional clinical fact that albuminuria bears no relation to the number of casts found in urine. There may be much albumin in urine and very few casts or none at all. On the other hand, we find casts, and especially hyaline casts, without albuminuria.

These facts make it very probable that casts never originate in the albumin of the blood serum. We must therefore admit that the transuded albuminoid substance coagulates at once to form casts and that casts do not originate from albumin in solution.

Finally he says, the fact that very broad casts are found in the collecting-tubes which can with difficulty have passed the narrow Henle's tubes is incompatible with any such view.

We must look, therefore, says Senator, to the epithelium of the renal tubules as playing the most important rôle in cast formation. This may occur in different ways: First, the death of epithelium and

its conversion into hyaline substance out of which casts are formed, a phenomenon which is confirmed by the microscopic picture wherein we see in one and the same cylinder the gradual transition of swollen epithelium into hyaline substance. Or the epithelium may die and thus is lost all resistance to the transudation of an albuminous fluid which by mixture with the material of the dead cell coagulates. According to still another view the epithelium furnishes a cast by a sort of secretion.

The "waxy casts," so called because of their glistening and yellowish waxy-like appearance, are mostly broader and more indestructible than the hyaline casts and show ordinarily no clefts or fissures. Their origin is more easily determined. It would seem that they are a conversion from other casts long retained in the urinary tubules. Sometimes these respond to the amyloid reaction by Lugol's solution, although they are not characteristic of the amyloid degeneration.

Senator regards casts an evidence of pathological changes in the kidney, or at least of the epithelium. There may be a simple nutritional and functional derangement which may amount to complete disintegration. Especially do epithelial casts point to a desquamation of epithelium; fatty granular casts or hyaline casts with fatty epithelium attached point to degeneration processes, while casts with attached leucocytes (which, by the way, are always mononuclear) point to an inflammatory condition and those with blood corpuscles attached or perfect blood casts point to hemorrhage within the renal substances.

Robert Saundby[1] (1896), in his recent Lectures on Renal and Urinary Diseases, makes but three varieties of casts: *Blood casts, epithelial casts* and *hyaline casts.* He regards as mixed varieties hyaline casts to which blood or epithelium may adhere, and granular casts which are either epithelial or hyaline casts, which have become opaque and granular by infiltration with fat granules or microörganisms.

I. *Blood casts* are really blood clots, that is blood corpuscles matted together with fibrin, the source of the blood being for the most part the capillary tufts of the Malpighian bodies, the blood becoming

[1] Second edition, Bristol and London, 1896.

coagulated in its passage down the tubes, whence it passes into the urine in the shape of cylindrical casts of the tubules.

II. *Epithelial casts,* according to Saundby, are of two main types. One is made of distinct small round granular cells like leucocytes but of smaller size, which "are, as their appearance suggests, proliferated renal epithelium."

The second type of epithelial casts is composed of a mass of epithelial cells crowded together so as to obscure their individual outlines, and are more or less opaque from fatty degeneration. These are formed by desquamation of the epithelium pushed off the basement membrane by the inflammatory exudate. They are usually of large diameter, being moulded in tubes bereft of epithelium.

III. *Hyaline* or *colloid casts* may reasonably have three modes of origin. The first is that of Langhans already described on page 66.

The second form of hyaline cast is pure fibrin formed by the action of the dead epithelium on the fibrinogen of the blood serum. This origin I suggested many years ago, but Saundby ascribes it to Salkowski and Leube. The third mode of origin of hyaline casts accepted by Saundby ascribes casts to an exudation or secretion from the tubular epithelium quite similar to that suggested by Œdmansson, Oertels, Aufrecht and Cornil already referred to. He considers this view confirmed by the more recent observations of Strauss and Germont.

Saundby believes that casts are rarely formed by transudation and he bases his opinion on their rarity in so-called functional albuminuria and the clinical fact that casts are only few and far between unless degeneration is present in the renal cells, due for example to long-continued excretion of bile by the kidneys, or chronic congestion such as is due to heart disease.

Dr. Charles W. Purdy[1] (1898), after naming the three principal views as to the nature and mode of production of casts, viz., disintegration of epithelium, secretion by the morbidly irritated epithelium, and coagulable elements of the blood which pass out into the tubules in consequence of pathological lesions in the latter, entangling any free or partly detached elements of the tubules, says the last is the view most generally accepted, at least so far as the nature and

[1] Purdy, Practical Uranalysis and Urinary Diagnoses, 11th edition, 1898, p. 189.

origin of the great majority of cases is concerned. He also says that "although the substance forming the basis of casts is evidently allied to proteids, it is certain that it is not identical with any proteid with which we are at present familiar."

Francis Delafield says (1899) :[1] "I believe that casts are composed of an exudate from the blood-vessels coagulated in the tubules of the kidney. If the exudate is by itself the casts are hyaline, if degenerated or desquamated epithelia are entangled in it, the casts are granular, nucleated, epithelial, etc."

Nestor Tirard,[2] in the most recent book written on Renal Diseases (1899), says: "Casts may be formed in various ways. Blood casts are undoubtedly formed by coagulation of extravasated blood, though sometimes the so-called blood casts are really hyaline casts containing red blood corpuscles." Quoting Langhans,[3] who thinks that hyaline casts are formed from epithelial cells, he admits that some casts may be thus formed by metamorphosis, but the theory is not universally applicable. He says it is far more probable, as Fagge suggests, that they are due to coagulation of albumin, though whether this coagulation is effected by acidulation of the renal epithelium (Saundby) or by the acid urine is doubtful. He also quotes experiments of Ribbert as going to confirm this view, of which only one appears to me to support it in any degree. This consisted in intravenous injections of carmine, succeeding which "the carmine was excreted by the glomeruli, and appeared not only in the albumin of the capsules, but also in the casts, while the renal epithelium remained free."

The Part of the Uriniferous Tubule in which Casts are Formed.

Casts may arise in all parts of the tubules of the kidney, but it is commonly asserted that most found in the urine have their origin in the looped tubules of Henle and the collecting tubes, because from these escape is easier than from the convoluted tubules; not, however, easier than from the *intermediary* or *intercalary* portion, in which each ascending limb terminates before it empties into a col-

[1] In a letter to the writer.

[2] Albuminuria and Bright's Disease. London, 1899, p. 87.

[3] Virchow's Archiv, Bd. LXXVI.

lecting-tube. This part of the tubule is identical in structure with the convoluted portion. Rindfleisch says that casts are formed only exceptionally in the convoluted tubules, and that when found *in situ* in the cortex of the kidney, it is in this intermediary piece of Schweigger-Seidel, and not in the convoluted portion, that they usually lie. While there are difficulties in the descent of a cast from the cortex of the kidney, and while such descent is doubtless more rare, I do not consider it impossible. The cast is smooth, flexible, and may contract its dimensions decidedly. Under these circumstances the *vis a tergo* of the newly secreted urine, which must be considerable, may be sufficient to force it downwards along the loop of Henle and through the intermediary piece into the collecting-tube. The convoluted appearance sometimes presented by casts does not prove that they have been formed in the convoluted tubules but rather that they have been forced through a narrow tubule or from a wider into a narrower. It is scarcely necessary to say that a blocking up of the convoluted tubules by casts is a very much more serious matter than obstruction of the straight tubes, and that if it were of frequent occurrence a larger proportion of cases of Bright's disease would become uremic.

It is not unlikely that those cases of chronic diffuse nephritis, with large albuminuria and very few casts, such as that of the young girl to be further alluded to on page 78, are cases in which the convoluted tubules are exceptionally involved; for in that instance the cortex was crowded with casts, while the urine contained but few, and the fatal uremia which terminated the case may have succeeded this involvement.

The Significance of Casts found in Urine.

The occasional occurrence of hyaline casts in urine otherwise normal is amply attested,[1] especially since the centrifuge has come into use; and it has also been said that epithelial casts are found as a result of the administration of diuretics.[2] It may, however, still be questioned whether kidneys shedding such casts are strictly normal.

[1] See Charcot on Bright's Disease, New York, 1878. Charcot says this was first pointed out by M. Robin in 1855, and confirmed by Axel Key, Rosenstein, and many others.

[2] Ibid.

That in many instances they are functionally sufficient, cannot on the other hand be denied. I should say that *numerous* casts even without albuminuria indicate a kidney more or less diseased.

In cases of irritation of the bladder, ureters, and pelvis of the kidney, there occur the *mucus casts* above described. Sometimes their resemblance to casts is even closer in consequence of precipitation upon them of granular urates or amorphous phosphate of lime. But this granular deposit, when present, incrusts everything which may be in the urine, epithelial cells, foreign matter, etc., besides forming a copious precipitate of its own.

Casts may also be produced artificially by constriction or ligature of the renal vein or artery or both. Even epithelial casts are said to have been thus produced.[1] Ligation of the ureter has the same effect, the over-filled tubules causing compression of the veins.

It is not unusual to find cases in which there have been albuminuria and casts, where, as improvement progresses, the albuminuria disappears, and casts are found in the urine for some time longer. The late Dr. Milner, of Chester, Pennsylvania, having had his attention called to the subject by a publication of my own, in which it was stated that during recovery from acute Bright's disease casts might be found in the urine some time after albumin had disappeared, examined carefully the urine of a child recovering from scarlatinal nephritis, and found casts for two weeks after albumin had disappeared. Such cases require no further comment. Bartels correctly says: "The formation and the excretion of a cast need be by no means contemporaneous events."

The following are also illustrative cases:

An adult woman, on admission to the Pennsylvania Hospital, exhibited a slight puffiness and pallor of countenance, which suggested an examination of her urine. No albumin was found by the physicians at the hospital, but a considerable number of slightly granular and hyaline casts. The late Dr. James H. Hutchinson sent me a specimen of the urine, and by no test could I discover the presence of albumin, but found delicate granular and hyaline casts. *One week later* a searching examination of the urine of the same patient revealed *neither casts nor albumin.* The case had probably been one

[1] Overbeck, quoted by E. Wagner, op. citat., p. 51.

of Bright's disease which was convalescent. Finally, A. Henderson reports for Osler, in the *Canada Medical and Surgical Journal,* Montreal, 1879, Vol. VII., a case of persistence of casts and blood-corpuscles in urine after albumin had disappeared. In the summer of 1892, a woman of 37 was under my care in the Hospital of the University of Pennsylvania for nearly seven weeks. At any time casts containing a few oil drops could be found in the urine which was always free from albumin. To these we should add cases of contracted kidney, in which occasionally for a time either casts or albumin may be wanting.

On the other hand, occasional instances of true renal albuminuria, and large albuminuria without heart disease, are sometimes met in which casts are absent. But even here, if the opportunity for repeated examinations is present, there comes a time when a few casts will be found, while later again an examination may fail to discover them. Such cases are not rare. In illustration, I saw a young girl of fourteen, who had copious albuminuria for nearly a year before I saw her. During this time her urine was examined for casts several times, but none were found. At my examination, although there was large albuminuria, *only a very few casts were found.* She died in a few days in uremic convulsions, and the autopsy revealed typical large white kidneys, weighing each about eight ounces. Upon microscopic examination of sections, the tubules of the cortex were found to contain numerous waxy casts. Finally, there are many instances of albuminuria where the absence of casts is reported in which the examination is at fault.

From these remarks some idea may be had of the significance of casts in the urine; and when we remember that urine is seldom investigated, unless we are searching for the cause of an evident or suspected ill health, we may lay it down as a rule, to which there are few exceptions, that when casts are found the kidneys whence they come are not normal. The condition may be temporary, but if so the casts pass away with it, while, if it is permanent, the casts continue. I think Charcot stated the case too strongly when many years ago he wrote in the volume above quoted, " in a general way, the clinical importance of urinary casts has been very much exaggerated "; also of epithelial casts, " it may be said that, from a clinical

point of view, they do not possess much importance"; and of hyaline casts, "even when renal disease exists, the hyaline casts are of no interest, except from their long persistence."

On the other hand, it dare not be said that we can determine in every case the nature of a renal malady by the casts present; but some of the varieties give us considerable assistance in making a diagnosis. The following general statements may be made:

1. Hyaline casts are found in all forms of Bright's disease, as well as in temporary congestions of the kidney, active or passive. The same is true of pale granular casts.

2. Epithelial casts are found in acute, subacute, and chronic parenchymatous nephritis. In the latter two forms the cells are generally degenerated and fragmentary.

3. Blood-casts are found in acute parenchymatous nephritis, and where hemorrhages have occurred in the kidneys.

4. Dark granular casts are found in parenchymatous nephritis, acute and chronic, and rarely in interstitial nephritis.

5. Waxy casts are found in both acute and chronic Bright's disease, and attend any of the three principal forms.

6. Oil-casts are found in subacute and chronic forms of Bright's disease, and may attend any of the three principal forms, but are most numerous in chronic parenchymatous (diffuse) nephritis.

7. Pus casts are found in acute nephritis of severe form.

8. Free fatty cells and free oil-drops are found in chronic parenchymatous nephritis.

9. The form of fatty cell known as the granular fatty cell or compound granular cell is found in acute and chronic parenchymatous nephritis. I consider the fatty cell as of real diagnostic value in favor of parenchymatous nephritis as distinguished from interstitial nephritis.

10. Blood discs in small numbers may be found in the urine from any form of Bright's disease, but are numerous only in acute varieties and in chronic hemorrhagic forms.

11. The number of casts in different specimens of urine varies greatly. They are very numerous in the urine of acute nephritis and commonly in chronic diffuse nephritis, and less numerous in chronic interstitial nephritis and amyloid kidney.

SECTION IV.

HISTORY OF THE DEVELOPMENT OF OUR KNOWLEDGE OF BRIGHT'S DISEASE.

The history of the development of our knowledge of Bright's disease begins almost suddenly with the discoveries of the distinguished Guy's Hospital physician whose name it bears. While a general notion of diseases of the kidney is coeval with medical knowledge such knowledge was confined in the Hippocratic[1] age (460 B. C.–367 B. C.) and the later Galenic period (A. D. 131–200) to injuries and suppurative affections of the organ and to stone. It was also known at that day that a falling off in the quantity of urine was associated with dropsy. Aretæus, who flourished about A. D. 100 and therefore preceded Galen, ascribed certain nervous symptoms to kidney disease. Aetius (died A. D. 367), at different times slave, goldsmith, charlatan, physician, deacon and heretic, ascribed dropsy to a hardening of the kidney. Avicenna (A. D. 980–1037) also held that dropsy supervened in the course of a hardening of the kidney, and sought to differentiate the cause of different dropsies, ascribing some to affections of the liver and others to diseases of the kidney.

In 1662 Van Helmont[2] considered the cause of dropsy lay in the kidney. Cases of renal disease associated with dropsy were reported by J. Schenk Von Grafenburg[3] (1600), Bonnet[4] (1670), Morgagni[5] (1761), Lieutaud[6] (1764), J. P. Frank (1745–1821), P. A. Portal[7] (1742–1821) and others.

[1] Hippocrates, Section 7, Aphorisms 34 and 37.

[2] Van Helmont, Oriatrike or Physick refined. London, 1662, p. 507.

[3] Von Grafenburg, Observationes medicorum rararum novarum, etc., libri 7, 1600.

[4] Bonnet, Sepulcretum anatomicum, 1679.

[5] Morgagni, De sedibus et causis morborum, 1761.

[6] Lieutaud, Historia anatomica medica, 1764.

[7] Portal, Observationes sur la nature et le traitment de l'hydropsie. Paris, 1824.

Observations multiplied, showing the association of dropsy and alterations in the kidney, though J. Baptiste Sauvages (1706–1767) ascribed an anasarca to stone in the bladder. In 1770[1] Cotugno discovered that a coagulable substance (albumin) could be precipitated by heat from the urine of dropsical patients and diabetics. After this Cruikshank[2] and Blackall[3] described cases of dropsy with and without albuminuria. Blackall ascribed albuminuria and the anatomical alterations of the kidney to a general inflammation and separated these from cardiac dropsies. Thus were distinguished the so-called active, idiopathic, inflammatory dropsies in which were included albuminous urines, from the passive or symptomatic dropsies without albuminuria. Even in his fourth edition published in 1825 he assigned a constitutional cause for dropsy and was inclined to believe that albuminuria was due to the elimination of the dropsical fluid by the urinary passages.

In 1807 Brande[4] and in 1823 Scudamore[5] showed that albuminous urine contained a diminished quantity of urea as compared with the normal secretion. Scudamore also found that there was albumin in the urine of gouty subjects and in dyspeptics. According to Rayer[6] Edward D. Allison, of Edinburgh, published in 1823 several cases of dropsy with albuminous urine associated with granular kidney. In 1826 Andral[7] described a case of granular kidney.

It remained for Richard Bright,[8] in 1827, to unite the three factors, a renal lesion, albuminuria and dropsy, to constitute therefrom a separate disease of the kidney. In his first paper he pointed out the frequency of the disease and described the chief anatomical varieties which he illustrated by five plates. He also gave the important symptoms and the chief features of treatment.

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

[2] In Rollo, Diabetes Mellitus, 1798, pp. 433, 447 and 448.

[3] Blackall, On the Nature and Cure of Dropsies. London, 1818; Philadelphia, 1820.

[4] Brande, An Account of Some Changes from Disease in the Composition of the Urine. London, 1807.

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

[6] Rayer, Traité des Maladies des Reins, T. H. Paris, 1840, p. 543.

[7] Andral, Clin. Med., 1826, III., p. 567.

[8] Bright, Diseased Kidney in Dropsy, Reports of Medical Cases, I., 1827.

Bostock[1] (1827) added to the preciseness of our knowledge by calling attention to peculiarities of the urine and some alterations of the blood. The more recent labors of Bright[2] added much to our information and approached astonishingly our present knowledge. Saundby[3] has well condensed them as follows:

"He had learnt that dropsy might be slight or altogether absent, and that albuminuria might require looking for. He described the various complications, the inflammation of serous membranes, hemorrhages, apoplexies, convulsions, blindness, and coma. He drew attention to the frequency of cardiac hypertrophy, and suggested an explanation which still holds its ground. He recognized the importance of alcohol and exposure to cold as etiological factors, while his views on prognosis were truer and more liberal than those which afterwards became current. But on the actual nature of the pathological process his ideas were cramped by the contemporary state of pathological doctrines. Just as in these days every disease is ascribed to a microbe, in Bright's time everything was regarded as due to a deposit. Laennec called tubercle and cirrhosis of the liver deposits. So Bright thought the various anatomical types of Bright's disease were stages in the evolution of a deposited material, and the hard granular kidney was the ultimate result of the process."

[1] Bostock, Report of Medical Cases, 1827, p. 75.

[2] Reports of Medical Cases, Vol. II., 1831. Guy's Hospital Reports, 1836, 40 and 43.

[3] Lectures on Renal and Urinary Diseases. Bristol and London, 1896, p. 83.

SECTION V.

CLASSIFICATION OF BRIGHT'S DISEASE.

WHATEVER may be the objections to retaining the term Bright's disease or Bright's diseases in medical nomenclature, there is every reason to believe it will remain in use for many years, if not as long as medical science exists. This being the case, I see no reason for excluding from the category any one or more of those affections of the kidney attended by albuminuria, dropsy, and tube-casts, either simultaneously or in close relation to each other. For, accurately described and delineated by Bright as were some of these forms of disease which he studied, it is evident that he had no correct notion of the intimate nature of the processes which constitute them; while it is almost certain that among those cases of dropsy and albuminuria which came under his notice were examples of forms of disease which certain authors would eliminate from the category of Bright's disease. Thus it is scarcely likely he could have failed to have had under his observation in a large hospital experience cases of the so-called lardaceous or amyloid disease of the kidney, though he failed to recognize it as a separate form, and probably included it under one or another of the three described by him. Rokitansky (1842) was the first to include amyloid disease of the kidney under Bright's disease.

Traube, Kelsch and Delafield are, so far as I know, alone in desiring to discard the term Bright's disease altogether.

Bright's[1] first paper appeared in 1827, and of the earlier writers after him, Rayer[2] was the first to recognize the inflammatory character of the changes in the kidney described by the great English physician. Rayer also said of the six forms which he himself described that they are "probably successive."

Reinhardt[3] (1850) and Frerichs (1851) after careful histological

[1] Bright, Richard, Report on Medical Cases. London, 1827.

[2] Rayer, Traité des Maladies des Reins. Paris, 1839–41.

[3] Reinhardt, Ann. d. Charité, Krank. zu Berlin, 1850. Frerichs, Die Brightsche Krankheit und deren Behandlung, 1851.

investigation also concluded that the conditions described by Bright were the result of inflammation, and first sought to establish the proposition of the "unity" of Bright's disease, that is, that the different forms represent three successive stages of this process: (1) hyperemia; (2) exudation with fatty degeneration of epithelium, and (3) new growth of connective tissue with resulting atrophy of the kidney. They introduced the theory of acute nephritis.

These observers laid especial stress upon the casts found in the urine during life and in the uriniferous tubules after death. Supposing their fibrinous nature established, they considered the inflammation a "croupous" one, and applied the term "diffuse croupous nephritis" to the entire process on account of its uniform distribution over the organ. Finally they included under Bright's disease all affections of the kidney attended by casts; among them, therefore, the results of passive congestion, or, as they are now called, cyanotic induration and amyloid disease. Traube (1856) first insisted that the former was a distinct process and should not, therefore, be included under Bright's disease. He also showed how amyloid disease could be distinguished from other renal diseases; and although Bamberger earnestly strove to replace the former in the category, the views of Traube have since generally prevailed in Germany.

Virchow (1852), in his famous paper on parenchymatous inflammation,[1] makes, (1) a milder degree of inflammation, which he terms *catarrhal* nephritis, in which there is, first, a hyperplasia of epithelial cells, and later an alteration and shedding of the same; (2) a *croupous* inflammation, wherein a fibrinous exudation is added to the catarrh; and, (3) a *parenchymatous* inflammation, in which, too, the cells are altered, swollen, cloudy, granular, and subsequently break up. To what he considers the very rare combination of these three conditions —catarrhal, croupous, and parenchymatous nephritis,—he suggests that the term Bright's disease, if used at all, be restricted. Samuel Weeks (1853) energetically opposed the doctrine of the "unity" of Bright's disease. Rokitansky and Johnson had previously recognized amyloid degeneration as a complication. Rokitansky was the first physician in Germany who made microscopic examinations of the kidneys.

[1] Virchow, Ueber Parenchymatöse Entzündung. Berlin, 1852.

In his *Cellular Pathology* (1858), however, Virchow includes under the term Bright's disease three conditions, one of which originates in the tubules (parenchymatous nephritis), a second in the intertubular tissue (interstitial nephritis), and a third in the vessels (amyloid degeneration). Thus Virchow was the first to call attention to the intertubular connective tissue as the special seat of a change. To this he had, in a more general way, alluded in his earlier paper. Arnold Beer[1] and Traube[2] located the entire primary process in this tissue, making the changes in the epithelium altogether secondary, and do not acknowledge such a process as parenchymatous nephritis. Kelsch[3] also attached great importance to the doctrine of interstitial nephritis.

Klebs (1870), in his *Handbook of Pathological Anatomy,* excludes cyanotic induration and lardaceous disease from *morbus Brightii.*

S. Rosenstein,[4] in the second edition of his work on *Diseases of the Kidneys* (1870), treats of congestive hyperemia, catarrhal nephritis, diffuse nephritis and amyloid degeneration, and says these are what have commonly been included under the term Bright's disease. But he himself uses the term as a synonym for his "diffuse nephritis." He adopts the older view of the "unity" of the disease, uses the term diffuse nephritis and says that it cannot strictly be said that there is pure parenchymatous nephritis or pure interstitial nephritis, both tissues being affected and "that large white and small red kidneys are alike the result of diffuse inflammation." Of this, however, he makes three stages, after the scheme of Reinhardt and Frerichs, a stage of hyperemia, one of exudation, and one of atrophy, the result of which is the granular contracted kidney. Thus atrophy may result from the parenchymatous process alone, by a fatty degeneration and breaking down of the cells; but is, for the most part, accompanied by changes in the interstitial tissue, which consists sometimes in a fibrillar and sometimes in a cellular hyperplasia, whose

[1] Beer, Die Bindesubstanz der Menschlichen Niere. Berlin, 1859.

[2] Traube, Zur Pathologie der Nierenkrankheiten, Gesammelte Beiträge zur Pathologie und Physiologie, 2 Bd., 2 Abtheilung. Berlin, 1860.

[3] Kelsch, Revue critique et recherches anatomo-pathologique sur la Maladie de Bright, Archiv de Phys., Vol. VI., 1874, p. 722.

[4] Rosenstein, Die Pathologie und Therapie der Nierenkrankheiten. Zweite verbesserte Auflage. Berlin, 1870, ss. 51, 100.

contraction coöperates to produce the atrophy of the organ. Rosenstein's catarrhal nephritis corresponds with Virchow's, that is, it is a slight degree of parenchymatous inflammation. Of interstitial nephritis as a special form he makes no mention. In his fourth edition (1894) Rosenstein[1] makes morbus Brightii synonymous with diffuse nephritis with the following subdivisions:

1. Acute morbus Brightii or acute diffuse nephritis.

2. Chronic morbus Brightii or chronic diffuse nephritis. The latter he subdivides into (*a*) The large white kidney, (*b*) The spotted or smooth contracted kidney, (*c*) the granular contracted kidney. In addition he treats of amyloid degeneration of the kidney as diffuse nephritis with amyloid degeneration; he also distinguishes from morbus Brightii, fatty kidney due to fatty infiltration, regressive metamorphosis, senile atrophy or increase of the surrounding fatty tissue.

Weigert[2] in 1879 emphasizes these views of Rosenstein's, maintaining that the parenchyma and stroma are involved in all cases of chronic Bright's disease and that pure parenchymatous nephritis exists only as an acute disease. Bamberger,[3] Grawitz and Israel support these views, the experiments of the last two having found that artificially induced nephritis was followed indifferently by the small red or large white kidney.

The English authors, and notably among them Sir George Johnson, were most instrumental in breaking up the notion of the "unity" of Bright's disease for a long time so stubbornly held by the German and French pathologists, and still maintained by Rosenstein and some others. Among those who have emancipated themselves most thoroughly from this doctrine are Bartels and Charcot. The former, in his article in Ziemssen's *Cyclopædia of Medicine* (1877), says that among the diseases originally grouped under the title Bright's disease, his clinical experience and pathologico-anatomical investigations have led him to include hyperemia, acute and

[1] Rosenstein, Die Pathologie und Therapie der Nierenkrankheiten. Vierte Auflage, Berlin, 1894.

[2] Weigert, Die Bright'sche Nieren krankung vom pathologisch-anatom. Standtpunkte, Volkmann's klin. Vortrage, Serie VI.

[3] Bamberger, H. von, Ueber Morbus Brightii und sein Beziehungen zu anderer Krankheiten, 1877.

chronic ischemia, parenchymatous inflammation, acute and chronic, interstitial inflammation or connective tissue induration, and amyloid degeneration. He also announces his firm allegiance to the English view of the nature of the disease. Charcot says:[1] "In my opinion, therefore, which is only, so to speak, the reflex of the English theory, Bright's disease is a class comprising several distinct species, not only from an anatomico-pathological point of view, but as regards etiology and symptomatology." These distinct species are parenchymatous nephritis, interstitial nephritis, and the amyloid kidney. Of modern French writers, Cornil and Ranvier, Lancereaux, Lecorché, Labadie-Lagrave and others, hold the same views.

Of the English writers above referred to, Johnson first promulgated his views in his larger work on *Diseases of the Kidney,* published in 1852, but his most recent views are found in his smaller treatise, entitled *Lectures on Bright's Disease,* published in 1873. He describes there an acute and chronic form. The former is represented by acute nephritis, the latter by the red granular kidney, the large white kidney, and the lardaceous or waxy kidney. Johnson laid special stress on the origin of the red granular independently of acute inflammation. Roberts, W. Howship Dickinson, and Sir Grainger Stewart, while differing somewhat as to the exact pathology of the different forms, adopt practically the same arrangement. Lionel Beale agrees entirely with Johnson. Grainger Stewart and Dickinson are the most systematic, and attempt a sharper differentiation of the different forms of parenchymatous nephritis. Stewart makes:

1. The *inflammatory* form, of which there are three stages, that of inflammation, that of fatty transformation, and that of atrophy.

2. The *waxy* or *amyloid* form, of which there are also three stages, that of degeneration of vessels, that of secondary changes in the tubes, and that of atrophy.

3. The *cirrhotic, contracting,* or *gouty* form.

Dickinson makes:

1. Acute tubal and diffuse nephritis, involving primarily the tubules, but extending, sooner or later, to the interstitial tissue, termi-

[1] Charcot on Bright's Disease, translated by Millard. New York, 1878, p. 36.

nating in fatty degeneration and subsequently contraction, if early death or recovery does not take place.

2. Granular degeneration.

3. Lardaceous disease.

Ernst Wagner[1] (1882) makes:

1. Acute morbus Brightii, including (*a*) infectious nephritis, due to scarlet fever and other infectious diseases; (*b*) toxic, due to icterus and diabetes mellitus; (*c*) septic nephritis, due to various forms of suppuration; (*d*) due to cold and unknown causes; (*e*) choleraic nephritis; (*f*) puerperal nephritis.

2. Chronic morbus Brightii, including subacute and chronic diffuse nephritis (the large white kidney of Wilks and others, and second and third stages of ordinary chronic Bright's disease, the so-called secondary contracted kidney); chronic hemorrhagic Bright's disease without edema, and acute hemorrhagic morbus Brightii superadded to previous symptomless chronic nephritis.

3. Genuine contracted kidney or granular renal atrophy.

4. Amyloid kidney.

He does not however include the last two under the term morbus Brightii.

Gull and Sutton[2] (1872) sought to make the form of chronic Bright's disease known as true contracted or granular kidney, a part of a general vascular condition which they characterize as "hyaline fibroid," primary to the renal disease instead of secondary to it, as especially held by Johnson and his school. Theirs and subsequent studies have established the existence of such a primary condition resulting in contracted kidney in a certain number of instances, but in by no means all and much less frequently than these authors believe, while the arterial condition is now commonly regarded as an arteriosclerosis.

E. Leyden[3] inclines to the doctrine of the unity of Bright's disease in that he opposes the dogmatic separation of parenchymatous and interstitial nephritis and prefers on this account the term diffuse nephritis instead of parenchymatous nephritis. He recognizes also

[1] Der Morbus Brightii. Leipzig, 1882.

[2] Medico-Chirurg. Transactions, Vol. IV., 1872, p. 273.

[3] Zeitschrift für klin. Med., 1881, II.

with Gull and Sutton a genuine contracted kidney whose starting point is a disease of the arteries closely akin to general arteriosclerosis. He adds also another form of sclerosis in which the kidney, notwithstanding histological alterations, is not reduced in size, and a contracted kidney associated with amyloid disease.

H. Senator[1] (1896), referring to Bartels' position in favor of the view that genuine contracted kidney was the result of a primary proliferation of intertubular connective tissue and did not represent the so-called third stage of acute nephritis, says that in 1878 he adopted this view of Bartels as to the existence of a genuine renal cirrhosis and its more frequent occurrence than secondary contracted kidney, but emphasized at the same time that a sharp demarcation between the two conditions is clinically and anatomically difficult or impossible, since the symptoms in either case may be the same, while on the other hand parenchymatous inflammation disposes to interstitial change. In 1880 he declares his belief with Gull and Sutton as did also Leyden, in the existence of a nephritis depending upon a general vascular disease leading to contraction, with this difference, that he as well as Leyden regards the arterial disease as a sclerosis. Senator considers that there is no justification for such a view as to the unity of Bright's disease in the sense of Reinhardt and Frerich's, according to whom all forms represent only different stages of the same disease process; while there is just as little reason for accepting the extreme dualistic view as held by Samuel Wilkes and Bartels, according to which the so-called contracted kidney or chronic interstitial nephritis has nothing whatever to do with the form of nephritis known as parenchymatous, but always arises as an independent disease. Each of these two views has something of truth in it from which it follows that neither can be entirely correct. He concludes his able preliminary consideration of the subject with the following classification of the hematogenous non-suppurative inflammations of the kidneys.

I. Acute nephritis.

(*a*) Parenchymatous nephritis (tubular and glomerulo-nephritis).

(*b*) Diffuse nephritis.

[1] Senator, Die Erkrankungen der Nieren, Wien, 1896.

II. Chronic diffuse nephritis without induration (chronic parenchymatous nephritis).

III. Chronic indurative nephritis (contracted kidney).

(*a*) Secondary induration (secondary contracted kidney).

(*b*) Primary indurative (chronic interstitial) nephritis.

(*c*) Arteriosclerotic induration.

He says also that within these groups still other forms occur, which furnish a certain variety in the disease picture but not sufficiently distinct to justify any further classification.

Fürbringer[1] (1895) says "thus our classification runs as follows":

I. *Diffused Nephritis.*

1. Acute kinds (including active hyperemia of the kidneys and febrile nephritis).
2. Chronic forms without decided atrophy.
3. Chronic forms with decided atrophy and genuine renal sclerosis; completely contracted kidney.
4. Amyloid kidney.

II. *Circumscribed nephritis* (suppurative), *inflammation of the kidneys, nephritis vera.*

Francis Delafield[2] (1882) makes the following classification:

1. *Acute Congestion of the Kidney.*—No change in the kidney except an engorgement of the blood-vessels. Caused by surgical operations, by injuries, by poisons, by extirpation of one kidney. Produces diminution in the quantity of urine.

2. *Chronic Congestion of the Kidney.*—Venous congestion, changes in the epithelium, dilatation of the capillaries of the glomeruli and of the capillary veins. Caused by any mechanical obstruction of the circulation. Produces diminution in the quantity of urine. Liable to be followed by chronic nephritis.

3. *Acute Degeneration of the Kidney.*—Degeneration or necrosis of the renal epithelium, to which may be added an exudation of serum from the blood-vessels. Caused by the introduction into the body of inorganic poisons, or the poisons of the infectious diseases. Milder forms give no symptoms. Severe forms are accompanied by scanty urine and constitutional symptoms.

[1] Fürbringer, Diseases of the Kidneys and Urinary Organs, English edition, Vol. I. London, 1895, p. 75.

[2] Delafield, Studies in Pathological Anatomy. New York, 1882.

4. *Chronic Degeneration of the Kidney.*—Degeneration of the renal epithelium. Caused by disturbances of the circulation and by chronic disease. Produces a diminution in the quantity of urine. May be followed by chronic nephritis.

5. *Acute Exudative Nephritis.*—Congestion, exudation of serum, emigration of white blood-cells, diapedesis of red blood-cells into the tubules or in the stroma; a growth of the cells which cover the capillaries of the glomeruli. Due to a variety of causes. Is accompanied by albumin, casts, and blood-cells in the urine, and by constitutional symptoms. Is a transitory condition terminating in the death of the patient, or his recovery.

6. *Acute Productive or Diffuse Nephritis.*—Congestion, exudation of serum, emigration of white blood-cells, diapedesis of red blood-cells into the tubules, or in the stroma; a growth of the cells which cover the capillaries of the glomeruli of the cells which line their capsules; a growth of new connective tissue in the stroma. Due to a variety of causes. Is accompanied by albumin, casts, and blood-cells in the urine, and by constitutional symptoms. Is apt be followed by chronic nephritis.

7. *Chronic Productive or Diffuse Nephritis, with Exudation.*—A growth of new connective tissue in the stroma, degeneration of the renal epithelium, changes in the glomeruli, changes in the arteries, an exudation of serum into the tubules. Due to a variety of causes. Is accompanied by albumin, casts, and blood-cells in the urine, a lowering of the specific gravity of the urine, changes in the quantity of the urine, and constitutional symptoms. Runs a subacute or chronic course, and is apt to terminate fatally.

8. *Chronic Productive or Diffuse Nephritis, without Exudation (Contracted Kidney).*—A growth of new connective tissue in the stroma, degeneration of the renal epithelium, changes in the glomeruli and in the arteries. Due to a variety of causes. Is accompanied by urine of low specific gravity and by constitutional symptoms. Runs a chronic course and terminates fatally. The two forms of chronic nephritis differ from each other anatomically only in the presence or absence of exudation from the blood-vessels. In the same patient, therefore, the nephritis may be at one time without exudation, at another time with it. And according to the presence or absence of the exudation, there will be a difference in the clinical symptoms.

9. *Suppurative Nephritis.*

10. *Tubercular Nephritis.*

William Henry Porter[1] (1887) adopts a classification similar to that of Delafield, as follows:

1. *Acute Parenchymatous Metamorphosis of the Kidney.*—Commonly known as acute parenchymatous nephritis, in which the epithelial cells lining the uriniferous tubules undergo metamorphic changes—namely, cloudy swelling and fine and coarse granular and fatty infiltration; in which, however, there is no change in the blood-vessels or interstitial tissue.

2. *Chronic Parenchymatous Metamorphosis or Chronic Parenchymatous Nephritis.* (First form of large white kidney.) The irritation of the epithelial cells has continued for some time and caused a progressive granular and fatty change. The slight alteration in the intertubular tissue is edematous in character and not inflammatory.

3. *Parenchymatous Metamorphosis of Pregnancy.* (Second form of large white kidney.)

4. *Parenchymatous Infiltration Metamorphosis of the Kidney with Wasting Disease.* (Third form of large white kidney.) A chronic, passive lesion similar to the fatty liver of phthisis and other wasting diseases. The epithelial cells become swollen and pale from the continued imbibition of fatty particles, which do not irritate the cell protoplasm sufficiently to prevent the performance of its function. Classed among the renal lesions on account of its gross appearances, so nearly like those of the more active type.

5. *Acute Diffuse Nephritis.*—The intertubular tissue is infiltrated with new cells in addition to a parenchymatous metamorphosis of epithelial elements. A true inflammatory condition, for there is migration of blood-corpuscles into the intertubular tissue and an exudation of all the constituents of the blood into the renal substance, most of which, however, escape with the urine.

6. *Chronic Diffuse Nephritis.*—First variety (fourth form of large white kidney). All the structures of the kidney are involved. The epithelial cells undergo a parenchymatous metamorphosis, and the

[1] A Practical Treatise on Renal Diseases and Urinary Analysis. New York, 1887.

intertubular tissue a cellular infiltration and thickening. There are three distinct varieties: in one, the kidneys grow large because the major part of the lesion is located in the epithelium; in the other two, the organs are diminished in size, in one with and in the other without a hyaline thickening and expansion of the afferent vessel of the Malpighian coil.

7. *Chronic Diffuse Nephritis.*—Second variety; second form of small kidney. The disease spends its force upon the epithelial cells, the interstitial tissue, the arterioles, and the capillary blood-vessels. The greatest intensity of action is located in the intertubular tissue and afferent vessels. There is a marked production of new interstitial tissue, and the small arterioles undergo a hyaline transformation which causes a thickening of their walls and an increase of the lumen.

8. *Chronic Diffuse Nephritis.*—Third variety; third form of small white kidney. This variety of chronic diffuse nephritis differs from the other two in that both the interstitial tissue and the epithelial cells are about equally involved, while the glands progressively diminish in size. In this variety there is comparatively little development of new connective tissue, but it is given a greater prominence owing to the rapid atrophy of the epithelial elements. There is no increased thickening of the arterial walls.

9. *Acute Hyperemia of the Kidneys.*

10. *Passive or Chronic Congestion of the Kidneys.*

H. B. Millard (1892),[1] in the third edition of his work on Bright's Disease, p. 105, says: "At present it appears from Bright's own writings that the name 'Bright's disease' has been applied to those diffuse inflammations of the kidneys accompanied by albuminous urine, either constant or intermitting." Millard treats of croupous nephritis, acute and chronic suppurative nephritis, catarrhal or interstitial nephritis, acute and chronic nephritis without albuminuria. He applies the term croupous nephritis to what is variously known by that name, as tubal nephritis, parenchymatous nephritis, non-desquamative nephritis, in advanced stages producing the large white kidney or atrophied kidney. He says: "The nature of interstitial

[1] Millard, A Treatise on Bright's Disease of the Kidney, Its Pathology, Diagnosis and Treatment, 3d edition. New York, 1892.

nephritis consists in edematous infiltration of the connective tissue, causing striation of the swelled cortical substance, the seat of the disease being principally the connective tissue." The result is the small, granular, contracted granular or cirrhotic kidney. Unaccountable is his application of the term "catarrhal" as synonymous with "interstitial" nephritis.

Robert Saundby[1] says in his recent work on *Renal and Urinary Diseases,* 1896, p. 85: "In 1880 I expressed the results of my own histological observations in the following words: The small red and large white kidney, and all the intermediate varieties, are the result of inflammation which affects all the tissues, but varies very greatly in intensity. The parenchyma, being the most highly organized tissue, suffers most in proportion to the intensity of the inflammation. The large pale kidney is the result of prolonged or repeated severe inflammation; on the other hand, the small red kidney indicates an inflammatory process of prolonged duration but of minimum intensity, and the intermediate varieties correspond to all the different degrees of intensity possible between the two extremes. The fact of the existence of an indefinite number of intermediate or mixed forms between the two typical varieties of the large white and small red kidney is a strong argument in favor of the doctrine of unity. Since that time there has been no conspicuous attempt to revive the doctrines of Virchow, and the opinion that the lesion is a diffuse nephritis in all forms of chronic Bright's disease has steadily gained ground."

In view of the difficulties in the way of classifying the various clinical forms on an anatomical basis, Saundby proposes the following etiological classification, which he hopes will be found to adapt itself to the facts of clinical observation as well as to pathology: (1) Infective nephritis, (2) toxic nephritis, (3) obstructive nephritis.

The first division includes all those cases of acute or chronic nephritis occurring as a result of acute or chronic infective disease. The nephritis is directly dependent upon the infective process, hence its name. Anatomically it includes most cases of acute parenchymatous nephritis, of chronic fatty kidney, and many of typical granular kidney, for numerous observations have proved that acute

[1] Lectures on Renal Disease, 2d edition. London, 1896.

nephritis following infective disease (*e. g.*, scarlatina, enteric fever, pneumonia) may develop this form.

The second division includes the great group of chronic Bright's disease due to lithemia, and is specially associated with the small red granular kidney, but owing to the occurrence of intercurrent acute and subacute attacks of nephritis the kidneys are often enlarged and fatty. It probably depends upon irritation of the kidneys by the excessive elimination of poisons of which uric acid is the type. It includes the acute nephritis of acute gout, of poisoning by animal, vegetable or mineral poisons, and certain cases of primary acute nephritis usually attributed to chill, but in which there is probably an already existing dyscrasia. Such acute cases are met with occasionally in individuals who get drunk on beer and lie out all night.

The third division includes all cases dependent upon obstruction to the outflow of urine. They occur commonly in males as a consequence of stricture or enlarged prostate, in females from pressure on the ureter caused by pregnancy or pelvic disease.

In each of these classes we may meet with the urinary and other symptoms of acute or chronic nephritis while the post-mortem appearances may be those of acute nephritis, of chronic fatty kidney, or of contracting kidney.

Lardaceous or waxy degeneration is not made a special group because it is only when associated with chronic nephritis that it deserves to be called Bright's disease.

Chas. W. Purdy[1] (1898 *et ante*) classifies as follows: (1) Acute renal hyperemia, (2) acute passive renal hyperemia, (3) acute diffuse nephritis, (4) chronic diffuse nephritis, (5) chronic interstitial nephritis, (6) amyloid disease of the kidney, (7) cystic disease of the kidney.

Nestor Tirard,[2] whose book on *Albuminuria and Bright's Disease* is the latest published (1899), does not state in definite terms what he includes under the term Bright's disease, but quotes Sir George Johnson's definition as fairly free from objection: "A generic term indicating several forms of acute and chronic disease of the kidney, usually associated with albumin in the urine, and frequently with

[1] Practical Uranalysis and Urinary Diagnosis. Philadelphia, 1898.

[2] Tirard, Albuminuria and Bright's Disease. London, 1899.

dropsy and with various secondary diseases resulting from deterioration of the blood. This definition is certainly fairly free from objection since it allows that Bright's disease may occasionally exist without albuminuria and that dropsy also does not form an essential or invariable feature." He says also (p. 245) that lardaceous or amyloid disease of the kidney does not truly represent a form of Bright's disease, but both anatomically and clinically the occurrence of lardaceous degeneration frequently accompanies the changes due to chronic nephritis.

We must not overlook the view which makes Bright's disease an affection secondary to alterations in the blood serum, makes it in a certain sense a constitutional or at least hematogenous disease. Even Bright and still more Blackall held views of this kind. Blackall stated explicitly that the albuminuria was due to the elimination of the dropsical fluid by the urinary passages.

The latest exponent of this view is the Italian physician Semmola, whose reasons are *first,* that no parallel exists between the seriousness of the disease of the renal parenchyma and the simultaneous albuminuria. *Second,* that the conversion of the albuminous substances of the blood, together with the elimination of non-assimilative albumin, is in itself capable of producing a histologically characterized nephritis; *Third,* that artificial nephritis can be produced, which, provided the hematogenous source of albuminuria be exhausted, does not allow any albumin to pass into the urine.[1]

In reviewing the preceding summary of classifications and seeking for the changes of view which have taken place since the first edition of this book was published, we may concede:

1. A more active participation of the interstitial tissue in acute processes and a less exclusive involvement of the parenchymatous or epithelial element of the kidney in acute as well as chronic inflammation.

2. The reassertion that typical contracted kidney may represent a third stage of acute nephritis coupled with the admission that the contracted kidney continues to be the product of a chronic process peculiar to it.

[1] Semmola, Bull. de l'Acad., No. 30, 1890, quoted in footnote on p. 75, Vol. I., of the English translation of Fürbringer's Diseases of the Kidneys. London, 1895.

3. The separation of the last-named condition with its resultant of a general as well as a local endarteritis and arterial sclerosis from the primary general arterial sclerosis of which the contracted kidney is one of the consequences.

4. The establishment through the labors of Biermer, E. Wagner, Klebs, Kelsch, Klein and Councilman of the existence of a condition of acute interstitial nephritis, more especially as a consequence of diphtheria, scarlatina and other infectious diseases, a condition which is not however clinically differentiable from acute epithelial nephritis.

5. The impossibility in every instance of diagnosticating by clinical symptoms the anatomical varieties which go to make up what has been called, since 1827, Bright's disease.

The frequency with which the latter difficulty has been encountered has occasioned some authors, and notably Saundby, to make such a classification secondary and to propose in its stead an etiological classification. I prefer, however, to retain it with all its defects to one which has a less scientific basis, with such modifications as seem necessitated by the more accurate knowledge of the present day as follows:

I. Acute Bright's disease represented by the different varieties of acute nephritis including:

1. Acute parenchymatous nephritis,
2. Acute diffuse nephritis,
3. Acute interstitial nephritis,

} not clinically differentiable.

II. Chronic Bright's disease, including:

1. Chronic diffuse nephritis represented by (*a*) its first or non-indurated stage (large white kidney), (*b*) its second or indurated stage (secondary contracted kidney).

2. Chronic interstitial (indurative) nephritis (primary contracted kidney).

3. Arterio-sclerotic induration.

III. Amyloid degeneration of the kidney.

IV. Cyanotic induration (passive congestion).

V. Suppurative nephritis including tuberculosis of the kidney.[1]

[1] For an excellent description with history of the development of the knowledge of acute interstitial nephritis see Councilman's paper on Acute Interstitial Nephritis in the Transactions of the Association of American Physicians, 1898. See also Section VIII. on Acute Interstitial Nephritis in this volume.

SECTION VI.

ACUTE PARENCHYMATOUS NEPHRITIS.

Synonyms.—First stage of the morbus Brightii of Frerichs and the older authors. Acute diffuse nephritis, acute desquamative nephritis, acute tubal nephritis, acute Bright's disease, acute catarrhal nephritis, croupous nephritis, albuminous nephritis, hemorrhagic nephritis (Traube), acute albuminuria, acute renal dropsy; epithelial nephritis.

ACUTE PARENCHYMATOUS NEPHRITIS IS AN ACUTE INFLAMMATION OF THE KIDNEY, IN WHICH THE PARENCHYMA OF THE ORGAN, THAT IS THE TUBULES AND GLOMERULES, ARE SOLELY OR FOR THE MOST PART AFFECTED, OR IT MAY BE IN ADDITION TO THE INTERSTITIAL TISSUE.

Etiology.

The infectious diseases are for the most part responsible for this form of nephritis, and of these *scarlet fever* most frequently. It occurs, therefore, very often in children. A certain number of cases originate in exposure to cold, especially cold and moisture, while the body is warm and perspiring. The latter cause is particularly potent if the person be fatigued or exhausted, or intoxicated.

As to the method in which *scarlatina* and other infectious diseases cause the nephritis, our present views hold responsible the specific organism of the disease or a toxin derived from it. That the effect of cold has little or nothing to do with certain cases of nephritis following scarlatina, is further attested by those instances, familiar to every practitioner of experience, in which the disease has succeeded upon scarlet fever during a convalescence in which the patient has been kept in bed, while the barefoot pauper may have run the streets with the eruption upon him with utter impunity. But while it cannot be claimed that cold alone can produce the nephritis of scarlatina, it is more than probable that it may coöperate with the peculiar poison in producing the same result. And in those cases of acute nephritis which succeed upon exposure, the immediate cause is probably a

congestion of the kidney due to the reflux of blood from the surface of the body; but here again, it is not unlikely that the extra work thrown on the kidney in consequence of the suppression of skin-excretion, contributes secondarily. The same may be said of the acute nephritis which succeeds upon extensive burns of the surface of the body.

In like manner, other grave infectious diseases, especially *typhoid fever, diphtheria* and *small-pox,* cause acute nephritis. In all it presents itself at the *acmé* of the disease. *Pyemia, acute endocarditis, acute articular rheumatism* and *influenza* are also occasional causes; while *pneumonia, measles, erysipelas, pyemia, jaundice,* and *diabetes* have been known to cause it. In a case of chronic Bright's disease under my care a hemorrhagic attack was evidently induced by an attack of *erysipelas;* and a pair of kidneys, removed post-mortem from a case of *diabetes,* presented all the signs of an acute congestion. *Syphilis* and the *malarial poison* must also be included among the causes. The alterations which take place in the kidney after *cholera* are generally acknowledged to be those of inflammation. *Skin diseases,* as well as *extensive burns of the skin,* are accepted causes, the former rarely, but the latter almost always if the burns be sufficiently extensive.

Pregnancy is the cause of a good many cases of acute parenchymatous nephritis, indeed so important a cause of it that some writers devote a separate section to the acute parenchymatous nephritis of pregnancy.

Most cases of acute nephritis due to other causes than scarlatina, cold, and pregnancy, are mild in degree; and even in cases due to pregnancy, if the patient is once through with her confinement, recovery is usually rapid, though this is not always the case.

In looking for the evidence of nephritis in acute infectious diseases it must not be forgotten that *intense febrile movement* may cause albuminuria, the so-called febrile albuminuria, independently of any inflammatory condition of the kidney. When thus caused the albuminuria is always small.

When acute nephritis supervenes upon scarlet fever it does not usually make its appearance until the end of the second week. Indeed it is often during supposed convalescence that it most unex-

pectedly occurs. Bartels, in a single case, detected it on the tenth day, and never later than the thirty-first. He found the twentieth day to be the mean limit, while the greatest number of cases also presented themselves on this day.

Dr. Tripe[1] concluded from his observations that dropsy may come on at any period of scarlatina, even the earliest, but that it most frequently appears on the fourteenth day. Dr. West says it is most frequently in the second week that it occurs, and that if delayed later the symptoms are generally milder. Dr. W. Howship Dickinson[2] found the majority of cases occurring in the third week, but says: "Speaking generally, it may be said that after the end of the first month the danger is small, but until after the lapse of the second the patient cannot be looked upon as safe." These are safe limits.

Certain specific *poisons* of vegetable and mineral origin may produce acute nephritis. *Alcohol* is one of these. Although by no means so frequent a cause of Bright's disease as formerly supposed, undoubtedly a few cases are directly traceable to it, in one instance, quoted by Dr. Dickinson from Dr. Goodfellow,[3] apparently to the inhalation of its vapor. Among the best known of these substances are *cantharides, turpentine, oil of mustard,* and *phosphorus;* in a less degree the *mineral acids, oxalic acid, chloroform, arsenic, nitrate of silver, lead,* and *mercury.* Arsenical albuminuria is a well-recognized condition, and mercurial nephritis has frequently been met. *Wormseed oil* may be placed in the same category, for in a case which came under my observation, an adult male died twenty-four hours after taking an ounce of this oil, death being preceded by coma and convulsions, while the urine was found to contain half its bulk of albumin.

Age and Sex.—As may be inferred from the etiology, acute nephritis is a disease of early age, although when caused by cold or any one of the causes named except scarlatina, it is as more likely to affect adults as these latter are more frequently subjected to such causes.

In very few instances have I known acute nephritis to originate

[1] Tripe on Scarlatinal Dropsy, Med.-Chir. Rev., 1854–55.
[2] Dickinson, op. citat., p. 90.
[3] Dr. Goodfellow on Diseases of the Kidney, p. 177.

in a person over thirty years of age. The possibility of its occurrence at any age cannot be denied. Dr. Dickinson says it is rare after forty, almost unknown after fifty. The oldest child I ever knew to have scarlatinal nephritis was a girl of sixteen, who recovered. Another of fourteen died.

More males are attacked than females in adult life, evidently because they are more frequently exposed to the causes. But even in childhood there is a slight preponderance of boys among those affected, which can hardly be thus accounted for.

Morbid Anatomy.

This varies with the stage of the disease as well as its severity. In the first place, as ordinarily caused, it is symmetrical, both organs being alike involved. The observations of Edebohls on kidneys examined at operations for the cure of chronic Bright's disease revealed a larger number of cases of asymmetrical disease than was supposed to exist but examination at the hurried period of operation can hardly be compared with the deliberate study of the autopsy room and laboratory. The alterations may be so trifling as not to be recognizable by the naked eye. But the kidneys are generally enlarged, in the latter stages always, sometimes to more than twice their normal volume, and they may weigh from eight to twelve ounces, those of children reaching the former, and those of adults the latter.

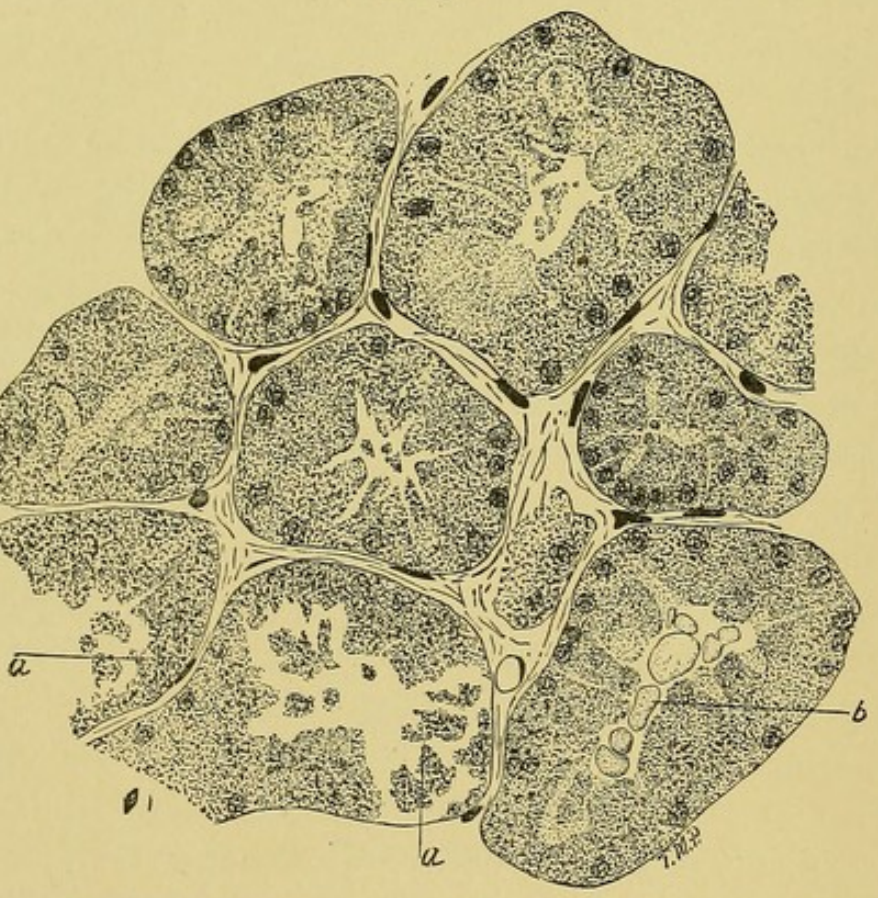
The capsule is distended by the enlarged organ, and, therefore, gapes when incised.[1] It may be otherwise unaltered or slightly injected, and strips off easily, without dragging parenchyma with it. Bereft of its capsule, the kidney itself is softer than in health, inelastic, doughy. Its surface is smooth and exhibits a peculiar mottled appearance, which is due to the fact that the little circlets of veins which form the boundary of the lobules are distinctly injected, while the area included by each circlet is paler than in health, and in the more advanced stages even yellowish-white in color. This "irregular mixture of congestion and anemia," as Dr. Johnson calls

[1] Dickinson reports a case in which the capsule of both kidneys burst from the extent and suddenness of the tumefaction. Dickinson, Albuminuria, 2d edition. London, 1877, p. 97.

it, is further contributed by the injection of other veins, indistinct in health. The stellate veins, which are also more or less injected, are not so conspicuous as in chronic parenchymatous nephritis. Spots of hemorrhagic extravasation are also often found scattered over the surface.

In acute cases, *on section* it is evident that the enlargement is due to change in the cortex and the interpyramidal convoluted portion. The cut surface is smeared over with a dark-red or chocolate-

FIG. 30.



Acute Parenchymatous Degeneration of the Kidney Epithelium from a Case of Yellow Fever. *a*, Swollen and granular epithelium desquamating and disintegrating; *b*, hyaline material in the lumen of the tubule. After DELAFIELD and PRUDDEN.

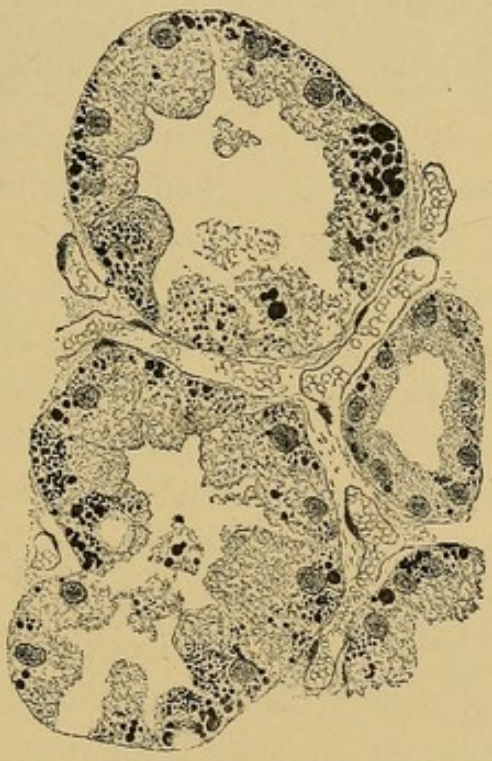
hued blood, but on scraping or washing it away, the vessels are found injected, and between them the same paleness or yellowish-white hue. The Malpighian bodies appear as distinct dark-red dots, and any linear vessels are distinctly filled, while punctiform hemorrhages may again be present as on the surface of the organ.

The *pyramids* are usually not much altered in appearance. They

may be congested, and this may increase the vivid contrast already existing between their dark-red color and the pale cortex. In cases of extreme swelling, the pyramids may be compressed in their central portions by the interpyramidal convoluted structure, which shares the enlargement of the cortex, producing the very characteristic appearance first compared by Rayer to a wheat-sheaf.

Minute Changes.—These are confined almost solely to the cortex. They begin at least in the epithelium, and vary a good deal with the

FIG. 31.



Fatty Degeneration of the Epithelium of the Convoluted Tubules of the Kidney. The fat droplets are stained black with osmic acid. After DELAFIELD and PRUDDEN.

stage of the disease. The earliest condition of the cells is undoubtedly that of cloudy swelling. In this state the cells are swollen, slightly more cloudy than usual, in consequence of a deposition of albuminous granules in their interior, which may accumulate to such extent as to obscure the nucleus. Although kidneys removed after death from cases of acute nephritis have as a rule advanced far beyond this stage, yet it is often possible to find points less advanced at which cloudy swelling exists alongside of more advanced stages, while alongside of these again may be tubes in which the epithelium

is healthy. As a result of the cloudy swelling, the cells are larger, and the tubes are therefore broader than in health. Still later the widening is more marked and the tubes are filled with more highly as well as moderately granular cells, to which are added free granular matter, often red blood-corpuscles and sometimes leucocytes. Under a low power the tubules appear as black, more or less opaque lines. The granules result from the breaking down of the cells, and the blood-disks are, of course, derived from the capillary vessels.

A closer examination of the *cells* at this stage, as obtained by scraping or examined *in situ,* shows them to be granular in various degrees. In some the nucleus is still visible, in others demonstrable only by the aid of staining fluids, and in others still, entirely obscured. Occasionally a few fat-drops may be present. In other situations the cells are so closely packed in the tubules that they cannot be differentiated, but are apparently fused in one continuous dark granular mass. This is the result of a hyperplasia of cells and it is these tubules thus distended with granular cells and their debris, dark by transmitted light, but white by reflected, which cause the pale or white color seen between the injected blood-vessels.

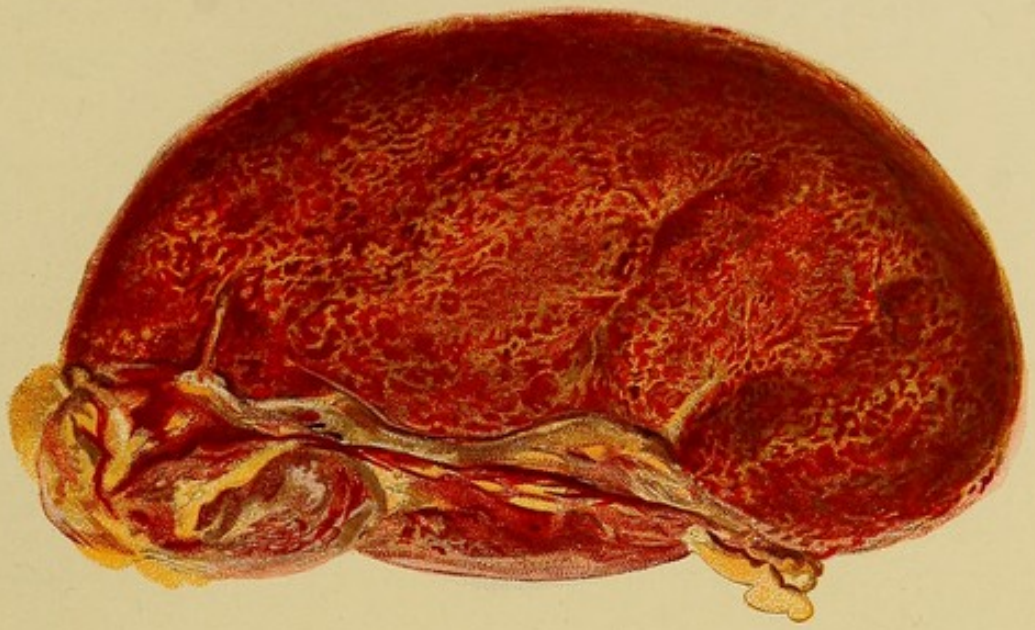
Minute extravasations of blood visible to the naked eye have been referred to. These are found in the tubules or between them and come either by diapedesis or rupture, from the capillaries of the Malpighian glomeruli, which, in the fresh condition, are also distended. In a still more advanced stage, however, the Malpighian bodies may be paler, in consequence of the compression exerted by the still more swollen tubules, or by the proliferated cells peculiar to the capsule and its glomerule (glomerulo-nephritis).

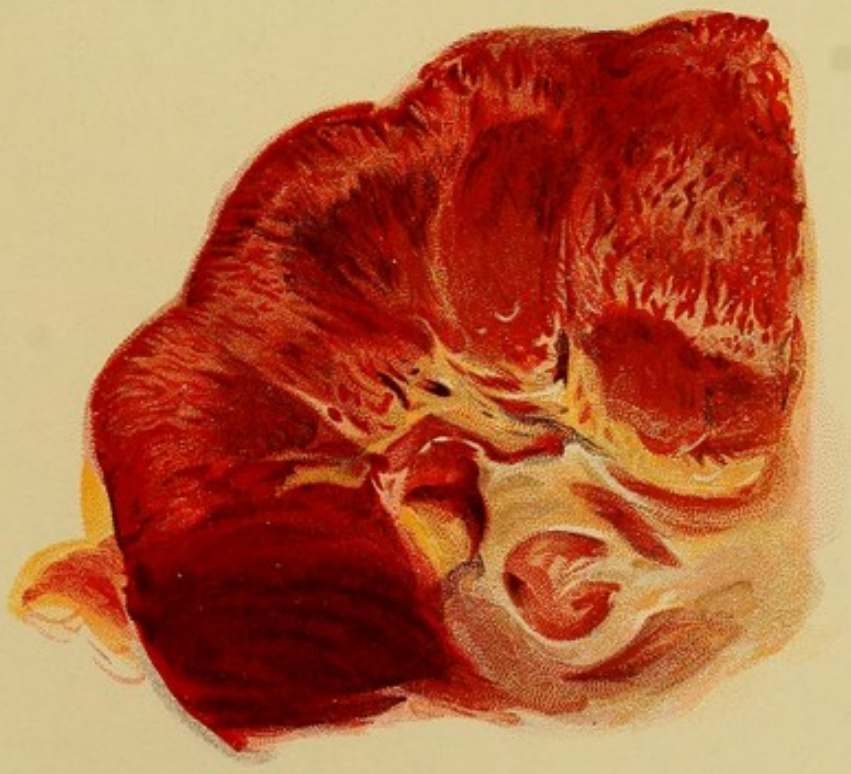
Casts of the uriniferous tubules are also often found *in situ.* These are either blood-casts or small hyaline casts. These hyaline casts are fibrin, and when expelled from the tubule they may carry the epithelium with them, thus making the epithelial cast.

Before bacteria were admitted as playing the role now assigned them in the causation of infectious disease, Oertel claimed that in renal diseases following diphtheria he had found "great numbers of *micrococci* and exuberant proliferations of the same," both in the renal tubes and Malpighian bodies. Heller[1] alleged he had repeatedly found the blood-vessels and their branches in acutely

[1] See Bartels, in Ziemssen's Cyclopedia of Medicine, Vol. XV., 1877, p. 272.

PLATE II





HEMORRHAGIC NEPHRITIS

inflamed and swollen kidneys from cases of pyemia, greatly dilated and plugged with masses, which under low powers presented a peculiar grayish-yellow appearance, and with higher powers were found to consist of extremely minute, highly refracting granular particles, placed at equal distances from one another. These particles he considered *spherical bacteria,* and the resulting masses *bacteria-emboli.* More recently many kinds of specific organisms have been found in the kidney as well as the urine, including the diplococcus of pneumonia, the spirillum of relapsing fever, the typhoid bacillus, the streptococcus and other pyogenic cocci.

The epithelium lining the tubules of the straight tubes is unchanged, but the tubes themselves often contain the same cellular and granular material contained in the convoluted tubes, which has descended from the latter.

Alterations in the Glomerule and its Capsule.

I have decided to describe here the pathological alterations of the Malpighian body, known as glomerulo-nephritis, because the changes are most frequently found associated with acute nephritis, although not exclusively, being met especially in the large white kidney. It may be stated at the outset that in mild forms the Malpighian bodies are not altered.

On the other hand the earlier writers on Bright's disease very generally described changes in the elements of the Malpighian body in both the acute and chronic forms. Thus Foerster[1] speaks of proliferation of the capillary nuclei, thickening of their walls, and desquamation of the enlarged epithelial cells lining the capsule. Virchow[2] described a cloudiness and increased number of nuclei in the capillaries of the Malpighian tuft in chronic nephritis, together with a thickening of their walls and greater width of the capillary coils. After these observers no allusion seems to have been made to such changes until Klebs published in his *Handbook of Pathological Anatomy,* in 1870, an account of some further changes in this body in acute nephritis after scarlet fever. These he included under the

[1] Foerster, Pathol. Anat., Bd. II., s. 512.
[2] Virchow, Gesammelte Abhandl., s. 485.

title *glomerulo-nephritis,* and ascribes them to a proliferation of the nuclei in the *interstitial tissue* of the glomerule, the existence of which Axel Key had previously asserted. In this condition, according to Klebs, the Malpighian bodies appear to the naked eye as little white bloodless points. The urinary tubules are often not at all altered, though sometimes the convoluted tubules are slightly cloudy. The microscope discovers neither proliferation of epithelial cells (the so-called renal catarrh) nor interstitial alterations—nothing but the phenomena of congestion, if the Malpighian bodies are ignored. But the cavity of the Malpighian capsule is filled with small angular nuclei imbedded in a fine granular mass which almost completely covers the vessels. This, Klebs says, is not the endothelial lining of the capsule, because, on careful dissection by needles, this endothelium is found very slightly altered; ordinarily clearer and more firmly adherent than in health, occasionally fattily degenerated. He believes it is the compression of the vessels of the Malpighian body by this hyperplasia which sometimes causes the sudden, almost total suppression of urine and acute dropsy in cases of scarlet fever, followed by uremia and death in from 12 to 24 hours.

Johnson[1] noted that the nuclei in the walls of the capillaries of the Malpighian body are abnormally conspicuous. Birch-Hirschfeld[2] describes a proliferation of nuclei between the vascular loops and the epithelium; Cornil and Ranvier[3] a swelling and granular condition of the capsular epithelium and nuclear proliferation with fatty degeneration of the capillary wall. Bartels[4] gives a drawing by Colberg of a glomerule from a case of chronic parenchymatous nephritis, in which the capillary nuclei are in a state of proliferation. And Litten[5] has described marked proliferation and desquamation of the epithelium of the glomerulus itself, as well as of the capsular epithelium in a case of scarlatina.

But Langhans[6] has furnished the most complete and thorough

[1] Johnson, Lectures on Bright's Disease. New York, 1874, p. 30.

[2] Birch-Hirschfeld, Pathol. Anat., Leipzig, 1877, p. 1021.

[3] Cornil and Ranvier, Précis d'Histologie Pathol. Paris, 1876, p. 1026. American ed., 1880, p. 616.

[4] Bartels, in Vol. XV., Ziemssen's Cyclopedia. New York, 1874, p. 373.

[5] Litten, Charité Annalen, T. IV., p. 30.

[6] Langhans, Theodore, Ueber die Veränderungen der Glomeruli bei Nephritis nebst einigen Bemerkungen über die Entstehung der Fibrincylinder, Virchow's Archiv, Bd. 76, 1879, s. 85.

account of the changes in the Malpighian body yet published. I have already made use of Langhans's paper in my account of the histology of the Malpighian body. It will be remembered that there are, according to him, three sets of cells contained in it, viz., the cells forming the lining of the capsule, the epithelial cells covering the glomerule or capillary coil, and the nuclei of the capillary vessels. Langhans was unable to convince himself of the existence of the stellate elements which Axel Key described as connective tissue

FIG. 32.

Proliferation and thickening of the capsular epithelium with compression of the glomerule. × 120.—After LANGHANS.

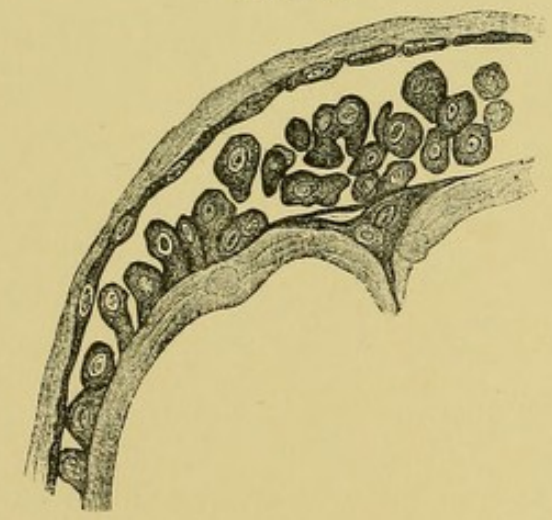
cells, nor of the presence of any connective tissue within the capsule, except the adventitia of the vas afferens, which extended only as far as the branching of this vessel. But of the three sets of cells described by him all share in the pathological processes of the kidney.

First, as to the *epithelium of the capsule,* it exhibits in its slightest degrees of alteration, such as occurs in a *congestion of the kidney,* a simple over-growth of the cells, so that instead of being flat they are more comparable to the epithelial lining of the tubules in their convoluted portion. The nucleus is larger, oval, and fills the cell almost completely. This degree of alteration occurs in any of the forms of Bright's disease. Increase in the *number* of cells, resulting in stratified layers, is a much more rare occurrence, but Langhans

has seen it in acute nephritis where there were hemorrhages within the capsule. Here the Malpighian body is elongated in a direction parallel with the axis of the medullary rays. See Fig. 33. This is due to the presence between the capsule and the glomerule of a crescentic mass of cells, of which the thickest portion is opposite, or nearly opposite, the point of entrance of the vas afferens. In the spaces between the layers of these cells, which are more or less epithelioid in shape, are found smaller and larger lymphoid cells. More frequent than this extreme degree is partial thickening of the capsular epithelium alluded to.

With regard to the effect of this proliferation upon the function of the kidney it is not unlikely that by exerting a pressure upon the

FIG. 33.



Desquamative glomerulo-nephritis. × 300. The surface of the capillaries, the details of which are omitted in the drawing, is covered with numerous cells.—After LANGHANS.

capillaries of the glomerule it diminishes the quantity of urine secreted, especially as in Langhans's cases such a diminution occurred, and especially also as proliferation of the interstitial tissue in contracted kidney is attended by an opposite result; and alterations of the epithelium of the tubules are not necessarily attended by such results. The hemorrhages which sometimes occur in the Malpighian body where these alterations exist, Langhans would locate, not in the capillaries of the glomerule itself, *but in those of its capsule,* since the blood is not found on the surface of the glomerule, but between the layers of the thickened capsular epithelium.

Next, as to alterations in the *glomerule-epithelium,* it is found that in *inflamed* kidneys the epithelium is not so readily removed in shreds, but rather in isolated cell elements; in other words, the cement substance uniting the cells seems to be dissolved, and the cells are probably also less closely adherent to the capillary loops. The cells themselves are very little altered, in some instances swollen; and when this is the case, the thicker nucleated portion of the cell is exclusively involved, and forms prominent button or club-like processes, which are attached to the convexity of the capillary loop, sometimes by a broad base, and sometimes by a delicate pedicle. This may separate completely, leaving the free nucleated portion as an independent cell between the capsule and the glomerule. Although the number of these is usually small, they may be so numerous as to enlarge and change the shape of the Malpighian body to an oval whose longer axis is parallel with the medullary rays and nearly .3 mm. ($\frac{1}{80}$ inch) in length. These cells are even sometimes found between the lobules of capillary vessels which make up the glomerule so as quite distinctly to separate them.

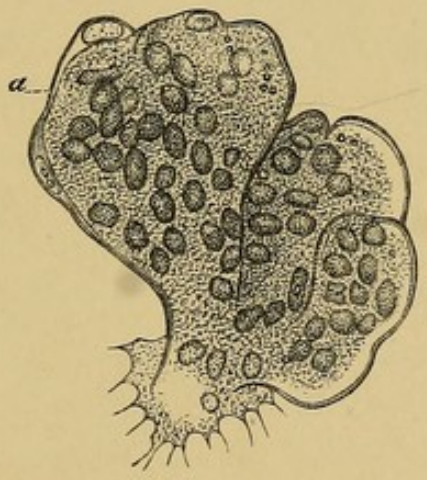
This condition, so far as the swollen state of the cells is concerned, is not infrequent. Langhans has never failed to see it in connection with the *large white kidney.* He also found it in a single case of acute nephritis along with marked hemorrhages from the glomerule and conspicuous thickening of the capsular epithelium; also in a slight degree in granular atrophy of the kidney. On the other hand, in five cases of scarlatinal nephritis he failed to find any considerable swelling of the glomerule-epithelium; also in a case of large white kidney, with hypertrophy of the left ventricle, attended during life by a very copious (4,000–5,000 c.c., 133–166 f℥) highly albuminous urine and numerous casts. Langhans thinks a good deal of light has been shed upon it by this condition of the glomeruli, in which alone the case differed histologically from other large white kidneys. To this he thinks may be referred the extraordinary increase in the quantity of urine, while the condition itself may be compared to a desquamative catarrh of the mucous membrane, which is in like manner attended by the exudation of a highly albuminous liquid. He does not, however, venture a decided opinion, since he lost the most favorable opportunity for investigating the condition of the capil-

laries. I cannot myself comprehend why such a proliferation should increase the quantity of urine, but would rather expect that it would operate similarly to the overgrowth of the capsular epithelium to compress the glomerule, and thus diminish the quantity of urine secreted.

Finally, as to changes in the *capillary nuclei,* according to Langhans these are by no means so rare as the silence of modern literature on the subject would lead one to suppose, although for their recognition more careful investigation is necessary than for the recognition of either of the two already considered. To this end complete isolation of the capillaries from each other and from the epithelium is essential, and is accomplished by means of dissection with and without artificial injection of the vessels. Even by low amplification a difference is observed between these Malpighian bodies in which the capillary nuclei are altered and those in which there is a proliferation of the epithelium. The glomerule is enlarged (.2 to .35 mm., $\frac{1}{125}$ to $\frac{1}{70}$ inch), and fills closely the entire cavity of the capsule, appearing, especially in the fresh condition, as a compact intensely clouded mass. But in hardened preparations its peculiar subdivisions are easily recognizable. The epithelium of the glomerule as a rule exhibits simply swelling, especially the nuclear portion, as well as a marked extension of the single cells whose convexity has a radius considerably longer than normal, corresponding to the increased lumen of the capillary. The capillaries themselves are increased in diameter to .03 mm. ($\frac{1}{833}$ inch). After removal of the epithelium of the glomerule, the lumen of the capillaries is found more or less occupied by a cloudy, finely granular substance, which sometimes contains a few and sometimes a large number of minute fat-drops, takes up carmine, clears up and swells somewhat on the addition of acetic acid. In it are found numerous small round nuclei, .006 to .008 mm. ($\frac{1}{4166}$ to $\frac{1}{3125}$ inch) in diameter, exactly similar to the normal capillary nuclei, and quite different from the large oval epithelial nuclei. They are separated from each other by a distance equal to half their own diameter. That these nuclei truly lie in the finely granular mass and are not adherent to the capillary wall, is seen at points of rupture, or still better on pressure, when nuclei and fine granular matter well up without breaking up into single cells.

These capillaries are still pervious to blood, but a higher pressure than usual is required to fill them, even then with but partial success. The extreme resistance results in a dilatation of the vas afferens outside of the Malpighian capsule and of the afferent arteries. Langhans found the diameter of the afferent vessel from a boy twelve years old, dead of acute nephritis, to be .06 mm. ($\frac{1}{416}$ inch) in diameter, as contrasted with .014 to .02 mm. ($\frac{1}{1785}$ to $\frac{1}{1250}$ inch) normal for an adult. From this resistance also result extravasations of blood into the capsule through the walls of the first branches of the vas afferens. Later, this finely granular mass appears to fuse more intimately with the membrana propria of the capillary wall and acquires the same optical properties as it. This process, although

FIG. 34.



Capillary loops with proliferation of the nuclei, the epithelium being retained only at *a*. × 300.—After LANGHANS.

apparently independent of the nuclei of the capillary walls, Langhans calls "proliferation of the capillary nuclei." He also says that evidence is wanting as to whether the colorless corpuscles share in the process.

As to the circumstances under which these alterations in the capillary nuclei occur, Langhans has *never* found them *absent in the large white kidney,* all the glomeruli being affected. He has also found them in *acute nephritis,* in one case along with proliferation of the capsular epithelium. Upon scarlatinal nephritis he had, however, made no observations. In granular atrophy the alteration is absent as a rule; it may be present, however, as a stage preliminary to contraction.

The influence of this nuclear proliferation of the capillaries upon the secretion of urine is difficult to determine in consequence of important alterations in the other elements of the kidney. It is very probable that it may cause a diminution in the quantity of urine secreted, and in this Bartels agrees with Langhans.

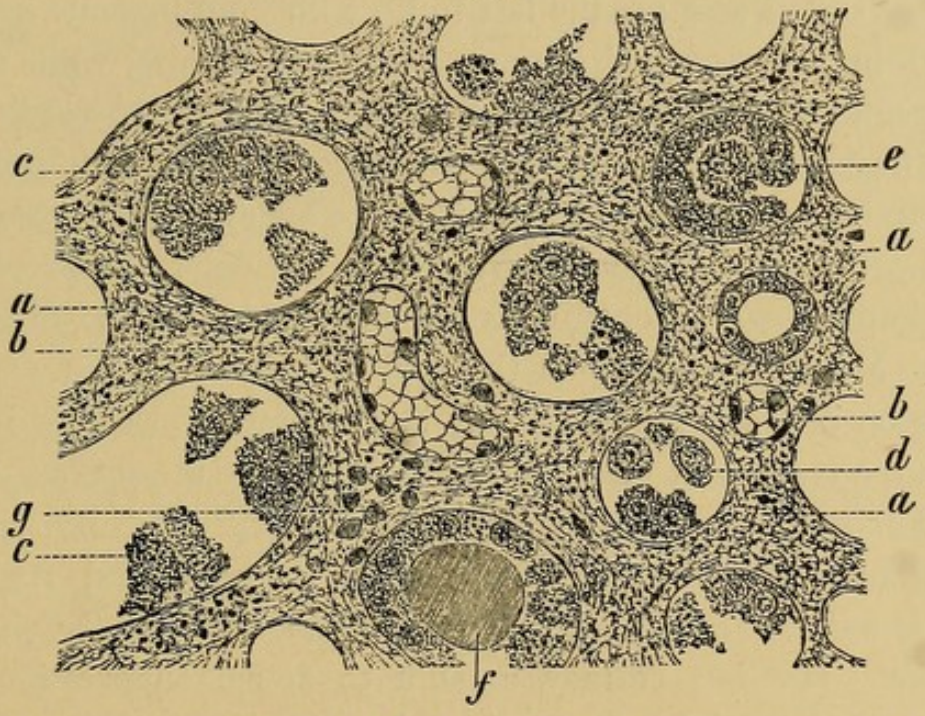
After carefully examining this subject I cannot but think that the proliferation of capillary nuclei is the same condition as that long ago described by Klebs as a proliferation of the nuclei of the interstitial connective tissue of the glomerule, but which Langhans has been unable to discover. Klebs's drawing in his *Pathological Anatomy,* p. 646, is very coarse and difficult of interpretation. Both authors describe a nuclear proliferation imbedded in a granular matrix, but while Klebs puts it outside of the blood-vessels, Langhans puts it within. The question is by no means an easy one to settle, and I would not pretend to decide which is correct. I have carefully studied preparations in which this nuclear proliferation in the glomerule was marked, but by the optical means at my disposal could not decide upon their exact seat. Reasoning from the fact that they were accompanied by a general nuclear proliferation in the situation of the connective tissue elsewhere in the kidney, it would appear likely that they should occupy it here in the glomerule. But Langhans's work seems to have been carefully done, and the difficulty of artificial injection as well as the dilatation of the afferent vessels point to the correctness of his views. Further researches are necessary to settle the question. In either situation the proliferation would necessarily have the effect of diminishing or suppressing the secretion of urine.

More recent studies than those of Langerhans have been made but they do not appear to be more complete or accurate.

The Interstitial (Intertubular) Tissue of the Kidney in Acute Parenchymatous Nephritis.—The changes above described, it is seen, belong to the tubules and blood-vessels. In typical cases of acute parenchymatous nephritis, there is no interstitial change, no formation or deposit of new material between the tubes. This assertion may be reaffirmed, but requires some further comment. It is certainly not present as a rule in the earliest stages; but sooner or later such changes do present themselves, and it is a matter of duration

of the disease as to whether they appear or not. If the disease continues without permanent amendment for three months or longer, they will certainly have made their appearance. But here the border between acute and chronic parenchymatous nephritis has been passed. It is impossible to say, however, precisely when they appear, and for some time before such changes are recognizable by the naked eye they are discernible by the microscope. They consist in a cellular infiltration by proliferated connective tissue corpuscles always present, or from the fixation of wandered-out colorless blood-cells.

FIG. 35.



Acute Diffuse Nephritis, with Sero-fibrinous Exudate and Catarrh of the Uriniferous Tubules (from a man who died of suppurative mediastinitis and pleuritis with nephritis on the tenth day after the beginning of the disease). *a*, Stroma distended by fluid and infiltrated with granules, filaments of fibrin, and several fat droplets; *b*, capillaries; *c*, epithelium of the convoluted tubules, in part fatty and desquamating; *d*, desquamated epithelial cells in a looped tubule; *e*, granular and fatty detritus in a looped tubule, the epithelium of which still remains but is the seat of cloudy swelling; *f*, hyaline tube cast in a convoluted tubule; *g*, round cells. × 350. After ZIEGLER.

Numerous reports attest also the occurrence of cases in which the process is interstitial from the outset, with no involvement of the tubules whatever in some cases and to a trifling extent in others. (See Section on Acute Interstitial Nephritis.)

Changes in the Pelvis of the Kidney. The mucous membrane of the kidney may be injected, but is otherwise unchanged.

Symptoms of Acute Parenchymatous Nephritis.

The mode of onset of acute nephritis is not uniform, but among the symptoms earliest noticed is slight swelling or puffiness in the face, below the eyes. This *edema* rapidly extends to the upper extremities and trunk, and thence, if the disease does not abate, into the lower extremities and abdominal walls. In the male, the scrotum and prepuce are favorite seats of swelling. The latter especially in little children is often so great as to obstruct the passage of urine and require catheterization, and that of the scrotum to result in sloughing. The great serous sacs are the last to fill with fluid in acute nephritis, although in bad cases ascites not unfrequently occurs, while there is more frequently transudation into the pleural and paricardial cavities. The extent of the general anasarca is sometimes enormous, resulting in the extremest distortion. The eyes may be actually closed by the swelling, and movement of the lower limbs rendered almost impossible. Dropsy does not always follow the order here named. Much depends upon the position of the patient. Thus if he be upon his feet, the latter may be the first to swell, or if he be lying in the recumbent position, the back may be the seat of the first swelling.

Simultaneously with the dropsical symptoms, and sometimes earlier, is a *diminution in the quantity and alteration in the quality of the urine.* The former may amount to actual suppression. The latter is manifested by change in color, specific gravity, sediment, and chemical composition.

First, as to *color,* instead of the normal amber or lemon-yellow hue, the urine presents, if acid in reaction, as it always is in this disease, when freshly passed, a peculiar *smoke-hue,* due to the presence of a small amount of blood. This peculiar hue is difficult of further description, although once recognized is always remembered. As stated, it requires an acid reaction for its production, and the same urine alkalized presents a brighter red color. The smoke-hue also becomes red if the quantity of blood is large, which is not often the case; but here again the peculiar tint returns if the blood is allowed to subside. If the urine is very small in quantity, and there is much sediment, the former is turbid, and may have a brownish

tinge. The bloody urine of acute Bright's disease usually disappears before the other acute symptoms subside, and may reappear.

In some cases the quantity of blood in the urine is very considerable and more or less constant. Such cases belong to the variety hemorrhagic nephritis, which is very serious and commonly fatal.

The *specific gravity* of the urine at first is high, 1025 to 1030, partly due to the diminished quantity and partly to the admixture of blood. Later, if the symptoms abate, the specific gravity diminishes with the increase in the quantity. Or if the disease lasts for any length of time, or passes over into the chronic form, a similar reduction in weight occurs; this may result in a specific gravity of as low as 1010.

As to *chemical composition,* the chief alteration is in the *presence of albumin.* This is generally large, the urine often solidifying on the application of heat and acid, while it constantly contains more than half its bulk. This albumin is derived in part from the extravasated blood, and in part is a result of the inflammatory action.

I have already referred to the carelessness of expression often used in indicating the quantity of albumin. Thus it is said that albumin is 50 or 75 per cent. when this proportion of the bulk tested is intended. In point of fact it is rare that more than a half of one per cent. is ever present. Bartels reports a case in which the albumin reached 1.525 per cent., or 12.962 grams (200 grains) in twenty-four hours, determined by the gravimetric method. This is rarely used on account of the time required to make it. Pains should, therefore, be taken to indicate exactly what is intended. I do not value highly instruments like the albumometer of Esbach by which the percentage is estimated from the bulk precipitated, as the results thus obtained are not constant. The actual amounts of albumin found in acute nephritis, though relatively large, may be as low as .2 of one per cent.

Next in importance is the reduction in the amount of *urea,* which occurs in every case more or less. The degree of diminution is quite variable. There is a good deal of range, within the limits of health, in the quantity of urea eliminated in twenty-four hours—from 20 to 40 grams may be admitted in the adult. In a case reported by Dickinson the amount declined to .72 grams (11.1 grains) in twenty-

four hours; in another, by Rosenstein, to 1.4 grams (21.5 grains); in another, by Bartels, to .8 of one per cent. (normal .015 to .03). More frequently the amount is reduced to one-fourth or one-half the normal. Such diminution, if large, is of the gravest importance, as some of the most serious symptoms are often associated with it.

In general it may be said of the other normal constituents of the urine, uric acid, phosphoric and sulphuric acid, chlorin, etc., that they are all diminished, but no clinical significance attaches to such diminution.

As to *sediment,* the urine of all cases of acute parenchymatous nephritis deposits a sediment which in the early stages, at least, is copious and brownish or reddish-brown in hue; later it may diminish in amount and assume a lighter color. *Microscopical examination* reveals this deposit to be made up mainly of casts of the uriniferous tubules, free cells from these same tubules, blood-corpuscles, red and colorless, and very constantly crystals of uric acid, together with granular urates. The casts include the varieties known as epithelial casts, blood casts, hyaline casts, pale granular and dark granular casts. The hyaline casts are probably pure fibrin. The epithelial consist of the same material, to which epithelial cells of the tubules and blood-corpuscles have become attached. The epithelium thus attached, as well as that which is found free in the urine, is variously altered. Some of the cells are merely the seat of cloudy swelling, others are decidedly granular, while others again are converted into granular fat cells by complete fatty degeneration. The latter indicate such extreme derangement of nutrition from pressure, remoteness of the cell from its blood supply, or other cause of loss of balance between the *nutriens* and *nutriendum,* that fatty metamorphosis occurs. Casts containing a few oil-drops may also be present; but much oil is not found until the case has continued for some time, in fact has become chronic.

Acute inflammation of the kidneys is rarely so intense that suppuration results; so that pus is seldom found in the urine from this cause. There may be an increased number of leucocytes which have passed through the capillary walls into the tubules during the inflammatory process, and thence down the tubules with such urine as may be secreted, but the number is rarely so great as to constitute

pus. Pus casts are, however, sometimes found. The blood found in the urine doubtless comes from the ruptured blood-vessels of the Malpighian glomerule.

Along with the diminished quantity of urine is often met a disposition to frequent micturition, the efforts at which are only partially successful, resulting in the emission of from a few drops to a tablespoonful. This frequent desire to pass water is a purely reflex symptom, the bladder being free from disease. It sometimes precedes, in point of time, all other symptoms.

The *train of nervous symptoms* usually known as *uremic*, and ascribed to the accumulation of excrementitious substances in the blood, is to be carefully watched for. When present it adds a phase of gravity which dare not be overlooked. We should, therefore, be always on the alert for these symptoms.

The first of these usually observed is *drowsiness,* which may be sudden or gradual in its onset, and may be slight or profound. From the latter degree the transition is easy to the next symptom, that of *coma,* which is indeed nothing but a profound sleep from which the patient may or may not be temporarily aroused. Alternating with the latter may be *epileptoid convulsions,* which are the most alarming and dangerous symptom of Bright's disease. This is not always the succession of these symptoms. Convulsions most frequently succeed drowsiness, but as often precede coma, and they may occur without being preceded by drowsiness while the child is playing and to the unsuspecting parents convalescing. Indeed there may be no suspicion of Bright's disease whatever until convulsions suddenly seize the child and possibly continue with alternating coma, and no return to consciousness before death closes the scene. Drowsiness, in like manner, may be the first symptom of the renal disease to attract attention, others being overlooked or possibly even absent. The convulsions exhibit every grade of movement, from the slightest twitching to the most violent epileptiform spasm.

Impairment of vision or *actual* blindness suddenly occurring is another symptom of acute uremia, which sometimes supervenes upon other symptoms, or it may itself usher in the unfortunate complication. This blindness, it must be remembered, is something altogether different from that which is the result of organic retinal changes,

which are rare in acute nephritis, but common in some of the chronic forms. It may be associated with a general edema especially around the optic nerve entrance producing the so-called peri-papillary edema with fulness and tortuosity of the renal vessels. The exact cause of this blindness, in acute uremia, is as yet undetermined. It is probably, however, toxic, either on the cortical centers or on the retina, it is not determined which. It may be on either. It is not limited to acute nephritis.

Headache and *irritability* of temper are occasionally due to uremia, while *nausea* and *vomiting* are not infrequent. They show themselves at different stages and in different degrees. When vomiting accompanies scanty or suppressed urine, the vomited matters sometimes exhibit a urinous odor, the elements of urine, more particularly urea and its derivative, ammonium carbonate, being thus supplementally eliminated.

Itching of the skin is another symptom sometimes present in uremia. It is probably due to the irritant action of the urea upon the nerves of the skin as it is being supplementally eliminated by that organ. That such increased elimination takes place is attested by that rare, but still unquestioned occurrence in which the entire integument is covered with a frost-like coating which has been found upon analysis to be crystals of pure urea.

Another rare symptom of uremia, which occurs rather in the uremia of chronic renal disease, is *asthma, uremic asthma* as it is called. This is a true asthma, a spasmodic contraction of the bronchial tubes, accompanied by the usual labored breathing, occurring in paroxysms, most frequent at night, and which break up with the appearance of copious frothy secretion just as in the ordinary spasmodic asthma. The view that these attacks are uremic in origin is sustained by Bartels,[1] Dickinson,[2] and Allbutt,[3] but denied by Rosenstein. They are to be distinguished from paroxysms of dyspnea due to edema of the lung, which is not infrequent in acute nephritis, by the absence of the fine, moist râles which attend the latter; and from other conditions involving the lungs and pleura, by

[1] Bartels, op. citat., p. 111.
[2] Dickinson, op. citat., p. 177.
[3] Allbutt, British Med. Journ., September, 1877.

the absence of the physical signs present in these conditions. Of course it is not impossible for nephritis to happen to an asthmatic whose attacks would then occur as before, independent of the uremic cause, or might be increased in frequency or rendered more unmanageable by the latter. Uremic asthma is also to be distinguished from cardiac asthma or the shortness of breath which occurs as a consequence of gradual failure of the heart succeeding dilatation. This occurs only in connection with *chronic* renal disease, and is the chief cause of dyspnea in this form.

The symptoms of acute nephritis which have been detailed are those which may be considered most essential to its recognition. There are, however, others which are less peculiar to it, or occur also in other diseases. These should be referred to in order to give completeness to our picture.

One of these is *fever*. It would be expected that in inflammation of the kidney, as in inflammation of any organ, there would be fever. Such is the case in some instances. But two circumstances combine to make this symptom of little diagnostic value. In the first place, the fever itself is not very marked, and in the second there is very constantly fever in the diseases to which nephritis is added, while the increased fever is not sufficient to be distinctive.

Pain over the region of the kidney is another of these rarer symptoms. It is more frequently absent than present, and when present it is not great. More frequently it may be elicited by strong pressure. When present it may radiate from its central seat to the groin and surface of the thigh.

Again, acute nephritis, after scarlatina, may be ushered in by *vomiting*, which is probably the result of reflex irritation of the stomach, and is quite independent of that which has been referred to as due to uremia. Obstinate indigestion may be similarly caused.

On the other hand, some of the best-known and most constant symptoms are sometimes wanting. This is true of dropsy, which is occasionally absent, especially in cases following diphtheria. But still more remarkable are those very rare cases in which albuminuria and casts, one or both, are wanting. This unquestionably happens in grave cases, for short periods of time, but has never been known to exist throughout a case where examinations have been

repeated and continued. Bartels, during an epidemic which prevailed in 1853–54, *met a few cases in which dropsy set in after scarlet fever, although the urine passed by the patients contained no albumin.* In all these cases very little urine was secreted, in one, only two tablespoonfuls in the twenty-four hours; *very soon afterwards a more abundant excretion of bloody urine set in,* while the dropsy increased and the cases passed through the course of scarlatinal nephritis. Henoch reports a case, which is quoted by Bartels, wherein a boy of twelve, three weeks after having had scarlatina, was admitted to the Charité, in Berlin, with edema of the face and scrotum. His urine was scanty, acid, deposited a sediment, but was *free from albumin.* The microscope "revealed no elements which would indicate the existence of a nephritis," the sediment consisting entirely of amorphous urates which disappeared on the application of heat. During the next two days the edema increased, but the urine remained unchanged. At the end of this time, at night, he had a violent convulsion followed by unconsciousness. The next day the urine, drawn off by catheter, contained a large amount of albumin and hyaline casts beset with fat-granules. He died two days later and the autopsy revealed well-marked parenchymatous nephritis in both kidneys. In another case of anasarca after scarlet fever, described by Henoch, the urine for two weeks sometimes contained albumin and sometimes not. The only explanation of these cases is that suggested by Bartels, that in the spread of the nephritis over the organ, portions become involved to the extent of actual suppression of urine while others remaining healthy secrete the only urine which enters the bladder. Of course such a thing would be impossible if the entire substance of both kidneys is involved, as ordinarily happens sooner or later. It is possible also that in acute nephritis we may have, temporarily, albuminuria without casts, and casts without albuminuria, but such conditions must be very temporary and exceptional; and the assertion of M. Phillippe, referred to by Dickinson as quoted by Jaccoud, that of sixty patients affected with scarlatinal dropsy, there was not one in whom there was albuminuria is incredible. I have already shown how in convalescence the albumin may disappear before the casts contained in the tubules had all escaped. On the other hand, the number of casts varies

greatly; generally quite numerous, they are sometimes scanty. As a rule too albumin is present in large quantity.

There are no symptoms by which the alterations in the Malpighian corpuscles which have been described under the term glomerulo-nephritis are recognizable. We only know that they are most frequently found in those dying of acute nephritis, and that in such cases suppression of urine is a frequent symptom, while the occurrence of this symptom is well explained by the histological changes which the Malpighian body has suffered. Nor are there any signs by which we recognize the pure interstitial forms.

Duration.

The duration of acute nephritis is very variable—from a few days to many months and even years. The short cases are usually fatal, for very few which recover do so in a few days. The most rapid usually require a month. As to cases of longer duration, the possibility of recovery at any time cannot be denied, but nothing is better determined than that the longer the duration the more difficult the cure.

An interesting question presents itself: Where shall we draw the line of demarcation between acute and chronic parenchymatous nephritis? A good histological landmark would seem to be the superaddition to parenchymatous, of interstitial changes. But these, too, may occur at various stages. They have been observed as early as the tenth week, but I should not call a case chronic that had lasted only for this length of time. Perhaps six months might be considered a suitable period, as by this time intertubular changes are probably established in all cases.

Complications.

These are not numerous in acute as compared with chronic Bright's disease, and some which are described as complications are not really such, but local symptoms. Thus, *edema of the lungs* may occur as a part of the general tendency to dropsy, and not as the result of an intercurrent bronchitis. *Pneumonia,* on the other hand, is an occasional true complication. *Inflammation of the serous membranes*

may also be a complication, but not every serous effusion is the result of inflammation, though it commonly is in acute nephritis. Pleurisy is the most frequent form of serous inflammation, pericarditis next, and peritonitis next.

Hypertrophy of the heart is not a frequent complication of acute nephritis. It is a well-recognized one of chronic Bright's disease. When present it is due to overstimulation of cardiac action ascribed by some to resistance of the arterioles to the admission of an impure blood, and by others to the resistance to the movement of the blood through the diseased kidney. In either event time is an essential condition to its production. It is not, therefore, until the kidney disease has existed for some time that it can ordinarily occur. It occasionally happens, however, that the hypertrophy appears earlier. Thus Dickinson reports a case recognized at eight weeks, and confirmed by post-mortem examination at ten weeks, in a child of seven years. In children the heart hypertrophies more rapidly than in adults. The hypertrophy may involve both left and right ventricles or left alone, but never the right alone. Hypertrophy of the right is a secondary result. F. Sibson in 1874, C. Friedlander in 1881, and others, confirm these observations. Others, as Galabin, F. A. Mahomed and Fr. Riegel, have shown an increase of arterial pressure in cases of acute nephritis before hypertrophy is apparent. Changes in the blood-vessels do not occur as a consequence of acute nephritis, and if present they have preceded the disease.

Allusion has been made to the gastric symptoms which very commonly attend acute nephritis, especially after scarlet fever. Dr. Fenwick[1] and Dr. Wilson Fox[2] have shown that these may be associated with organic changes in the structure of the stomach. According to Dr. Fenwick they are those of gastritis, as evidenced by increased vascularity of the mucous membrane, distention of the tubes by a confused mass of cells and granular matter, and occasional thickening of the basement membrane. To these Dr. Fox has added thickening of the intertubular tissue.

Notwithstanding the frequency of convulsions in acute nephritis,

[1] Fenwick, Samuel, The Morbid States of the Stomach and Duodenum, 1868, p. 177.

[2] Fox, Wilson, Medico-Chirurg. Transac., Vol. XLI., p. 361.

structural alterations in the brain are almost unknown. Apoplectic effusions do not occur, probably because of the comparative structural integrity of blood-vessels in the brain of the young, in whom the disease is mainly seen.

In like manner the blindness which not infrequently occurs as a symptom of uremia, is unattended by retinal changes, and albuminuric retinitis is met in acute parenchymatous nephritis with the extremest rarity.

Diagnosis.

The diagnosis of acute parenchymatous nephritis is ordinarily quite easy. The previous history, the usually easily recognizable cause, the suddenness of the attack, the scanty and bloody urine with its high specific gravity, the copious albuminuria, the blood-casts and epithelial-casts and dark granular casts, the blood-corpuscles, free epithelium and granular fatty cells in the urine,—these are a combination of symptoms which admit of only one interpretation. At a later stage, the absence of one or more of these symptoms may somewhat increase the difficulty, but it is scarcely possible to err if those which remain are duly considered. It must be remembered also that an acute condition, such as this described, may supervene upon any one of the chronic forms of Bright's disease to be described.

It is very desirable for the sake of treatment that the renal complication caused by scarlet fever should be recognized at the earliest possible moment. To this end the test of Dr. Mahomed for minute traces of hemoglobin which are present in the pre-albuminuric stage of scarlatina may be used. According to him, the first result of the high vascular tension which forms part of the nephritic process, is the transudation of a minute trace of hemoglobin, before the albumin makes its appearance. Indeed the test is inoperative when albumin is present in the urine. Dr. Stevenson's modification of the test,[1] acknowledged by Mahomed to be the more brilliant in its results, is performed as follows: To a drop or two of urine in a small test-tube, add one drop of the tincture of guaiacum and a few drops of ozonized ether; agitate, and allow the ether to collect at the

[1] Dr. Mahomed's original test may be found in the author's Manual on the Practical Examination of Urine, 3d ed., 1880, p. 73.

top. If hemoglobin be present, the ether carries with it the blue color that is produced, leaving the urine colorless below. The discovery thus made, according to Dr. Mahomed, often enables the practitioner to avert the inflammation by a brisk purge or copious sweat. The test will also respond just after the albumin has disappeared, as well as just before it shows itself. Saliva, nasal mucus, iodin in minute quantities, all strike a blue color with tincture of guaiacum, some without and some with ozonic ether. Their presence should therefore be guarded against.

Methylen-blue administered by the mouth or by hypodermic injections has recently been suggested for the diagnosis of nephritis, but as it is applicable only to chronic nephritis its consideration will be deferred until that form of Bright's disease is treated. There appears to be no obstruction to the filtration of methylen-blue from the blood into the kidney tubules in epithelial nephritis.

Prognosis.

Grave as is justly considered this disease, recoveries from it are numerous, and the prognosis is generally favorable. Even without treatment cases are known to have recovered, and much may be accomplished by a judicious treatment. The prognosis should, however, always be guarded, as insidious causes may produce death when it is least expected. Among the most important of these is uremia, and I can best illustrate my meaning by narrating a case:

A child about five years old had an imperfectly developed attack of scarlatina, which was considered simple sore throat, and he was allowed to go out of the house in winter weather. Dropsy supervened, and the mother carried him to a physician, who failed to appreciate the condition or its cause. He prescribed, however, directing the child to return. He did so several times, growing constantly more edematous. Another physician was consulted who recognized the condition. A little examination satisfied him as to its cause. The smoky urine was highly albuminous, almost solidified on application of heat and nitric acid, and contained blood- and epithelial casts, with numerous blood-corpuscles. He was placed on appropriate treatment, when the dropsy and albu-

min diminished. He was a wilful boy, and his indulgent parents again allowed him to be exposed to cold. The dropsy increased, and the albumin as well. So great was the edema of the prepuce that his urine had to be drawn, and so difficult the introduction of the catheter that it was finally allowed to remain *in situ*. The scrotum was also enormously swollen, and sloughing ensued. Under appropriate treatment, however, all these symptoms subsided; the catheter was no longer required, the albumin rapidly diminished, and the quantity of urine was sufficiently abundant. I saw him at 2 P.M. of a Saturday, and believed him to be convalescent. Between five and six of the same evening, after slight vomiting, he became suddenly unconscious. I did not reach him for several hours; but all efforts to revive him were unavailing, and he died very soon. Very careful questioning of the mother elicited that he seemed a little drowsy on the previous day, but was particularly bright on the afternoon in which coma supervened.

Bartels says that death from uremia has never occurred in his experience, except when the disease has resulted from scarlatina or diphtheria; but Dickinson narrates a fatal case resulting from exposure, in which death was preceded by coma and other symptoms of evident uremic origin.[1] I am sure I have met fatal cases of uremia in acute nephritis originating from other causes than scarlatina.

Pulmonary edema is another cause of sudden death, the patient drowning as it were in his own secretions. Its onset is characterized by shortness of breath, frothy expectoration, and abundant small râles.

The symptoms of gravest import are therefore those of uremia, to which may be added the presence of any of the complications alluded to, and especially suppression of urine. Cases should not, however, be despaired of even when there is complete suppression of urine. My friend Dr. Wharton Sinkler reports a case of recovery in which there was suppression of urine for five days, following scarlatina.[2] Always, however, suppression of urine is the gravest of

[1] Op. citat., p. 75–78.

[2] American Supplement to the Obstetrical Journal of Great Britain and Ireland, Dec., 1878.

symptoms, and death generally ensues within a couple of days after it sets in. The possibility of sudden death should always be borne in mind, and mentioned to the relatives of the patient, although the number of cases in which this occurs is not very great. Of course the longer the duration of the case, the less likelihood of recovery.

Treatment.

Doubtless many cases of acute nephritis recover while the conditions of *rest, quietude* and *warmth* are maintained. And it is further certain that, whatever other means of treatment are used, these three measures are absolutely necessary to recovery. A patient with acute Bright's disease, therefore, whatever its mode of origin, ought to be put to bed, kept quiet, and warmly covered.

I should seldom, however, be satisfied with this treatment alone. The selection of other remedies will depend somewhat upon the severity of the case. If the urine be suppressed, *dry cups,* or in severe cases, *cut cups* to the loins, will so divert the blood as to relieve the stagnation which always exists in the acutely inflamed kidney. These cups should be followed by a warm, moist *poultice* to the same region, which, indeed, should be used under any circumstances, whether the cupping is necessary or not. Poultices should, therefore, always be resorted to in children, and if the symptoms are at all severe,—that is, where there is complete or almost total suppression of urine, nausea, headache, or delirium,—should be preceded by cupping. Although at first thought it would seem that the kidneys are quite remote from the seat whence the blood is immediately removed, it must be remembered that we are relieving the blood pressure in the lumbar arteries which come off from the aorta near the renal arteries, and thus divert the blood from the latter. Under all ordinary circumstances, dry-cupping is sufficient; cut-cupping should be reserved for the most extreme symptoms, where the strength of the patient has not been previously reduced. Some care must, however, be exercised in the use of dry-cupping, lest we defeat its end. The object of dry-cupping, as rightly observed by Sir G. Johnson, is to facilitate the movement of the blood through the capillaries into the veins,—to draw the blood rapidly through the

part, and thus relieve the pressure in the renal vessels. To do this, the cups must be removed as soon as there is a decided redness, and placed on another part in the vicinity. By allowing them to remain too long, the blood stagnates in the capillaries, its onward movement interfered with, and there is, therefore, no derivation of blood from the involved organ.

The above means have for their object the direct relief of the engorgement of the kidney. But blood may also be diverted in other ways, especially by the bowels and skin.

First the bowels. *Purgatives* are useful for this purpose, as well as to aid in elimination. But they serve also another purpose, a purpose which applies not only to the treatment of Bright's disease, but also to that of all diseases. It is a well-known fact that absorption does not take place rapidly when the blood-vessels are congested and there is a slowly-moving current. The classic experiment of Magendie beautifully illustrates this. He injected into the peritoneal cavity of an animal a colored fluid, which at first was not appreciably absorbed, but, after the animal was bled, disappeared rapidly before his eyes. The treatment of acute Bright's disease is therefore well commenced by a cathartic, and after its effect the prompt action of other remedies may be looked for. The purgative most suitable is a saline. A simple dose of bitartrate of potassium, of magnesia for children, or citrate of magnesium or epsom salts for adults will be sufficient. The compound jalap powder in drachm doses is an admirable purgative. The indication is to get a watery stool as soon as possible. In view of the fact that the stomach is often sensitive, an aperient is desired which is not nauseous or irritating, and to this end, some one of the delicate effervescing preparations so common in modern pharmacy may be used.

Next, or simultaneously, we promote the action of the skin. This is favored by maintaining warmth and avoiding cold, already insisted upon. But we are not limited to these protecting measures. The skin may be further stimulated by *diaphoretics*. Of these none is better than the ordinary sweet spirit of niter, especially if it be combined with neutral mixture and small doses of ipecacuanha. The solution of the acetate of ammonium or spiritus Mindereri is another excellent simple diuretic.

If more active measures are required, some one of the preparations of *jaborandi* may be used; the dose varying with the effect it is desired to obtain. If moderate diaphoresis only is desired, doses of from ten to fifteen drops of the fluid extract may be given to adults every two hours, and increased, if necessary, until the effect is brought about. To children, five to ten drops may be given in the same manner. Or *pilocarpin* may be given in $\frac{1}{12}$ grain doses to adults. The further use of jaborandi, and its active principle, pilocarpin, will be again referred to in treating uremia.

Another method of accomplishing the same end is by *warm baths,* or, better still, by the so-called *warm pack,* in which the patient is wrapped in a hot wet sheet and then enveloped in a sufficient number of blankets. Perspiration is thus copiously induced, and when thus caused, is agreeable, being never attended by the faintness which sometimes follows the use of the hot-air bath and vapor bath,—a further means of accomplishing the same end, which will be again considered under the treatment of chronic Bright's disease. In an ordinary severe case of acute Bright's disease, a single pack of this kind may remove all symptoms which cause anxiety, and happily inaugurate convalescence, while it may be repeated daily, if necessary.

Nothing has been yet said of the use of *diuretics,* which naturally early suggest themselves in the treatment of Bright's disease, acute or chronic. Yet the propriety of their use has been questioned, and at first thought there would seem to be sound objection to them; for with the idea of increased secretion of urine is generally associated that of an increased flow of blood to the kidney. And the question naturally arises, shall a kidney already congested and inflamed be further jeopardized by crowding more blood into it?

On the other hand, it is well known that convalescence in a case of acute Bright's disease which has been left to recover without treatment is commonly ushered in by copious diuresis. This may be explained by the fact that urea itself is a diuretic, as may be shown by injecting it into the blood-vessels of any animal. Early in acute Bright's disease the blood becomes charged with urea and allied substances, and when it flows freely through the kidney they exert a diuretic action. It will be observed, however, that this takes place only after the circulation becomes free, and it must be looked upon,

therefore, not so much as a cause, as a result of an improvement in the circulation of the organ. Nevertheless, to facilitate copious secretion of urine, and with it the elimination of those effete matters the accumulation of which constitutes the chief danger of Bright's disease,—uræmia,—can only be considered desirable if it can be done without congesting the kidney.

The secret of the proper use of diuretics lies in the selection of such as effect their object without producing stagnation. To understand this, it must be recalled that the secretion of urine is largely a process of filtration, a process of squeezing out the water and dissolved elements by pressure from behind, in the Malpighian bodies. It will be remembered that there are two sides to the renal capillary circulation, an *arterial* side and a *venous* side. The first consists in the afferent arteriole and the Malpighian body; the second, of the capillary network formed by the splitting up of the efferent vessel after it leaves the Malpighian capsule, and closely embraces the convoluted tubules. The area of this is great, and the movement of the blood slow. As a consequence, a condition favorable to increasing the blood pressure in the Malpighian body exists. Such pressure is obtained by increasing the force of the heart's contraction, or by the introduction of fluid within the blood-vessels. Thus more rapid filtration is secured, that is, more water forced from the blood-vessels into the Malpighian capsules, and down in the tubules. Now, whatever remedies increase cardiac propulsion, or arterial pressure by absorption of fluids will increase the amount of water filtered out. Such remedies are *digitalis, strophanthus, spartein,* the *salines,* and *diluent drinks* generally,—digitalis and its class by increasing the force of the heart's action, the salines and diluents by increasing blood-pressure through their absorption.

Digitalis is the diuretic most to be relied upon, and when combined with the salines, freely diluted, affords a powerful agent for good. It is necessary, however, to have a reliable preparation, and unless one is sure of the quality of the tincture, it is best to use a freshly prepared infusion. At the same time it is also true that much smaller doses of the tincture are usually given than of the infusion. Thus, of the latter, f℥ss. is often administered, equivalent to three and three-quarter grains, while eight minims or sixteen

drops of the tincture, equivalent to one grain of the powder, are considered a full dose, a discrepancy which will account for at least a portion of the slower effect of the tincture. Digitalis should therefore be given in sufficient quantity,—f℥ss. to f℥i of the infusion to children, and f℥ij to f℥ss. to adults,—repeated every four hours until an appreciable effect is produced on the secretion of urine and on the rate of the pulse, when it should be diminished. Digitalis, when thus administered, should, of course, be watched, and the patient should be seen at least daily until an effect is produced. I prefer to give it at first alone. It is, however, often combined with salines of which acetate, citrate, and bitartrate of potassium are to be preferred. Their diuretic action doubtless depends upon the impetus they give to the osmosis of fluids which hold them in solution, thus increasing the arterial tension and contributing to the flushing of the kidney. To adults 20 grains of these may be given every two or three hours in solution freely diluted, because water itself is an excellent diuretic; ten grains to children as often. If there be general anasarca less water should be administered in association with diuretics because we already have an excess of water in the body.

The *tincture of strophanthus* may be given in the same doses as the tincture of digitalis. *Spartein sulphate* is an efficient diuretic and may be given in doses of one-fourth to one-half grain every three or four hours in lieu of digitalis or in alternation with it.

The different preparations of *digitalin* are of such various and uncertain strength that they are not to be relied upon when urgency is present.

Caffein in doses of three grains every four hours is an efficient diuretic, but it is not always to be relied on and sometimes requires prolonged use before its effect is seen. I am fond of alternating it with digitalis. Caffein citrate is a weaker preparation than caffein. A similar remedy is *theobromin* which in doses of seven and one-half grains every four hours, often acts promptly.[1] *Diuretin,* which is a natrio-salicylate of theobromin, sometimes produces a temporary effect, but it is a nauseating dose and should only be used as a *dernier ressort.* Its dose is 10 to 15 grains four times a day.

[1] Caffein is trimethylxanthin and theobromin is dimethylxanthin.

Another admirable diuretic combination, including several of these elements, is Trousseau's diuretic wine, which consists of:

Junip. contus., ... 3x
Pulv. digitalis, ... 3ij
Pulv. scillæ, ... 3j
Vin. xerici, ... Oj
Macerate for four days and add
Potas. acetatis, ... 3iij
Express and filter.
S. Tablespoonful three times a day for an adult.

A simpler and similar remedy is a mixture of juniper and bitartrate of potassium made by adding a pint of boiling water to an ounce of contused juniper berries and an ounce of bitartrate of potassium, strain and take four ounces every four to six hours.

A remedy both aperient and diuretic which has lately been reintroduced in the treatment of anasarca and uremia, is the *apocynum cannabinum* or American Indian hemp root. Now and then a patient is found who will bear this drug, which is a powerful irritant hydragogue purgative and diuretic. It is also emetic, and this property makes it difficult to administer for the diuretic and aperient effect. The dose is five to sixty minims of the tincture. It should be used only in extreme cases.

By such means as these, started after unloading the blood-vessels by a purge or a sweat, we may greatly serve our patient by diuretics.

On the other hand, turpentine, cantharides, copaiba, and the class of diuretics which produce a congestion and stagnation of blood in the second or venous capillary network, are mischievous, and should not be employed.

Infusion of digitalis may also be used in the shape of fomentations. Cloths wrung out in hot infusion of digitalis and laid over the abdomen of the patient, have been known to produce diuresis when all other measures have failed. I have never been successful with it.

The *diet* of patients with acute Bright's disease, while it should be nutritious, should be simple and easy of digestion. The irritability of the stomach in this disease has been alluded to, and it is important that it should not be excited. Milk may be considered the typical food, not merely because of its bland and unirritating qualities, but also because albuminuria diminishes under its use, while the proportion of proteid is less than in animal flesh. While solid animal food

is not allowable, there is no reason why light animal broths should be precluded whenever it may be desirable to break up the monotony of a milk diet. Rice and farinaceous preparations generally, are suitable adjuvants to the milk diet. The combination of lime-water, and still better of carbonated water or Vichy with milk, should not be overlooked in the treatment of the sensitive stomach.

Treatment of Acute Uremia.—The alarming and dangerous nature of this condition lead me to a separate consideration of the measures required in its treatment. The treatment which has just been described is such as would be called for in an ordinary case of acute nephritis of decided severity. Its tendency will be to prevent the accumulation of such toxic matters, whatever their nature, as cause uremia. But our best efforts in this direction sometimes fail, and we are called upon to combat convulsions or coma, or both. How shall they be met? The indication has already been explained. Retained toxic substances cause the uremia. These must therefore be eliminated. The kidneys are not acting and the secretion of urine is suppressed. There remain therefore but the bowels and skin to operate upon. Since the patient is probably unconscious and cannot swallow voluntarily, such remedies must be used as do not require his coöperation. Such are *croton oil* and *elaterium*. Of the former two drops, slightly diluted with plain oil or glycerin may be carried to the back of the throat and swallowed; or in case of extreme urgency, may be introduced without dilution into the mouth, whence it is quickly absorbed. Its operation may be facilitated by a rectal injection. Of elaterium a quarter of a grain in powder may be given by the mouth. Both may be repeated if necessary.

In like manner the skin may be made to substitute the action of the kidney. At the present day *jaborandi* or its active principle *pilocarpin* is the most efficient agent by which to accomplish this. The most convenient method of administration is by subcutaneous injection of pilocarpin. For an adult one quarter of a grain of the dissolved muriate thus administered is generally sufficient to excite the most profuse diaphoresis and salivation within half an hour. Should it not, the dose may be repeated. In the absence of pilocarpin the freshly prepared infusion of jaborandi may be injected

into the rectum, with almost equally prompt results. Care must be taken to keep the bulk within limits lest it be rejected. Four ounces of hot water may be poured upon a drachm of jaborandi leaves, and when sufficiently cool strained and injected. The doses here referred to are intended for adults. My friend Dr. Horace Williams has used the fluid extract in suppository, with excellent results. A fluid drachm may be inspissated and put into a single suppository, suitably reduced in size, for children.

I have rarely seen any of the extreme prostration which is said sometimes to result from the use of jaborandi. Should edema of the lungs appear it may be combated by the hypodermic use of atropin in $\frac{1}{100}$ gr. doses. There is undoubtedly a feeling of weakness and relaxation after a copious sweat from this as from other causes, which may be combated by stimulating and supporting measures where they can be applied. Dysuria is said to occur occasionally, resulting from jaborandi. I have never met it. The single hypodermic dose of pilocarpin should not exceed a third of a grain. Smaller doses suffice when artificial heat is associated.

The *vapor* bath, *hot-air* bath, *warm-water* bath, and *warm pack* which were our sole resources for these purposes before jaborandi and its preparations came into use, should not be forgotten, indeed had better be tried first if available. The vapor bath is easily used. A tin pipe two or three inches in diameter with an expanded extremity is placed over a steaming kettle of water while the other end is placed under the bed clothing. An ordinary rain-spout may be used. Hot air may be used instead of vapor, but it is neither so pleasant nor so efficient. The warm pack or bath is not so available in acute uremia because of the unconsciousness of the patient and his inability to help himself.

Blood letting is a rational measure for the relief of uremic convulsions and coma. No one doubts the efficiency of bleeding in puerperal convulsions, and if puerperal convulsions are uremic as I believe they mainly are, then bleeding should be of service in the uremic convulsions of acute Bright's disease. The blood should be replaced, however, by the normal salt solution (three-fourth per cent. of chlorid of sodium) either by hypodermoclysis or intravenous injection. Nitroglycerin and nitrate of amyl are indicated for their

dilating effect on the blood-vessels in $\frac{1}{100}$ grain doses frequently repeated.

To control the convulsion itself there is no better remedy than *chloral hydrate,* and it should be one of the first measures tried. In the case of an adult, a drachm may be injected into the rectum in solution; fifteen to thirty grains for a child, care being taken to secure its retention. *Chloroform* may be used for the same purpose, but its continued use is undesirable.

The use of *opium* requires to be alluded to. The caution which has always been suggested in its use I believe to be, in the main, a wholesome one, and I should prefer to produce hypnotic, sedative, and antispasmodic effects by chloral and the bromides whenever it is possible. There is not however the same objection to it in acute as in chronic nephritis, nor in parenchymatous nephritis as in interstitial nephritis.

Treatment of Complications.—Complications should be treated by remedies called for by such conditions independent of the renal cause. Effusions into the pleural cavities and abdomen are often best relieved by paracentesis, or aspiration; pneumonia and bronchitis by counter-irritation.

These same measures which have been detailed, excepting the general bloodletting and chloral, may also be employed in the treatment of suppression of urine or of obstinate dropsy without uremic symptoms, with such modifications as circumstances may suggest, due regard being paid to the strength of the patient. They will be further referred to when discussing the treatment of the chronic forms of Bright's disease.

Sooner or later also, in the treatment of acute parenchymatous nephritis, supporting treatment is rendered necessary to repair the losses which the blood suffers by the albuminuria, and to some extent also by the depleting measures of treatment. These effects should indeed be anticipated by proper diet, tonics, quinin, especially iron, wine, malt liquors, whiskey, or brandy as indicated. These measures will also be more particularly alluded to in the *treatment of chronic Bright's disease,* which see.

SECTION VII.

CHRONIC DIFFUSE NEPHRITIS.

Synonyms.—Chronic diffuse non-indurative nephritis; chronic parenchymatous nephritis; chronic epithelial nephritis; chronic tubal nephritis; chronic catarrhal nephritis; large white kidney.

CHRONIC DIFFUSE NEPHRITIS IS A CHRONIC HYPERPLASTIC PROCESS IN THE KIDNEY, WHICH COMMONLY STARTS IN THE EPITHELIUM OF THE TUBULES, BUT IN WHICH INTERSTITIAL CHANGES OF THE NATURE OF NUCLEAR PROLIFERATION ARE ALSO MORE OR LESS CONSTANTLY PRESENT.

Etiology.

The etiology of chronic parenchymatous nephritis cannot always be traced. It is more common in men. While it is frequently a simple continuation of a process which begins as acute parenchymatous nephritis, as often it originates *de novo*. To the former category, *scarlatina* and *pregnancy* contribute the greater number. Of a certain number of the second category, the causes are undiscoverable. *Habitual exposure* to *cold* and *moisture* doubtless produces some cases. Residence in damp houses may thus cause it. *Chronic constitutional diseases, especially such as are associated with suppuration,* as phthisis, tertiary syphilis, psoas abscess, etc., are among the causes of this disease, with which amyloid disease is often found associated. It is probable that in the majority of cases some slowly operating toxic agent is responsible. Among these are included the toxic products of imperfect digestion which not only irritate the epithelium of the renal tubes but arterial walls as well. Habitual constipation may further add to this causation.

Long-continued exposure to *malaria* is now a recognized cause of chronic parenchymatous nephritis. The experience of different observers is widely different; Frerichs found on the North Sea no such origin. Bartels says that next to chronic suppuration it is the most frequent cause. Rosenstein found 23 per cent. of all cases in the neighborhood of Dantzic due to malaria; in N. Holland an emi-

nently fever country, it was rarely a cause. I have never myself been able to trace a case to this cause. Dr. S. C. Busey, of Washington, D. C., presented a paper at the session of the American Medical Association, in 1880, on "Malaria as a cause of Bright's Disease in Children," and in 1898 W. Sydney Thayer, of Baltimore, read a paper before the Association of American Physicians on the same subject. Certainly in Philadelphia malaria is not a common cause.

Alcohol is commonly regarded as a less frequent cause of chronic parenchymatous nephritis than of interstitial nephritis. It is still, however, a cause and the chronic nephritis which we find in confirmed drunkards, those who are always saturated with whiskey when they can get it, is probably due to the latter agent. To be sure it cannot be denied that the exposure to which these outcasts are subjected, may contribute. *Chronic valvular heart disease* has been included among the causes. It certainly is a favoring cause through the passive congestion and cyanotic induration it induces.

That *mercury* is a common cause of chronic nephritis, as was believed by the older physicians, is denied by Bartels, who bases his denial upon the most extended experience in the use of mercury for syphilis in the hospital at Kiel. Recently attention has again been called to this subject and Dr. J. M. Swan[1] in a paper read before the College Physicians of Philadelphia has adduced evidence of such a cause.

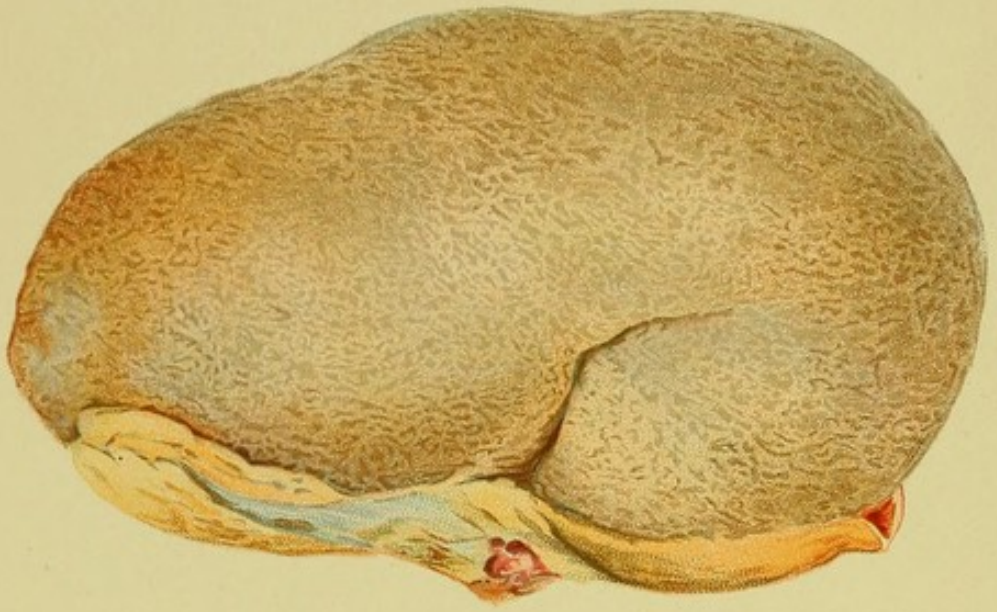
In all the modes of origin of chronic nephritis the rationale would seem to be that some noxious agent in the blood, whether introduced from without or retained there from defective elimination, produces the condition by a slow but constant irritation of the epithelium which attempts to remove it.

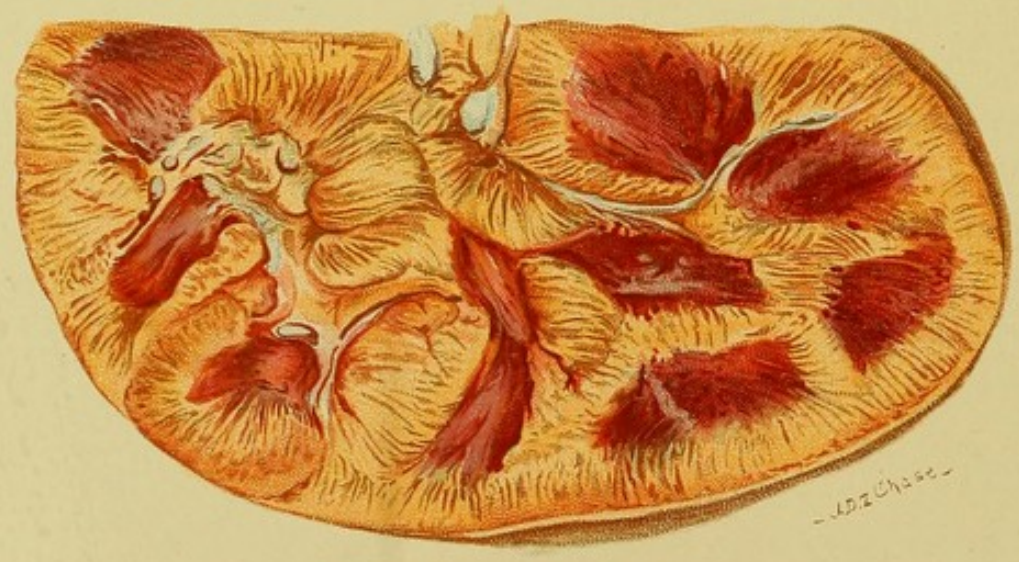
Morbid Anatomy.

There are two distinct stages in the morbid anatomy of chronic diffuse nephritis, if the disease is of sufficient duration, viz., the stage of enlargement, or the *large white kidney,* and that of contraction, or the *fatty and contracting kidney.*

I. *Stage of Enlargement.*—There are few more striking objects in morbid anatomy than a typical example of the *large white*

[1] Transactions, College of Physicians, Philadelphia, 1903.





LARGE WHITE KIDNEY

kidney, as the product of this stage of chronic parenchymatous nephritis is called. The kidney is large, smooth, white, or slightly tinged with yellow; weighs generally from seven to ten ounces, but is often much heavier. It is usually doughy, rarely elastic in consistence.

The capsule, which may be thinner than in health, strips off easily, but occasionally drags a little of the parenchyma with it. When the smooth white surface thus uncovered is examined, the little capillary circlets bounding the lobules in the normal organ are in some places indistinct, in others conspicuous; the same is true of the stellate veins of Verheyn. Numerous yellow specks are seen scattered over the surface. Hemorrhagic extravasations are also occasionally present, but very much more rarely than in the acute form. Alongside of these the greater translucency of more nearly normal areas contributes to a mottled hue.

On section it is at once evident that the enlargement resides mainly in the *cortex,* which is at the same time markedly anemic, its intense white contrasting strongly with the pink hue of the cones, which, though paler than in health, is still less so than the cortex. Closer examination of the cortex reveals the same yellow specks as on the external surface. In consequence of distention and swelling of the convoluted tubes which dip down between the cones, there may be produced the same sheaf-like distortion of the latter referred to in acute parenchymatous nephritis.

The pelvis of the kidneys in chronic parenchymatous nephritis may be the seat of catarrhal swelling and a slight degree of hyperemia.

Minute Changes.—Minutely examined thin sections show the involvement of both *tubes and intertubular substance.* Turning our attention first to the former, many are found choked with granular cells and the granular debris of cells, causing the tubes to appear, under the microscope, as black opaque lines by transmitted light, very similar, indeed, to the tubes in acute nephritis. In other situations the tubules are filled with fat-globules and fatty cells. In places the lumen of the tubes is preserved, in others not. In other situations the cells are nearly normal. The parts presenting a yellow tinge are those in which the fat is most abundant, and this is the

composition of the yellow specks already alluded to as visible to the naked eye. They represent a coil of tubules filled with oil-drops or fatty cells.[1]

Certain tubules also contain casts, often of the waxy kind. Sometimes, indeed, they are very numerous. Rarely hemorrhagic extravasations are also found in the tubules.

The *capillaries* of the cortex are completely or nearly empty of blood, which has been expressed from them by the distended tubules. To this, is due the extreme whiteness of such kidneys, whence the name by which they are known. The Malpighian capillaries are subject to the changes already described, under acute nephritis, viz., proliferation of capillary nuclei; so, too, the alterations of the epithelium of the glomeruli there described may also be present as well as those of the capsular epithelium. From the first would result thickening and more or less opacity of the capillary walls. The muscular coat of the afferent arteriole is sometimes thickened, but general arterial hypertrophy is not constant in this stage of the disease. The intertubular capillaries and veins present no changes except those already referred to as the result of the compression by the distended tubes.

The *medullary cones* are more altered than in the acute form, but the changes are secondary in importance, and their microscopic appearance is scarcely altered. They are sometimes a little paler, owing partly to granular and fatty alteration in the cells lining the straight tubules, and partly to the presence of similar cells descended from the convoluted tubules above them. The straight tubes of the cones as well as the looped tubes of Henle often contain waxy casts.

In chronic parenchymatous nephritis the *interstitial tissue* is always increased, and, it may be said, proportionately to the duration of the disease. It has already been said that any case of parenchymatous nephritis, sufficiently prolonged, is attended by a hyperplasia of connective tissue, although it is difficult to say when this overgrowth begins. Langhans reports[2] a case in which death, occurring five weeks after the appearance of the first symptoms directly traceable

[1] Very great differences are noted in different kidneys in the amount of oil present in the cells, not, as yet, satisfactorily explained. Dickinson says the cells have a greater tendency to be fatty when cold is the cause.

[2] Loc. citat., p. 105.

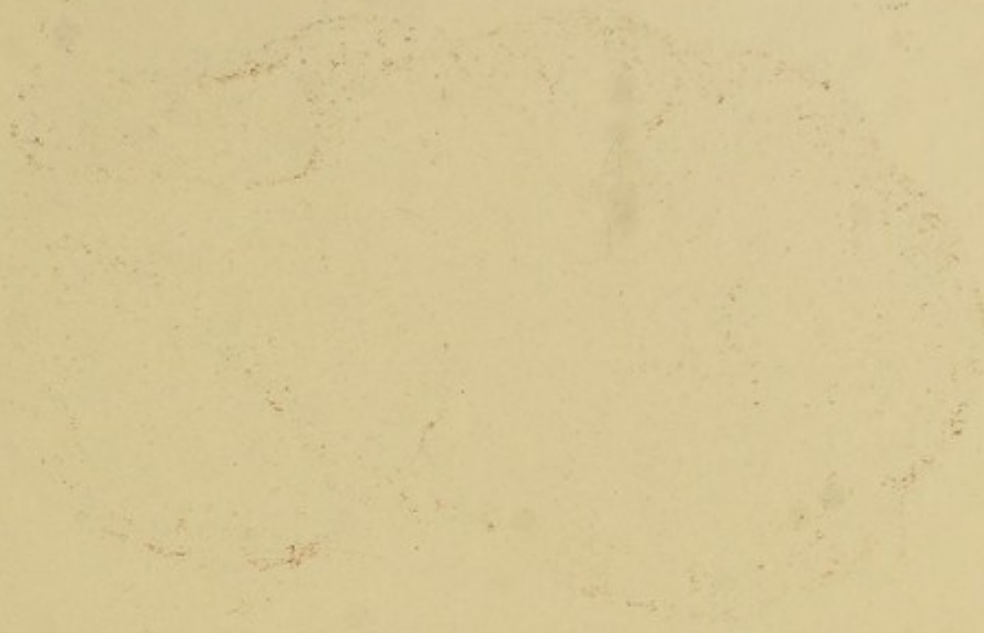
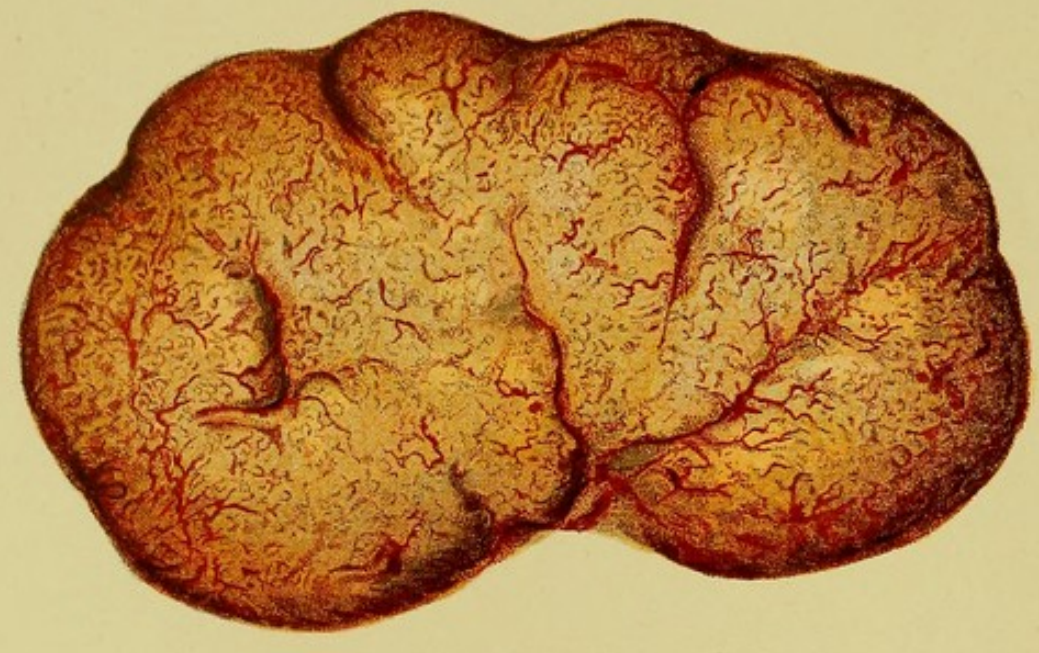
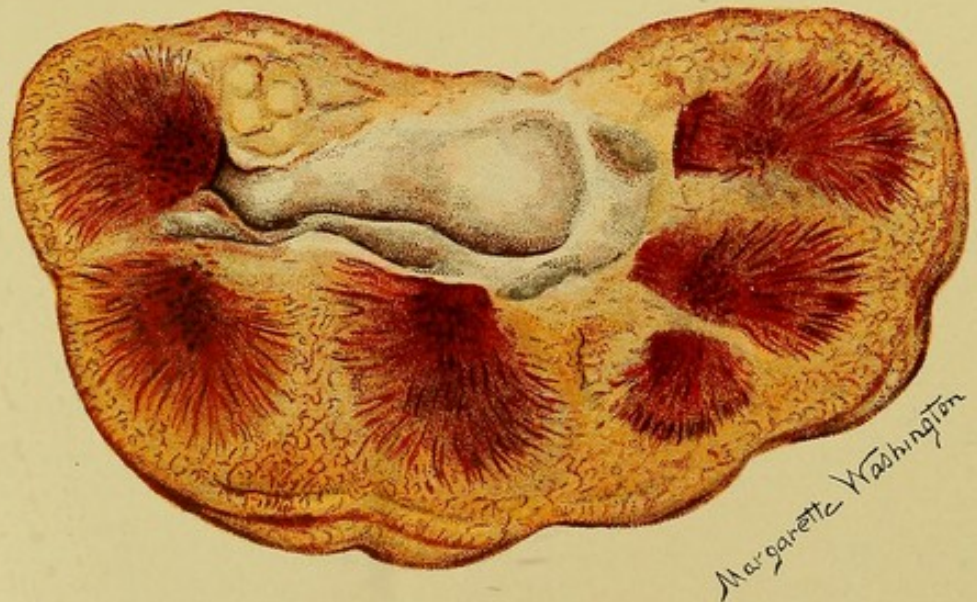


PLATE IV





FATTY AND CONTRACTED KIDNEY

to a thorough wetting, the stroma was *markedly thickened*. And in a case of Dickinson's already alluded to, intertubular cellular formation, "though approximating as much to pus as to fiber," was found within six weeks of the outset.[1] Again, cases of much longer duration may be entirely without it. Interstitial fibrosis may, however, be considered as a superaddition of chronicity, and wherever a case is distinctly chronic one may infer, with tolerable certainty, that it is present.

In this overgrowth the thickness of the trabeculæ of tissue between the tubules varies extremely, being sometimes so slight as to be discoverable only on microscopic examination of thin sections; at others it is appreciable to the naked eye. Minute examination reveals the change to consist of numerous round and oval nuclei, between which may be a homogeneous or more or less distinctly fibrillated intercellular substance. In the *hemorrhagic variety* in addition to the changes described extravasations of blood are found between the tubules while the tubules themselves are in various degrees filled with extravasated blood. See Fig. 36.

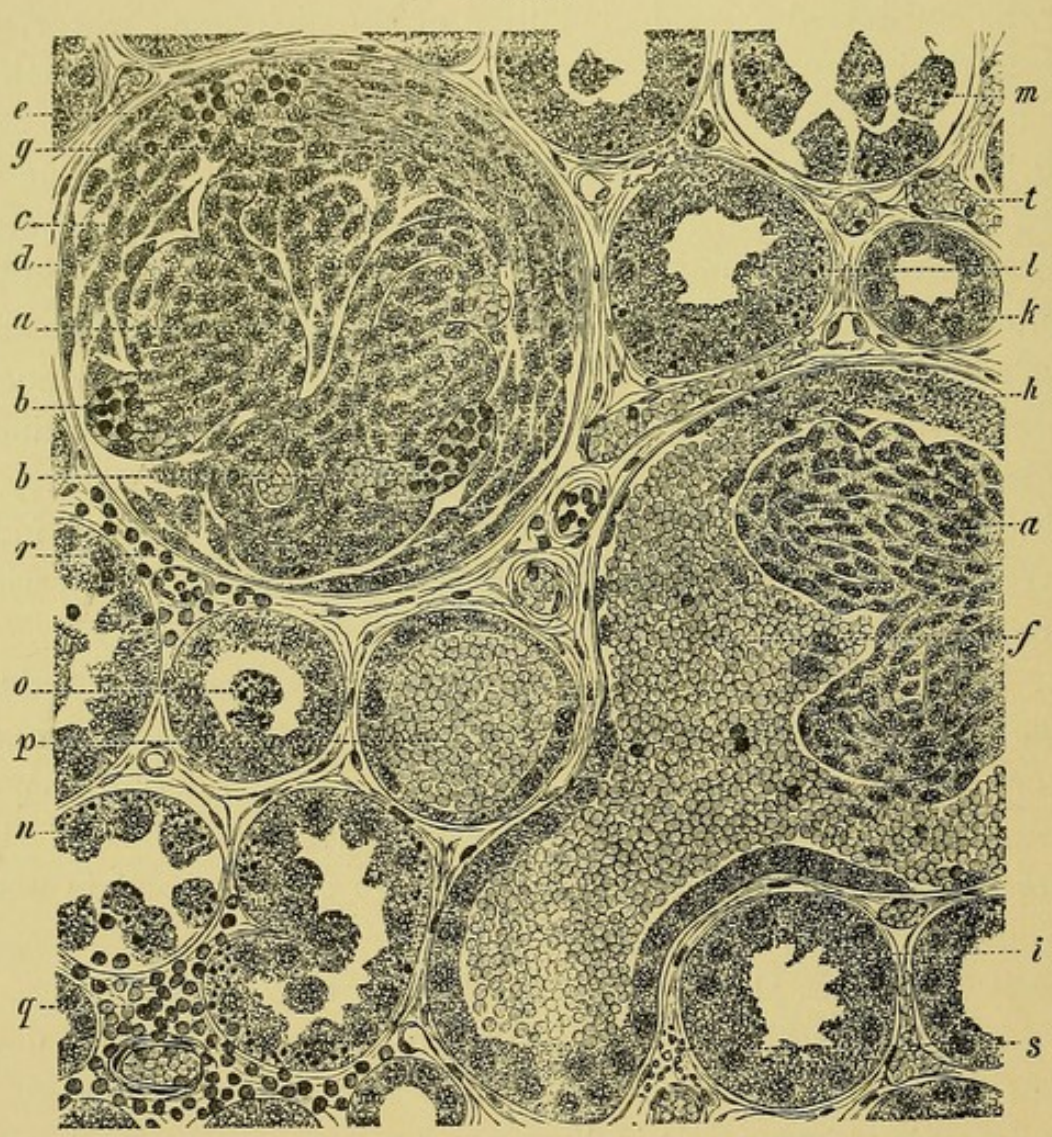
II. *The Stage of Atrophy—The Fatty and Contracting Kidney, or the Large Contracting Kidney.—Chronic Diffuse Non-indurative Nephritis.*—The interstitial new formation above referred to possesses all the characteristics of new connective tissue formed elsewhere. It invariably exhibits a tendency to contract, and in doing so, it gradually distorts the shape of the previously enlarged organ, while it obliterates also a variable quantity of its tubular structure. The degree of this distortion varies greatly, increasing with the duration of the process. The kidney continues as large and even larger than the normal organ. It is, however, smaller than the large white kidney, uneven, lobulated, but never presents the hobnailed or granular appearance of the kidney of interstitial nephritis. Some well authenticated cases of much smaller kidneys thus arising are reported. The capsule does not strip off easily as from the large smooth organ, but drags with it considerable of the tubular structure. The capsule removed, however, the surface of the kidney exhibits,

[1] In the light of more recent studies these acute cases fall into the category of acute interstitial nephritis on which I have added a separate Section VIII. in this edition. I have thought it interesting to retain the allusion to these cases at this place.

between the constrictions, the same pallid speckled appearance, distinct stellate veins, etc., already described; and on section the same enlarged anemic cortex.

Microscopically, sections exhibit the same alternation of groups of

FIG. 36.



Chronic Hemorrhagic Nephritis. *a,* Normal coil of capillaries; *b,* capillaries filled with leucocytes; *c,* desquamated glomerular epithelium; *d,* capsular epithelium; *e,* exudate consisting of leucocytes, erythrocytes, and granular material; *f,* hemorrhage in one of the capsular spaces and extending into the beginning of a uriniferous tubule; *g,* granular and lamellated exudate containing nuclei of the desquamated glomerular epithelium; *h,* disorganized blood enclosing desquamated glomerular epithelium; *i,* convoluted tubule; *k,* looped tubule; *l,* uriniferous tubule containing pigmented and fatty degenerated epithelium; *m,* pigmented epithelium desquamating; *n,* fatty and in part desquamated cells; *o,* desquamated and fatty epithelium in the lumen of a normal uriniferous tubule; *p,* tubule filled with blood; *q,* perivenous, *r,* pericapsular, cellular exudate; *s,* pigment in the connective-tissue stroma; *t,* capillary filled with blood. × 300. After ZIEGLER.

normal and choked tubules already described, alongside of other places in which the tubules together with the Malpighian bodies at their extremities are obliterated. Between them is found a large amount of interstitial tissue, and the Malpighian bodies are surrounded by concentric layers of the same. Even minute cysts, the result of obstruction of tubules by the constricting tissue, are found. These will be more fully described when we come to consider the contracted kidney of interstitial nephritis, with which also this stage of atrophy in chronic parenchymatous nephritis will be more carefully contrasted. The indurated kidney of chronic diffuse nephritis is sometimes indistinguishable from that of typical chronically contracted kidney.

It not infrequently happens that along with the changes constituting chronic parenchymatous nephritis, are found, to a certain extent also, those of lardaceous disease. Thus in a large white kidney, the Malpighian bodies will often strike the mahogany red reaction with iodin, characteristic of this condition, although the alteration may not be recognizable by the naked eye. Occasionally the alteration may even affect the afferent and efferent vessels. This secondary amyloid change was ascribed, by Sir George Johnson, to the exhaustive drain caused by the long-continued albuminuria, such drains, as will be more fully considered under lardaceous disease, being the supposed cause of this form of disease of the kidney.

Symptoms.

There are few distinctive symptoms of chronic parenchymatous nephritis, but by a thorough investigation of the case in all its bearings a diagnosis may generally be made.

In typical cases *dropsy* is almost always present, and it is very apt to be general, at least involving the subcutaneous connective tissue generally—the eyelids, face, hands, feet, legs, thighs, and trunk. It may disappear during night and recur during the day. The serous sacs also frequently contain fluid, almost always in severe cases. But dropsy is not always thus general. It may be confined to the extremities or to the face, and even to the scrotum. Dropsy may be entirely wanting, but when present no symptom gives the patient so much inconvenience, as this one. In the advanced stage

the legs and thighs may be twice their normal dimensions. They are so heavy the patient cannot lift them, while they are often excoriated, and moist with exuding serum, and smart with irritation. Sometimes, as the result of spontaneous rupture of the skin, the discharge of serum is profuse, saturating the bedclothing, occasionally, also, with relief to the patient.

Another very constant symptom is *anemia,* producing a peculiar translucent waxy appearance, which is very characteristic when present in marked degree, and is often alone sufficient to suggest the diagnosis. Between this and slight degrees scarcely appreciable there are all intermediate degrees.

Again, the *debility* of those suffering with this condition is very striking. In bad cases, if able to walk at all, they soon get out of breath, are immediately exhausted. Locomotion may be impossible in consequence of the extreme swelling, even if the strength otherwise permit it. Others continue to walk about long after general anasarca prevails.

Now if such a patient be questioned, and it be found that he took cold three or four months earlier—cold followed by this dropsy, which did not disappear, or which disappeared and returned; or if it be found that he had scarlet fever some months or even years previous, if these points are made out the diagnosis is easy. For it has been a case of acute parenchymatous nephritis which has become chronic. If, however, there be no such history, but an insidious beginning, traceable to any one of the causes named, or to no cause, the case is not so clear.

Condition of the Urine in Chronic Parenchymatous Nephritis.—The urine is diminished, but somewhat variable in quantity, pale in color, of low specific gravity, highly albuminous, and deposits often, but not always, a copious white sediment.

First, as to *quantity.* This, as stated, is diminished, but quite variable, ranging from 300 to 1,200 c.c. (10 to 40 oz.). It is, however, more seldom suppressed than in acute nephritis. The quantity of urine also increases as the patient improves, or as the stage of contraction is entered upon, so that it may even exceed the normal.

The *specific gravity,* notwithstanding the small quantity of urine, is less than the average of health. It varies somewhat, inversely

with the quantity of urine, but the most usual range is from 1008 to 1015.

The *albumin,* commonly large, varies as to its percentage amount with the quantity of urine passed—from 1 to 3 per cent., or from one half to seven eighths the bulk of the urine tested. The variation in the 24 hours' quantity of urine should not be lost sight of. This is particularly important in testing the value of various therapeutic measures, some of which, by increasing the quantity of water passed, diminish the percentage of albumin without diminishing the 24 hours' quantity. This is often overlooked. The amount of albumin lost in the urine is sometimes very large. It has even occurred that the percentage proportion of albumin in the urine has exceeded that in the serum of the blood from the same patient. Bartels accurately determined the 24 hours' quantity in several cases under his observation, and found in one instance an average of 17.36 grams (267.85 grains) daily, for the last month of the patient's life; in another an average of 15.28 grams (235.76 grains) daily, for two months; and in a third 10.04 grams (155 grains), for six months. The last lost 6,804 grams, or about 18 pounds troy, in a period of 27 months. The largest amount found by Senator was 2.8 per cent. From this may be appreciated the enormous drain upon the system by this "hemorrhage" of albumin. The quantity of albumin has very little effect upon the specific gravity of the urine. Indeed, the lighter urines are generally those which have the larger amount of albumin, because highly albuminous urines contain little urea.

The *flocculent white sediment* is made up of variously granular casts, among which the *dark* granular are conspicuous by their numbers and size, and especially their width. There are also found oil-casts, and casts containing entire and fragmentary epithelial cells, which are also granular and fatty. Finally, yellow waxy casts are also found. These, which are also generally of larger diameter, are of especial value in indicating the chronic nature of the disease though waxy casts are not limited to chronic disease. Casts generally increase in numbers with the progress of the disease, being at first less numerous. They are not, however, always thus numerous, being indeed sometimes wanting. Much granular debris, similar to that making up the black granular casts, and probably therefore

derived from the disintegration of epithelium, is also found free in the urine. Free fatty cells and granular fat cells (compound granule cells) are also often present.

Leucocytes are also often very numerous in the sediment of chronic parenchymatous nephritis, while red corpuscles, although occasionally present, are much less common. In the variety known as chronic *hemorrhagic* nephritis on the other hand blood is abundant. In other respects the symptoms of hemorrhagic nephritis do not differ much from those of other forms of nephritis.

The sediment, when mixed with the urine, gives the latter a turbid, dirty appearance, which is sometimes permanent, but when the sediment has subsided the supernatant fluid is tolerably clear.

The *normal constituents* of the urine are *generally diminished* in quantity. The most important of these is *urea*. To the reduced amount of solids, and particularly of urea, the reduced specific gravity is largely due. Estimations for urea must always be considered in connection with the amount of proteid food ingested. And although the quantity of albumin is large, and must therefore increase somewhat the specific gravity, such increase is not ordinarily sufficient to compensate for the decline.

The above statements with regard to the urine are not without exception. At the height of the disease, when the smallest quantity of urine is secreted the specific gravity may be above normal. The proportion of albumin may *rise as the specific gravity rises,* diminishing as the specific gravity falls. Furthermore tube casts are by no means always as numerous or as distinctive. Especially may they be reduced by a treatment which increases the quantity of urine.

Notwithstanding the small amount of urea excreted in this affection, *uremia is infrequent,* especially before the stage of contraction is reached. And if it be asked why this is the case, I know no better reason than that assigned by Bartels, that all the physiological sources of urea production are less active. The appetite and digestion are bad, less food is taken, and thus the principal source of urea in the economy is cut down. Further, the nitrogenous tissues are wasted and tissue change is less active, so that the urea from these sources is less pronounced. Furthermore, some of it may be

stored in the abundant serum which occupies the interstices of the tissues and the serous cavities which share in the dropsy.

Visual symptoms are much more uncommon than in interstitial nephritis. They are due to the same retinal lesions as in that disease and will be described when considering it. Amaurosis may be among these symptoms.

Are there any symptoms whence we may infer that the stage of contraction has been reached, provided the patient lives? Presumably it has if there is hypertrophy of the left ventricle. Although the possibility of an earlier hypertrophy in children cannot be denied, it is very seldom that it occurs prior to the stage of contraction. Long duration of the disease also affords presumptive evidence that contraction has taken place. The duration cannot, however, always be ascertained. But if a case come under observation as one of parenchymatous nephritis, and continues thus for a year or more, the process of contraction is likely to have commenced. Yet contraction does not always follow on such duration, the large white kidney continuing at times to the very end.

The *dropsy* diminishes and may disappear as the stage of contraction is entered upon. So also the urine changes. The quantity, previously small, is increased, while the specific gravity remains low; the amount of albumin is also much less than during the stage of inflammation. In these respects—absence of dropsy, increased amount of urine, and small amount of albumin—it resembles the true contracted kidney of interstitial nephritis, with which indeed it may be confounded in the absence of a previous history. The casts may, however, continue numerous, and exhibit much the same character as in the stage of enlargement, although they too may become scanty; and if we have not a knowledge of previous history the diagnosis between contraction secondary to previous enlargement, and primary contraction the result of interstitial nephritis, may be impossible.

Uremia is rather more common in the stage of contraction than during enlargement, but still comparatively infrequent. When present it exhibits the symptoms already detailed under acute parenchymatous nephritis.

The duration of chronic parenchymatous nephritis is very variable.

Many cases terminate unfavorably within a year after they have been established; but I have one now under observation in the stage of contraction which I have known to exist for 25 years.

Complications.

The complications of chronic parenchymatous nephritis are the same as those of acute. Edema of the lungs, bronchitis, pneumonia, inflammation of serous membranes and serous effusions are all liable to occur. Pericarditis is a less frequent complication than in acute nephritis. Hypertrophy of the left ventricle is more common than in acute nephritis, for the reasons already referred to, but still very much less so than in interstitial nephritis. Derangements of digestion are very frequent. The acute blindness unattended by retinal changes, described as occurring in the uremia of acute nephritis, rarely happens, while retinal changes are rather more frequent, but still infrequent compared with interstitial nephritis, under which they will be described.

Diagnosis.

The diagnosis of well-marked cases is ordinarily easy. The extreme pallor of the patient, the diminished urine of low specific gravity, the very large amount of albumin, the numerous dark granular, oil- and waxy casts of large diameter, free fatty cells and granular fatty cells, especially if we are able to trace a history of long duration, all point to the disease. And if there is an antecedent history of scarlatina or exposure to cold, pregnancy or chronic infectious disease, there can be no mistake.

The symptoms of amyloid or lardaceous kidney very closely resemble those of the large white kidney, and it has been mentioned that the same causes may produce both. Occasionally it is absolutely impossible to say which form of disease is present. It has usually been thought that if there be enlarged liver and spleen, or persistent diarrhea, along with a cause which may produce lardaceous disease, it may be inferred that the latter condition exists; but recent observation has shown that the first two at least may be present, together with all the causes and other symptoms which are regarded as favoring lardaceous disease, and yet the disease be parenchymatous ne-

phritis.[1] As a rule there is not so much dropsy in lardaceous disease, casts are more scanty, and generally hyaline, though sometimes oil-casts are found. Often, too, the two forms of disease coexist, either as the result of the same cause, or the amyloid disease may supervene on long-continued parenchymatous nephritis.

The stage of contraction is more difficult of recognition unless the case has been for some time under observation, and traceable to its beginning. The resemblance to a case of contracted kidney due to interstitial nephritis may otherwise be very close. But the albuminuria of secondary contraction is usually larger and the casts more numerous, and varied as compared with the scanty, small pale granular casts of chronic interstitial nephritis. In the latter the quantity of urine exceeds the normal, while in the former, although larger than in the first stage, it is still not abnormally large.

While there is little or no difficulty in distinguishing a well-marked case of chronic parenchymatous nephritis with the symptoms just described from one of interstitial nephritis, there are certain border line cases in which it is most difficult to decide what form is present, a matter of importance since the prognosis in the two conditions is different.

It is in such cases as these that the methylen-blue test may be of service. In 1897 Achard and Castaigne[1] suggested methylen-blue for this purpose, gauging the rapidity of its excretion by the blue color it imparts to urine. It is harmless and no chemical analyses are needed as it diffuses with great facility and its presence is indicated by the blue color produced even when present in very minute quantity. Achard and Castaigne dissolved five centigrams of powdered methylen-blue in twenty parts of sterile water and injected it deeply into the buttock under antiseptic precautions. They advise the administration of the drug hypodermically in order to eliminate variations in the rapidity of gastric and intestinal absorption. At the time of the injection the patient is directed to empty his bladder and again at the end of one, two, four, eight and twelve hours as long as the color lasts. In normal cases the blue or bluish-green tinge appears

[1] See an article by Dr. Paul Fürbringer, Zur Diagnose der amyloiden Entartung der Nieren, Virchow's Archiv, Bd. 71, 1877, s. 400.

[2] Soc. Med. des Hop., April 30, June 18, 1897. La Semaine Med., 1897, pp. 170, 239. Gaz. Hebdom., May 9, June 24, 1897.

within the first half hour and always within an hour, while in certain forms of nephritis several hours elapse before the urine shows any color. In normal cases the maximum coloration, a deep indigo, is reached in about three hours and the urine is not clear for two or three days.

Among others Bard and Bonnet[1] in France repeated Achard and Castaigne's observations confirming their results (slow permeation) for interstitial nephritis but finding that in the epithelial or parenchymatous varieties of nephritis the blue passes through the kidneys if anything more quickly than normal, showing an excess rather than a diminished permeability. Richard C. Cabot,[1] of Boston, repeated these observations on sixty cases giving the blue in all cases, except four, by the mouth because of the painful effect of the injections as compared with the absence of "untoward results" claimed by foreign observers. In 35 *normal* cases the blue color appeared in from one hour to two hours, average one and one-third hours; the height of the reaction occurred in from three to seven hours and disappeared in from 30 to 90 hours, average 64 hours, the rate of elimination depending largely on the amount of fluid ingestion.

In seven cases of *active hyperemia* the blue appeared in from half an hour to one hour, average $\frac{4}{7}$ hour; the height of the reaction in two to four hours, average 2.7 hours; and the end of elimination in from 47 to 74, average 57 hours.

Of two cases of *acute nephritis* both failed to show any coloration in half an hour but it appeared in both at the end of one hour. In one case the urine reached its maximum color in four hours, in the other in five. The first case ceased to eliminate in 90 hours, the other in 102 hours.

In two cases of *chronic diffuse nephritis* without much contraction of the interstitial tissue, the blue appeared in an hour, was at its height in two and three hours respectively, and lasted in one case 72 and in the other 144.

In five cases of *interstitial nephritis* of which two had general arterio-sclerosis the blue color began to show in from $2\frac{1}{2}$ to 21 hours —average 7 hours. Three showed no increase in depth of color, but

[1] Bard and Bonnet, Archives Generales d. Med., February and March, 1898.
[2] St. Paul Medical Journal, 1899.

a gradual decrease to the end. In the remaining two the maximum was reached at the fourth and twenty-eighth. One case finished eliminating at the one hundred and forty-fourth hour. In the others the cessation could not be determined. One case never showed any color beyond a slight greenish tinge in a specimen passed at the twenty-first hour.

Cabot's results accord entirely with Bard's and his summing is as follows:

1. Cases of interstitial nephritis excrete methylen-blue much more slowly than normal cases.

2. Other forms of nephritis excrete normally, or, if anything, faster, than normal.

3. The test is harmless and easily performed, and promises to be a real addition to our means of diagnosis and prognosis in cases of nephritis.

4. The time of the first appearance of the color would appear to be the most important and reliable of the data furnished by the test.

Prognosis.

The prognosis of chronic parenchymatous nephritis is unfavorable so far as recovery is concerned. Many cases linger along for many years, and a few recover at least symptomatically.

In many cases the end may be long averted by treatment, and if the disease is prolonged to the stage of contraction the patient may be tolerably comfortable for some time, seems indeed to have another lease upon life. But sooner or later the dropsy returns, and the patient dies of exhaustion. Or some one of the complications, or possibly uremia, intervenes to carry him off. Of the former, edema of the lungs or of the glottis, and pneumonia, are particularly dangerous. In the stage of enlargement, uremia, while it is of rarer occurrence, is also less apt to end fatally than in the stage of contraction.

It occasionally happens, more frequently than I once supposed, that a patient has a large albuminuria with oil-casts, dark granular casts and fatty renal cells, and maintains with these a fair degree of health, indeed excellent health, for years.

Treatment.

While it occasionally happens that spontaneous recoveries from acute nephritis occur, this is far from the case with the chronic form. Here the expectant plan of treatment does not suffice. The patient with chronic parenchymatous nephritis, if left alone, as a rule, grows steadily worse, and although measures of treatment may not frequently result in recovery, they very often, if judicious, cause marked improvement, and long avert the fatal end.

There is always an intermediate stage between that of acute nephritis and the condition of the large white kidney, from which recovery often takes place, which calls for a modification of the treatment described for the acute form. This is indicated by an impaired quality of the blood, due partly to the gradual accumulation of toxic substances, and partly to the drain upon the system by the large albuminuria. But, as it is a condition growing out of the prolonged presence of the disease, it is practically covered by the treatment of the chronic form, and does not require, therefore, to be separated from it.

The chief indications in the treatment of chronic parenchymatous nephritis are two: *first* to improve the quality of the blood, and through it the nutrition of the kidney; *second,* to combat the symptoms and complications which form a source of great inconvenience and danger to the patient.

The first of these indications is chiefly fulfilled by the use of iron and strychnin, nourishing food and proper hygienic influences; and also by depurating the blood of its retained urea. Much judgment is required in the use of iron. Too often it is given regardless of indication of anemia and as though it was a specific, and sometimes with harmful result. The well-known Basham's mixture, really a solution of acetate of iron, and made by adding to tincture of the chlorid of iron, acetic acid and solution of the acetate of ammonia, has the advantage of at least tending to eliminate, while it also strengthens.[1] On the other hand it is often recklessly given. But

[1] The formula for Basham's mixture, which I commonly write, is as follows: ℞. Tinct. ferr. chlorid., f℥ij; Ac. acet. destillat., f℥ij; Liq. ammon. acetatis, f℥iij; Curaçoæ or syrupi simpl., Aquæ, āā q. s. ad f℥vi; M. et S. Tablespoonful three times a day, in half a tumbler of water.

the tincture of the chlorid of iron, alone, is a useful preparation, which is always accessible, and when combined with the sweet spirit of niter, is perhaps as efficient as the Basham's mixture. To either, the quinin and strychnin salts may be added, if desired; while to the latter the infusion or tincture of quassia makes a compatible addition.

With regard to *food,* while it is true that an abundance, and of good quality is desired, a question as to the propriety of using the highly nitrogenized substances, as animal flesh, is always present. Since urea formed in the liver and eliminated in the kidneys is derived chiefly from the azotized elements of the food, it is evident that the more nitrogenous food we take in the more urea are the disabled kidneys called upon to remove. Practice sustains these conclusions, and it has been observed that where the appetite is good and large quantities of meat are eaten, uremia is more frequent, whereas, when the appetite has been bad, and little food taken, uremia in chronic nephritis is rare. On the other hand the nutrition of these cases suffers. It is, therefore, not desirable to omit all such food, though it *is* imperative to limit it, and while drawing elements of mixed food from the vegetable kingdom, to make up the deficiency in meats by the free use of milk. The good results of the milk treatment in chronic nephritis are now generally acknowledged as shown by diminished albuminuria, and dropsy, increase in the quantity of urine passed, and general amelioration of symptoms. Of the different methods of employing milk, the pure milk diet is most satisfactory. From three to three and a half quarts a day meet the requirements of an adult male. The milk should not be skimmed, for it is by retaining the cream that the proteid principle, the casein, is maintained disproportionately small. The better way is to drink a fixed quantity at stated intervals, say, six to eight ounces every two or three hours. There is nothing peculiar in its action. It is simply an assimilable food *freely diluted,* which can be taken in sufficient quantity to nourish the body without surcharging the blood with nitrogen. When the idiosyncrasy of the patient is such that a pure milk diet cannot be borne, it should constitute as large a proportion as possible. Buttermilk is sometimes a palatable substitute for ordinary milk and, perhaps because of the lactic acid it contains, it is less apt to constipate than fresh milk.

Rest is a most important adjuvant in the treatment of chronic nephritis. It not infrequently happens after an albuminuria has been reduced to a minimum by a milk diet in a walking case that if the same patient is put to bed and milk diet continued, a still further reduction of albuminuria immediately ensues. A reversal of the method has been as promptly followed by the opposite condition. The beneficial effect of rest upon edema from any cause is too well recognized to require more than an allusion. The advantages of rest in bed are sometimes more than counterbalanced by the disadvantage of confinement, the absence of fresh air and of outdoor life. These of course must be weighed, and that one adopted which serves the patient best.

Under hygienic measures is included *suitable clothing*. That next the body should be of wool; for it must be remembered that, on the one hand, the skin is a powerful aid to the kidney in its elimination, and, on the other hand, that any interference with the action of the skin must throw more work on the kidney. Cold is the agent which produces such interference, and warmth the means by which the action of the skin is encouraged, while no texture prevents the former or secures the latter more effectually than wool. For the same reason, while the maximum amount of fresh air is desirable, *cold* and *dampness* should be avoided or guarded against.

The second indication is to depurate the blood of accumulated impurities, as well as to combat the symptoms and complications which cause inconvenience or jeopardize life. These symptoms are dropsy, effusions into the serous cavities, and congestions. The patients suffering from them are usually confined to the house. Of the presence of dropsy there is abundant evidence to the naked eye; but of the necessity of depuration there is, unfortunately, no direct evidence except such as is obtained from a volumetric analysis of urine. Fortunately the hypochlorite process is made so easy by means of Squibbs' and like apparatus that such analyses are now comparatively easy, but due regard must be had to the food ingested and the proportion of nitrogen it contains. Fortunately the measures which are best calculated to relieve the one are most likely to relieve the other. These are, in addition to diuretics, other measures which stimulate the action of the skin more than any yet alluded to, and certain purgatives.

With regard to diuretics, nothing need be added to what has been already said under acute nephritis, bearing in mind that digitalis is the most efficient of these. But as to measures which promote the action of the skin, I desire to add something more. They are the *warm bath, hot-pack,* the *hot-air bath* and *vapor bath,* already alluded to. The latter, in consequence of its more ready application, is to be preferred whenever it can be borne. The following observations made in my wards at the Philadelphia Hospital, point to the value of the hot-air bath. A patient with large white kidney was under my observation for more than a year. During a part of this time his urine was carefully measured, and the urea estimated by Liebig's volumetric process, which was repeated to insure accuracy. He was a very large man, passing copiously of urine, and the quantity of urea estimated for 24 hours, was 35 grams (540 grains), the total quantity of urine being 2,000 cubic centimeters (66⅔ f℥). He was then ordered a hot-air bath daily, during which he perspired most freely. The twenty-four hours' urine was of course diminished; but on estimating the urea in the same period after the sweating had been continued three days, it was found to be 46.3 grams (714 grains) in 1,700 cubic centimeters (56⅔ f℥) urine,—an increase over the amount secreted when not using the baths. If we add the quantity of urea contained in the perspiration, probably considerable, we will understand how efficient an agent for elimination is thus available. There is a common impression that it is troublesome and difficult of application. But this is not the case with the simple appliance described on p. 133. A still simpler method is to place the patient upon a chair with a perforated seat, placing a spirit-lamp properly guarded under the latter, and covering the patient and chair by an india-rubber waterproof.

Occasionally, the hot-air bath is not well borne by patients; they do not perspire, the head and face become flushed, and the former throbs and aches. These symptoms may often be relieved by tying a wet handkerchief about the head, as is done in the Turkish bath. In the event of failure, however, the "warm" or "cold-pack" may be used, or the warm bath. In the former the patient is wrapped up in a wet sheet, either warm or cold, and further enveloped in a sufficient number of blankets. A very comfortable sweat generally

ensues. In the use of the warm bath the patient is immersed in it at a temperature of about 40° C. (104° F.), for from 15 minutes to half an hour. He is then removed and wrapped in blankets.

These measures may be resorted to on alternate days, or for a short time daily. It may be objected that they are exhausting to the strength of the patient; but I think they will be found less so than is commonly supposed. Due regard should, of course, be paid to this tendency, and the strength of the patient may at the same time be maintained by alcohol, milk, and tonics.

It has been said under the treatment of acute parenchymatous nephritis that these effects may be more conveniently and as efficiently brought about by the use of *jaborandi* and its derivative *pilocarpin*. The directions for their use, given in connection with acute nephritis, need not be repeated here. They may be used about as often as the baths, usually on alternate days, occasionally daily, with advantage. The drugs should, however, be used more cautiously in chronic cases than in acute.

The use of *purgatives* for depurative purposes and to reduce the dropsy has long been common in the treatment of chronic nephritis, and to this end it has been the practice to select a special class of purgatives, viz., those which produce profuse watery evacuations, as elaterium, scammony, gamboge, and jalap. The advantage to be derived from the use of a brisk, prompt cathartic has already been alluded to. But it must be remembered that in chronic Bright's disease it is not a temporary cause the effects of which we desire to obviate, but a constantly acting one, so that to be of service the purgative must be continued day after day, or every other day at least. Such use of the hydragogue cathartics above mentioned cannot be continued for any length of time without materially reducing the strength of the patient, much more than by the daily sweat. Their effect in diminishing the dropsy is undoubted, but pari-passu with this there may be such reduction of strength as more than counterbalances the advantage derived. I am, not, therefore, very partial to the continued use of cathartics in chronic Bright's disease. To relieve a sudden emergency, as the occurrence of uremic symptoms,—in a word, under the same circumstances under which I would use them in *acute* Bright's disease,—would I give them in the chronic form. So, too, it may be

sometimes of advantage to alternate their use with the sweat treatment referred to.

Of the remedies mentioned, a most efficient is *elaterium*. The profuse painless discharges which it effects in doses of one-sixth to one-quarter of a grain given every three hours are well known, while the small dose required makes it especially easy of administration. Another is compound jalap powder in morning doses of half a drachm to a drachm.

Massage is a measure of undoubted value in the edema of chronic nephritis and should be employed whenever possible.

But in most cases of chronic nephritis, a stage is finally reached at which all treatment of the kind described fails to relieve the dropsy, which becomes eventually the sorest burden of the malady. The body becomes greatly increased in weight, the integument of the extremities is stretched almost to bursting, and sometimes it does rupture, resulting in a leakage, which, although in one way inconvenient, is in many senses a great relief to the patient, by diminishing the tension referred to. Acting upon this, physicians have long been in the habit of puncturing the swollen parts to draw off the water. In my early experience I once had such unpleasant result in the sloughing away of the entire scrotum of a little child with scarlatinal nephritis after puncturing it, that for a long time I never repeated it. But as other cases came under my observation my prejudices gradually disappeared, and I now resort to puncture when it seems likely to give relief. It is a common practice to make a number of minute punctures with a needle or sharp-pointed bistoury. The late Sir George Johnson, recommended making a free incision half an inch long, just above the outer or inner ankle of each leg, and deep enough to enter the areolar tissue beneath the skin. This may be done with a bistoury; but Dr. Johnson used an instrument mounted like a spring-lancet, which he recommends as more efficient and less painful than the repeated fine punctures. He relates an instance which is so remarkable and so admirably illustrates the possibility of recovery at an advanced stage, that it is worth narrating. In July, 1861, he saw a clerk, aged 22, who had suffered from general dropsy since the end of March, after exposure to cold. The urine became nearly solid on addition of acid and heat, while it con-

tained numerous oil-casts. Purgatives and diuretics failed to lessen the dropsy, and at the beginning of September the swelling was so great that the skin cracked and water oozed through the fissures. The legs were now incised; a copious discharge of water occurred, and the urine became more copious. From that time he steadily improved; the dropsy passed away, and gradully the urine ceased to be albuminous; but it was not until the end of April, 1862, more than a year from his illness, that all traces of albumin had disappeared. The chief medicinal treatment after the incision of the legs was the use of tincture of perchlorid of iron three times a day, and a dose of broom tea in the morning. Such recoveries as this are rare, but their possibility shows the value of hopeful perseverance in treatment. I have never seen the instrument referred to, but have made the large incisions with satisfactory results, almost if not quite as satisfactory as Dr. Johnson's. Dr. Dickinson,[1] on the other hand, relates a case in which, for the relief of dropsy, one leg was punctured by a needle, and on the other a lancet was used. He does not say how deep were the incisions by the lancet, or whether they were mere punctures; but the openings made by the needle healed without any bad results, while those made by the lancet gave rise to deep suppurations, pus being discharged through five of the punctures.

The treatment of the complications is in no way different from that of the same conditions in acute nephritis. The point to be impressed is the importance of being constantly on the lookout for them. *Edema of the glottis* requires separate allusion as a complication most alarming and threatening to life. Inhalations of steam may be tried, but prompt punctures or incisions are the only certain means of relieving the patient and saving his life.

Special Methods of Treatment.—The above described principles of treatment are those which, modified by the special requirements of each case, are usually found most satisfactory. As to special curative measures directed to producing structural change of the kidney and a return to its normal histology, or directly diminishing albuminuria, I believe there are none, and most of the measures which have been from time to time suggested are completely useless. The reader may, however, care to know them:—

There is a good deal to be said in favor of iodid of potassium, and

[1] Op. citat., p. 67.

lately I have returned to its use, in some cases, in small doses as recommended by the French and some German physicians, not more than five grains three times a day; but kept up for some time. Dr. Leonard Weber[1] says of Professor Vierordt that after careful investigation of the action of this drug, an investigation begun with an idea that it would prove useless, he concluded that there could not be the slightest doubt of its efficiency in the small doses referred to. Such evidences dare not be ignored. Non-syphilitic cases are of course referred to. In syphilitic cases of nephritis, which I do not find frequent, the large doses usually advised in this disease, viz., thirty grains to a dram three times a day should be given.

Calomel has been used for long periods to the production of its specific effects. For what object, except to hasten the blood dyscrasia which is the ultimate cause of death in this form of nephritis, I do not know. It requires to be mentioned only to be deprecated. On the other hand calomel as a diuretic is sometimes of advantage. The best method is to give three grains every three hours until 15 grains are taken.

Tannic acid and *gallic* acid I have tried systematically without any result in diminishing the albuminuria.

Ergot in some one of its forms has been recommended. It is useless, but some may care to use it sometimes. The most convenient form of administration is a pill of ergotin containing three grains, of which two or three may be given at a dose. The fluid extract of ergot may be given instead, in the dose of half a drachm to a drachm three times a day, but is not so well borne by the stomach.[2] The fluid extract of *eucalyptus globulus* was strongly recommended by Drs. J. B. Leary and William Anderson,[3] of Brooklyn, New York, in doses of ten drops three times a day. Dr. Anderson used it in connection with the milk diet, to which some of the effect must be attributed. I have sometimes thought that the use of sandal wood oil was followed by a

[1] Treatment of Chronic Nephritis, Transac. New York Acad. of Medicine. Med. News, Vol. LXXXII., 1903, p. 141.

[2] The preparations of ergotin made by different manufacturers are probably not of the same strength. That of McKesson and Robbins, of New York, purports to be such that 1 grain equals 10 grains ergot, a 3-grain pill being equal to half a teaspoonful of the fluid extract.

[3] Proceedings of the Medical Society of the County of Kings, N. Y., Vol. IV., No. 6, August, 1879.

fall in albumin. As it is efficient in catharrhal conditions of the bladder it is not unreasonable to expect it to be useful in catarrhal nephritis.

Among remedies suggested for albuminuria are *fuchsin* and *rosanilin*. Feltz and Bouchet[1] were apparently the first to use them in pills and mixture in doses of three grains a day. They say that under their use, albumin soon disappeared from the urine, and that both these coloring agents are relatively harmless and well borne by the organism. Professor E. di Renzi,[2] of Genoa, has published the results of treatment by fuchsin. He reports a decided fall in the quantity of albumin under its use, as well as of mucus, which he says is often present in the urine of Bright's disease. He ordered it in solution or in pills, preferably in the latter shape, 2½ centigrams (3.8 grs.) to a pill, beginning with 5 centigrams (7.7 grs.) and increasing it to 25 (38.5 grs.) in the twenty-four hours. The remedy produced a marked coloration of the urine. If it does not pass over into the urine it is useless in diminishing the albuminuria. Methylen-blue is similarly used, but I have little confidence in it.

Professor di Renzi also made use of *apomorphin* in doses of 5 to 6 centigrams (7.7 to 9.2 grs.) a day without any effect whatever upon the albuminuria. He found *rest in bed* a very useful measure, *and when united with the milk diet* found it more effectual than any other measure in reducing the albuminuria.

I have already expressed my preference for these latter measures with a view to diminishing the albuminuria. Should they fail, others of course may be tried. For the reduction of the dropsy the systematic diaphoretic treatment, preferably by the hot air and warm bath, are most useful, having due regard to the strength of the patient, which must be kept up by iron, tonics, and, if necessary, by alcohol in the shape of the malt liquors, wine, or even the stronger alcoholic preparations.

[1] Deutsch. med. Wochenschr., 1879.

[2] Virchow's Archiv, Vol. 80, p. 510, June, 1880.

SECTION VIII.

ACUTE INTERSTITIAL NEPHRITIS.

Definition.—AN ACUTE INFLAMMATION OF THE KIDNEY CHARACTERIZED BY A NON-PURULENT CELLULAR EXUDATE ASSOCIATED WITH DEGENERATION OF THE EPITHELIUM BUT NOT DEPENDENT UPON IT.

The undoubted existence of this form of nephritis as a pathological entity and the increased attention it has received of late demand for it a separate consideration although it is not associated with a clinical picture by which it can be recognized before necropsy. The first case was described by Biermer[1] as far back as 1860, and since then the literature has accumulated to such an extent that it would not be profitable to pursue it further here.[2]

Morbid Anatomy.

As to the morbid state itself the interstitial cellular infiltration may be general throughout the kidney or focal, though even when the former prevails the disposition to focal arrangement is marked. The kidney is variously enlarged, more when the infiltration is general, when it may reach twice or more the normal size.

It is soft, edematous and pulpy and on section opaque and grayish in color, being compared by Councilman to the leukemic kidney, with which it may be confounded. The foci are found in three places, in the boundary zone of the pyramids, in the subcapsular region of the cortex and around the glomerule. The cells are found in the vessels as well as in the interstitial tissue, and they may be so crowded in these and in the surrounding tissue that it is impossible to distinguish the vessels. The vessels in which they are found are generally the small veins in the upper part of the pyramid.

The cells mainly round and lymphocytoid are by some regarded

[1] Biermer, Virchow's Archiv, 1860, XIX., p. 537.

[2] For a full and complete history of the development of knowledge of the subject see a paper by W. T. Councilman on Acute Interstitial Nephritis, Transactions of the Association of American Physicians, Vol. XIII., 1898.

as emigrant cells and by others as proliferated connective tissue cells. Orth for example says they are not similar to emigrated cells, but appear as "due to growth of the connective tissue cells, although their frequent relation to the small veins would rather speak in favor of emigration," while Councilman, whose studies are among the most recent, says there is but one source for these cells and that is the blood. He describes them as varying somewhat in size and shape but generally larger than polymorphonuclear leucocytes and from two to four times the diameter of a red blood corpuscle. Single cells not in contact are round, but when closely packed their shape is influenced by pressure. In most cases there is a single nucleus. The most characteristic feature of these cells is the staining of the protoplasm. "With most of the nuclear stains used singly, the protoplasm stains faintly with the nuclear stain, but more intensely than the protoplasm of the epithelial cells. When stained with strongly alkaline methylen-blue the protoplasm stains deeply, and the blue color is preserved after counter-staining with eosin. A faint bluish tint, giving with eosin a lilac tint, is often seen in the protoplasm of the epithelial cells, but in the interstitial cells the color is a deep blue. The cells can be instantly distinguished in a section, even with a low power, by their characteristic color. (Councilman.)

In the marked cases in which the kidneys are soft there are other cells resembling lymphoid cells in the interstitial tissue.

The large cells described Councilman regards as plasma cells originally described by Waldeyer and identical with the cells originally separated from the cell collections in the interstitial tissue by Unna, who, however, regarded them as hypertrophied connective tissue cells since as they appear the connective tissue cells disappear. Unna studied them more particularly in pathological processes in the skin. Councilman, as already stated, holds they are derived from lymphocytes because of the similarity of their nuclei to those of lymphoid cells and from the presence of transitional forms between the lymphoid and plasma cells. He also finds large epithelioid phagocytic cells. In the paper referred to, W. T. Howard confirms Councilman's observations as to the occurrence of plasma cells, lymphocytes and polymorphonuclear leucocytes, but finds also large

numbers of typical eosinophile leucocytes in the interstitial exudation and in the blood vessels. In some places these were the most numerous cells in the exudation. These he says are mostly brought to the part by the blood vessels and reach the interstitial tissue by emigration, but there is evidence that they may be formed *in loco* from the plasma cells.

No sufficient explanation has been found for the focal character of the lesions. While they have been found in connection with disease of the kidney of bacterial origin they have been more frequently found independent of it, neither cultures nor microscopical examination discovering bacteria. Councilman thinks there is some ground to believe that the physical condition in the circulation may account for their accumulation in the vessels in certain places; or there may be some substance in the tissues which exerts a positive chemotaxis for these cells which causes them to accumulate in the vessels and migrate therefrom into the tissues.

As stated in the definition the epithelium of the tubules exhibits degenerative changes. These begin with cloudy swelling and end with globular masses of hyaline material which is also found in the lumen of the tubules. Again the cells may be swollen, vacuolated and disintegrated about a pale and shrunken nucleus. In places the tubules are not at all visible. The glomerules usually show no changes although there may be glomerulo-nephritis as a complication. It is generally conceded that there does not seem to be any dependence of the epithelial degeneration upon the interstitial cellular infiltration.

Symptoms.

No distinctive symptoms have been observed in this form of nephritis. It is found especially in the nephritides of diphtheria and scarlet fever, but also in those accompanying other infectious diseases of children. Friedlander alone found so small a proportion as 12 cases in 229 autopsies in cases of nephritis complicating scarlet fever, but Councilman suggests that systematic microscopic examination might have found a large proportion. Three cases are reported by Councilman in which the interstitial process was due to the local action of bacteria only, in addition to 42 associated with general disease.

The nephritis is characterized by appearing early in the course of the disease which it complicates and is most common in the so-called septic cases. It has a rapid course and the urine may be found normal 24 hours before death. Klein considers that cases which die after the ninth or tenth day of the disease will as a rule show more or less marked interstitial change in the kidneys. There is generally no edema, though in one of Sörensen's there was slight edema and ascites. Albumin may be absent and there may be no symptoms relating to the kidneys. Pus and pus casts are more likely to be found in the urine.

The *prognosis* is unfavorable and the *treatment* is in no way peculiar.

SECTION VIII.

CHRONIC INTERSTITIAL NEPHRITIS.

Synonyms.—Chronic indurative nephritis. Contracted kidney, chronically contracted kidney, renal cirrhosis, cirrhotic kidney, granular degeneration, granular kidney, red granular kidney, gouty kidney, renal sclerosis.

CHRONIC INTERSTITIAL NEPHRITIS IS A SLOW DESTRUCTIVE PROCESS CONSISTING IN A GRADUAL DISAPPEARANCE OF THE SECRETING STRUCTURE OF THE KIDNEY AND ITS SUBSTITUTION BY INTERSTITIAL TISSUE, WHICH SUBSEQUENTLY CONTRACTS, REDUCING THE SIZE OF THE ORGAN AND PRODUCING OTHER CONDITIONS MORE OR LESS COVERED BY THE SYNONYMS, OR MORE CLOSELY DESCRIBED IN THE SECTION ON THE MORBID ANATOMY OF THE DISEASE.

Etiology.

Of all the recognized forms of Bright's disease, interstitial nephritis presents the largest number of instances in which the cause is undiscoverable. There are, however, some well-determined causes.

Among the most tangible of these is *gout*. Gout is associated with so many cases of contracted kidney, that the term *gouty* kidney has come to be a well-recognized synonym for the product of interstitial nephritis. There are probably no cases of gout, which have continued for any length of time, which are not accompanied by this condition of the kidney. It would seem to be the accumulation in the blood of the poison of gout,—the excess of uric acid and its congeners,—which causes the interstitial inflammation.

I am satisfied that simple overeating, specially of proteid foods, with or without wine or other spirituous drinks is the cause of many cases of interstitial nephritis. It is almost incredible to the moderate eater what enormous quantities of meat are eaten by some persons. Several slices of rare roast beef are frequently consumed at a meal where a single slice would be sufficient. A patient with

interstitial nephritis informed me that six eggs at a time, with other articles of food, was not an unusual meal for him. It is evident that with such over-ingestion of albuminous food the kidneys must be greatly overworked and irritated, and it is not surprising that they become the subject of this slow degenerative process known as interstitial nephritis.

Another well-recognized cause is *lead poisoning*. The lead in the blood plays the same rôle as the essential poison of gout, whatever this is. Hence painters, glaziers, workers in lead in any shape, are frequent victims. Dr. Dickinson considers it safe to assert that, of painters, at least one half eventually die of granular degeneration of the kidneys. I am sure this is not the case with painters in the United States.

Hereditary influence is a cause of the contracted kidney. A remarkable instance of this hereditary tendency has come to my notice. I was consulted in 1880 by a gentleman who had granular kidneys, and was at the time thirty years old. The disease was discovered in 1880 and he died in 1898. His father and mother both died of Bright's disease, aged fifty-six and sixty-three years respectively. The mother had convulsions. A maternal uncle died of Bright's disease when about sixty-four. A cousin, a daughter of the above, died when about twenty-seven of supposed Bright's disease, having had convulsions. A brother died in 1877 of Bright's disease, without convulsions, at the age of thirty-seven. Two children of this brother had Bright's disease when four and seven years of age. A second brother died in 1871, at the age of twenty-nine, with convulsions. A third brother died in 1892 of Bright's disease at thirty-eight. A fourth brother in 1880 was known to have had Bright's disease for about six years and has died since. A sister died of uremia in 1890 at forty-four, having had Bright's disease for thirteen years. A brother died in 1897, aged forty-two, but not of Bright's disease, and a sister, aged fifty-seven, has as yet no signs of Bright's disease. Other members of the family, belonging to previous generations, died with symptoms which suggest Bright's disease. There is no gout in the family. Dr. Dickinson also relates the history of a family in which a hereditary albuminuria existed, apparently independent of gout.

Alcohol, always thought to be a potent cause of the cirrhotic kidney, is probably less so than once supposed. The analogy of this condition to the cirrhotic liver suggests a similar irritant action of the alcohol on the kidney. But although the portal blood contains a large amount of alcohol after its liberal ingestion into the stomach, by the time the blood passes through the heart and lungs and gets into the kidney, much has been consumed. There can be no doubt, however, that when enormous quantities are ingested, enough remains in the blood passing through the kidney to irritate the renal secreting cells. More acute irritation may result in acute parenchymatous nephritis as referred to in discussing the latter disease.

The relation of the chronically contracted kidney to the kidney of passive congestion—more especially that due to chronic valvular heart disease, the cyanotic kidney—is an interesting one. In chronic valvular heart disease the kidney is in a state of passive hyperemia. At first this is unassociated with any other change. After a certain lapse of time, however, there results a hyperplasia of connective tissue, at first around the Malpighian bodies. This may extend between the tubules and after a while undergoes contraction which may go so far as to produce a slight unevenness of surface which suggests the appearance of a contracted kidney. The result is, however, brought about in a different way. In the chronically contracted kidney the cells and tubules are destroyed by the toxic action of its cause, their place being taken by substituting connective tissue, while in the cyanotic kidney the overgrowth of connective tissue is primary and the destruction of the renal parenchyma secondary.

The granulations are never so large or distinct as in the typical granular kidney, nor is the organ ever so much reduced in size, perhaps never below the normal size. Dickinson and Lecorche regard the conditions as identical. The former,[1] in 153 post-mortem examinations of persons dying with valvular disease of the heart, found the kidneys in 67 having granular surfaces, and more or less contracted cortices. In 29 the kidneys were hard, congested, and increased in bulk, but still smooth. Dr. Barclay,[2] in an analysis of 79 cases of valvular disease, found 28 having granular kidneys. Bartels, on the other hand, prefers to consider cyanotic condition a

[1] Dickinson, op. citat., p. 155.

[2] Med.-Chirurg. Transac., Vol. XXXI., p. 96.

separate process, especially characterized by its chronicity. He compares it with brown induration of the lung as it occurs in connection with valvular heart disease, or the thickening of the peritoneum which follows upon portal congestion.

Pregnancy is rarely, if ever, a cause of interstitial nephritis. I have already named it among the fertile causes of acute and chronic parenchymatous nephritis, being here in accord with Bartels and against Dickinson. Indeed I am unable to understand how the latter writer draws the conclusions which he does from the cases he reports. For the morbid appearances he describes seem to me more those of acute and chronic parenchymatous nephritis than of interstitial nephritis, some of those which most resembled the granular kidney being in the stage of contraction.[1] The direct cause is undoubtedly the accumulation of toxic matters generated during the pregnant state and imperfectly eliminated.

Long-continued *cystitis,* especially following gonorrhea, is undoubtedly a cause in a few instances, the inflammation travelling up the ureter to the pelvis of the kidney and thence to the intertubular tissue.

Among the causes, the operation of which cannot be so directly proven, is *mental anxiety*, whether the result of grief or of business and financial cares. Dr. Clifford Allbutt quoted by Dr. Robert T. Edes,[2] goes so far as to attribute "twenty-four out of thirty-two cases, in private practice, to some long-continued anxiety or great grief." Certain it is that this disease very often exists for a long time undiscovered in business men who have lived under a state of constant mental tension. Such men are apt, however, to be free eaters and drinkers.

Age and Sex of those Affected.—Interstitial nephritis is commonly considered a disease of middle age. And so it is in the sense that the majority of persons in whom it is discovered are past forty.

[1] The reader who is sufficiently interested in the subject is referred to a paper by the writer on "The Causal Lesions of Puerperal Convulsions," read before the Pathological Society of Philadelphia, April 28, 1878, and published in the Transactions for 1878–1879. The entire subject of Puerperal Convulsions in its relation to albuminuria and Bright's disease is here discussed.

[2] Edes, Robert T., Some of the Symptoms of Bright's Disease, Boston Med. and Surg. Jour., Vol. CIII., No. 2, July 8, 1880.

And I confess to some surprise when, on investigating the matter, I found that there were so many cases, although still a small number under thirty. The youngest patient whom I have had was twenty-six. But it will be seen from the appended tables by two of the largest observers, Dickinson and Bartels,[1] that the number of cases occurring under forty years of age is not inconsiderable. The figures indicate the age at which death occurred, and there was an autopsy in each case.

Bartels.	Dickinson.
1 was 18 years.	1 was between 11 and 20 years.
1 was 19 years.	24 were between 21 and 30 years.
2 were 20 years.	50 were between 31 and 40 years.
4 were between 20 and 30 years.	93 were between 41 and 50 years.
9 were between 30 and 40 years.	76 were between 51 and 60 years.
4 were between 40 and 50 years.	47 were between 61 and 70 years.
7 were between 50 and 60 years.	17 were over 70 years.
5 were between 60 and 73 years.	
33	308

It must be remembered that there is a tendency to overgrowth in the interstitial tissue of the kidney as of other organs in old age. Hence the term *senile atrophy* of the kidney. It is not safe, therefore, to call every instance of atrophied kidney met in the post-mortem room a case of interstitial nephritis. The clinical history, or some one of the well-marked symptoms of the disease, as albuminuria or uremic symptoms, should have preceded to sustain the diagnosis. This was the defect in the method followed by Gull and Sutton,[2] who, in the post-mortem examination of a large number of cases, independent of previous disease, noted that out of thirteen cases examined between the age of sixty and seventy, twelve had contracted kidney. At the same time, this atrophy of old age may proceed to such degree as to attain positive pathological degrees, manifested not only by the morbid anatomy of the kidney, but by the symptoms of interstitial nephritis.

As to *sex*, nearly twice as many males are subjects of the disease, because of the more frequent exposure of the former to the causes.

[1] Bartels, op. citat., p. 411. Dickinson, op. citat., p. 145.

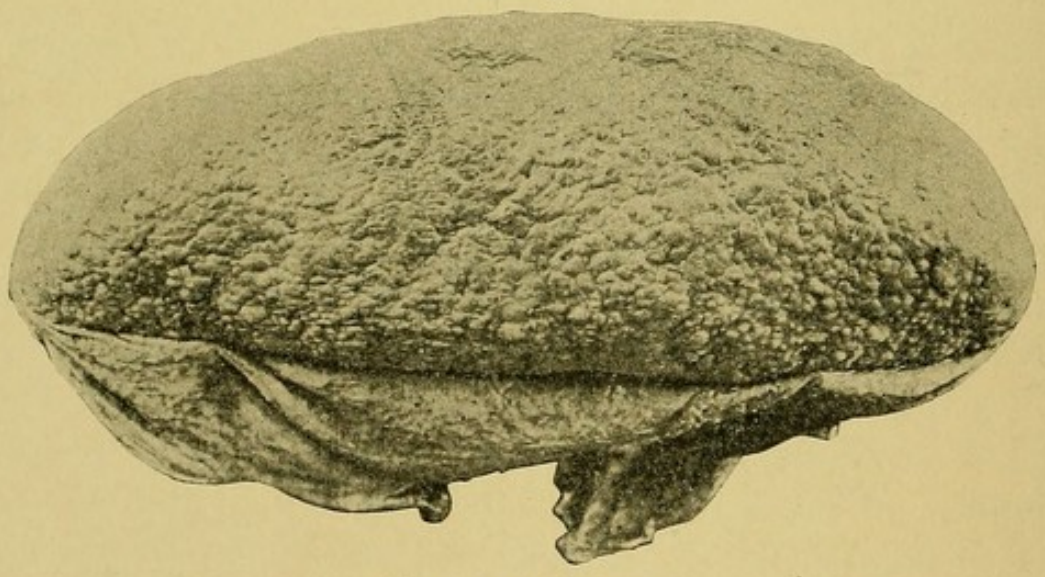
[2] On the Pathology of the Morbid State Commonly called Bright's Disease with Contracted Kidney (Arterio-capillary Fibrosis), Med.-Chirurg. Transac., 2d series, Vol. XXXVII., 1872.

Morbid Anatomy.

In interstitial nephritis, both kidneys are involved, but there is often a marked difference in the amount of disease in each.

Macroscopically the organs are evidently smaller than in health, often less than half as large. I have occasionally seen them less than five centimeters (two inches) in length. Next to this reduction in size, the most striking feature of the contracted kidney is its uneven or granular surface, which is, however, not always recognizable until after the capsule is removed. Very characteristic also is the presence of *cysts* with more or less clear watery or gelatinous contents, often visible through the capsule. These are not invariably, but quite often present. The *capsule,* itself thickened, strips off with difficulty, dragging portions of the secreting structure with it. Owing to the resistance which the blood meets in its passage through the kidney, a larger portion of it passes out of the organ by

FIG. 37.

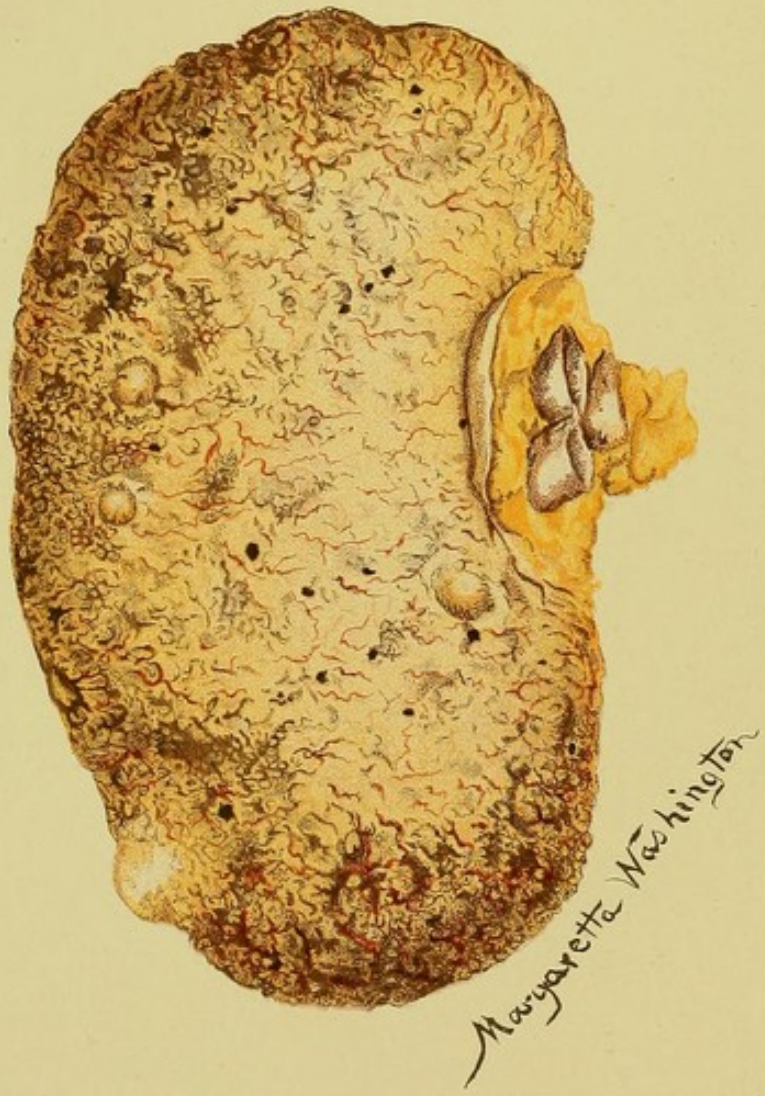


Contracted Kidney.

way of the capsule. Hence the blood-vessels of the latter are dilated, as are also the lymph spaces.

Bereft of its capsule, the kidney is granular, hard, tough, and usually darkened in color; whence one of its names, the "red granular kidney." This color is in strong contrast to the white or slightly yellow tinge of the *fatty and contracting* kidney, and although not always marked, but sometimes even substituted by a paleness, it is still easily distinguished from that of the contracting kidney of parenchymatous nephritis.

PLATE V



CHRONICALLY CONTRACTED KIDNEY

The *granules* on the surface of the contracted kidney are distinct round and oval elevations of the surface, ranging in size from that of a pin's head to a pea, or from one to five millimeters ($\frac{1}{25}$ to $\frac{1}{5}$ of an inch). Those of smaller size are most numerous, and at first correspond with the lobules, the bases of which are visible on the surface of the normal organ. The larger ones result from the coalescence of two or more smaller. The granules themselves are of a lighter color than the depressed circlets between them, which are tinted with vascularity, and have a purplish or faint red hue.

The *cysts* already referred to are now more distinct (after removal of the capsule), and vary also greatly in size. While many are as small as the smallest of the granules, some of them are as large as a walnut. The larger are apt to be ruptured on stripping off the capsule.

On section it is at once evident that the reduction in size of the kidney is almost wholly due to a narrowing of the cortex, although the medulla is also contracted. The former may not be more than three or four millimeters ($\frac{1}{8}$ to $\frac{1}{6}$ inch) in width, and exhibit every degree between this and the normal. The Malpighian bodies are smaller, less numerous, and can scarcely be detected by the naked eye, while the small arteries are more prominent from thickening of their walls. The increased density and firmness of the organ are apparent. If the conditions occur in a gouty subject, linear chalk-marks of urate of soda may be present, more particularly in the pyramids of straight tubules, and are contained within as well as between the tubules. The little cysts in varying numbers are scattered throughout the section from cortex to papillæ, but they are more numerous in the former. Rindfleisch held that the cysts in the medulla, in the neighborhood of the papillæ, are formed in the flexures of the looped tubes, where they originate in the colloid metamorphosis of cylinders of fibrin. The cysts may be altogether wanting.

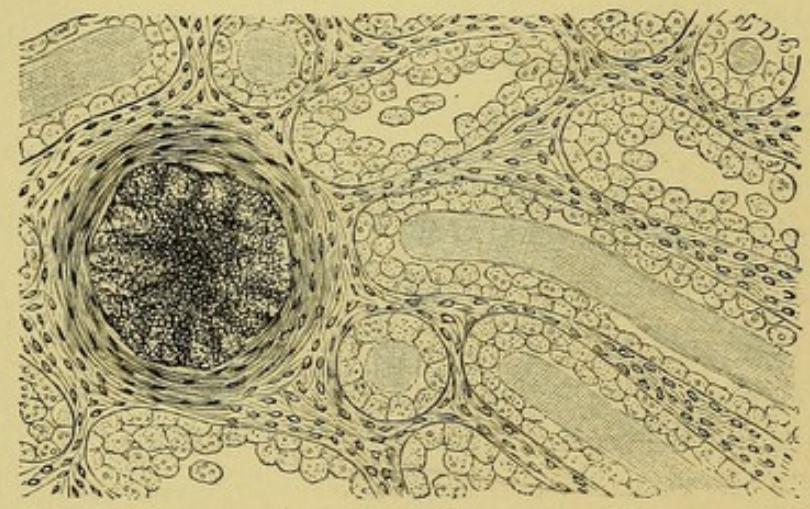
The *pelvis of the kidney* may be unaltered. It is sometimes enlarged from retraction of the pyramids. The calyces may be elongated. On the other hand if the kidney is very much reduced in size, the capsule may be pursed up, and proportionately smaller.

Da Costa and Longstreth called attention to the constant presence

of an increased amount of fat surrounding the contracted kidney, even in emaciated subjects.[1]

Minute Structure.—Minute examination of thin sections through the cortex clearly reveals the change to consist in overgrowth of connective tissue, with destruction of the tubules and blood-vessels. The process is best studied if the sections include the capsular edge, as it progresses from without inwards. In these may be seen extensive tracts of connective tissue of different ages, separating tubules which, in sections of healthy kidneys, are seen to be closely in contact without appreciable intertubular substance. The younger connective

FIG. 38.



Chronic interstitial nephritis—minute structure.

tissue exhibits a simple hyperplasia of cells, with a scanty transparent intercellular substance, while that which is older contains fewer corpuscles and a more or less distinctly fibrillated intercellular substance.

The *tubules* themselves appear, in places, quite normal; in others they are represented by fragmentary portions in which the cells are still unchanged; in others again the cells exhibit a granular degeneration; some are evidently dilated; others still are completely shrivelled, while it is evident from the larger areas of connective tissue that many have completely disappeared. In a few tubules, waxy casts are present. The Malpighian bodies are surrounded by concentric layers of nucleated connective tissue. Many

[1] Researches on the State of the Ganglionic Centers in Bright's Disease, Am. Jour. Med. Sci., N. S., Vol. 80, 1880, p. 25.

of them are shriveled and atrophied and an attempt to inject them with colored injecting fluids fails either partially or completely. Some thus altered lie detached from the tubules with which they should be continuous.

The *cysts* begin as dilatations of obstructed segments of the uriniferous tubules, and of the Malpighian capsules. Proof of the latter mode of origin is found in the fact that compressed capillary tufts are sometimes found lying up against one side of the wall of the cyst. Minute examination of the granules on the surface of the kidneys shows them to be made up of tubules in a tolerably perfect state, the mass having been caused to project by the constriction of the connective tissue encircling its base.

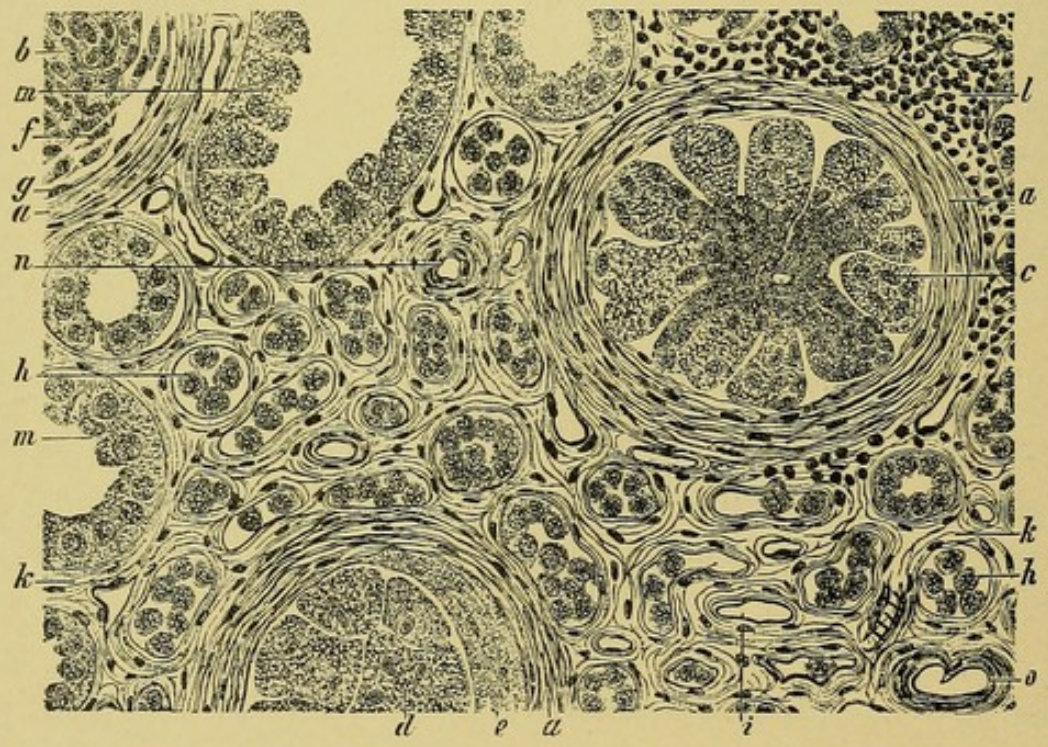
The same overgrowth of connective tissues takes place in the *medulla,* but it appears here later, extends more slowly, and never reaches the degree found in the cortex. For this reason the contraction is not nearly so great, but the medullary area is still somewhat diminished by retraction of the pyramids. The excreting tubes in the medulla are in some places dilated, and in others twisted.

The blood-vessels of the contracted kidney are the seat of important changes. In the first place they share with the tubules the compressing effect of the contracting new formation. As the result of this, a part of the capillary system is destroyed, and in the part thus destroyed are many capillary coils in the Malpighian bodies. Hence, as many afferent arterioles send their blood directly into the second capillary network, which is also cut down by the pressure. The vessels which remain are often dilated and twisted, and in consequence of the destruction of numerous Malpighian bodies, send much of their blood out through the capsule.

A further very striking vascular alteration is a hypertrophy, with subsequent degeneration of the muscular coat of the arteries and arterioles, and thickening of the external fibrous coat. This alteration has given rise to a good deal of discussion. Dr. Bright noted changes in the renal artery in kidney disease, but Dr. George Johnson, in 1867, described the change more thoroughly, and showed it was common to the whole body. He considered it a pure muscular hypertrophy,—a reflex reactive overgrowth, whose object is to resist the entrance of the contaminated blood into the tissues. Drs. Gull

and Sutton, in 1872, showed that along with the muscular hypertrophy there was also a thickening of the external fibrous coat. They, however, made the condition of the renal arteries a part of a general one, affecting the entire arterial system, which, while it commonly begins in the kidney, may begin primarily in other organs. Indeed, according to them, the kidneys may be but little if at all affected, whilst the morbid change is far advanced in other organs. They characterized the condition as a "hyaline fibroid" formation

FIG. 39.



Chronic Diffuse Indurative Nephritis with Atrophy of the Renal Tissue. *a*, Thickened and fibrous Bowman's capsule; *b*, normal glomerular vessels; *c*, glomerulus with partly impermeable and homogeneous vascular loops and almost entirely devoid of epithelium; *d*, obliterated glomerulus; *e*, homogeneous coagulation mass with nuclei, exudate, and epithelium; *f*, desquamated glomerular epithelium; *g*, capsular epithelium; *h*, collapsed urinary tubule with atrophic epithelium; *i*, collapsed tubule devoid of epithelium; *k*, hyperplastic connective-tissue stroma; *l*, collection of small round cells; *m*, normal, but somewhat dilated, urinary tubule; *n*, afferent vessel; *o*, vein. × 250. After ZIEGLER.

in the arterioles and capillaries, and suggest for it the name "arterio-capillary fibrosis." They said further, that the morbid state is allied to the conditions of old age, and that we cannot refer the vascular changes to an antecedent change in the blood due to defective renal excretion, but that they are due to distinct causes not yet ascertained.

The element of thickening of the external coat, in addition to the hypertrophy of the muscular, these observers have established; that it is a part of a general condition, which may be primarily quite independent of kidney disease, is now also acknowledged. Their views as to its causation have not, however, been confirmed. The present view, to which the studies of Councilmann and Arthur Meigs have added confirmation, ascribe these changes to an inflammation of the intima which extends more or less into the muscular and external coat and which is further associated with degenerative changes. The cause of this inflammation is the toxic substance which accumulates in the blood. These changes in the blood-vessels may be primary and precede the Bright's disease.

This vascular condition is invariably associated with *hypertrophy of the left ventricle* of the heart. The two increase *pari passu,* and it is therefore impossible to disassociate their consideration. That they may both be the *result* of the renal disease it seems to me requires no further proof.

As to the immediate cause of this hypertrophy and overgrowth, though Johnson's view is still held by a few observers, notably by Nestor Tirard, the inflammatory origin is generally acknowledged at the present day. Johnson's view was, however, so plausible that it is worth preserving as a historical fact in the development of our knowledge of Bright's disease. I have already said that he ascribed the thickening of the middle coat to a reactive overgrowth. This is promoted in two ways. The arterioles contract forcibly to resist the admission of the blood poisoned with the accumulation of excreta usually eliminated by the kidneys. This is the first stimulus. The heart then contracts with additional power to overcome this resistance, and thus it hypertrophies. But the arterial vessels contract still more forcibly to resist this impulse, whence the second stimulus to overgrowth of the muscular coat.

The older view of Bright also ascribed the cardiac hypertrophy and thickening of the muscular coat of the arteries to a toxic agency, but placed the resistance in the capillaries. As to the toxic substances which produce these changes it cannot be said that they are certainly known except that they are excrementitious in nature.

Experiments[1] have shown that not only urea, but also the alloxuric bases, xanthin, hypoxanthin, etc., introduced into the blood are capable of producing irritative effects on the capillaries and arteries, resulting in arterio-sclerosis and hypertrophy of the heart.

The degenerative changes alluded to, as succeeding the thickening of the blood-vessel wall, are of the kind which usually succeed hyperplasias, viz., fatty. In the muscular coat the nuclei of the fiber-cells waste, and finally disappear, leaving the coat recognizable only by its transverse striation, although this appearance may also be obscured by the presence of fat-drops, and even crystalline matter. The subsequent changes in the external sheath consist in the conversion of the thickened fibroid adventitia into a more hyaline material as shown also by Councilman.

The final effect of these alterations is to produce a brittleness in the arteriole walls, which disposes them to rupture on very slight increase of intravascular pressure. Hence, the frequent fatal termination of cases of interstitial nephritis by apoplexy.

Drs. Da Costa and Longstreth, some years ago,[2] described as more or less constant in Bright's disease, and especially in the contracting kidney, certain changes in the ganglia of the renal plexus, which consist essentially in a hyperplasia of the connective tissue and a fatty degeneration of the nerve-cells. They said that while this lesion might be looked upon as forming a part of the general process of degeneration in connection with the kidney disease, they think it is the *cause* of the renal malady and precedes the degenerative changes. Also that the diseased condition of the ganglia furnishes the clue to the alterations of the vessels of the kidneys. And finally, that similar changes producing similar results may exist in other ganglia; for instance, in the cardiac plexus, explaining the hypertrophy of the heart.

Da Costa and Longstreth in the paper alluded to, held that the heart hypertrophies, not because of the resistance the blood meets in the renal circulation, but because of a central nervous stimulus;

[1] See a paper on The Role of the Alloxuric Bases in the Production of the Cardio-Vascular Changes of Nephritis, by Alfred Careño Croftan, A.M., M.D., containing numerous references to other papers on the subject.

[2] Amer. Jour. of the Med. Sciences, N. S., Vol. 79, July, 1880, p. 17.

and that the renal vessels thicken in consequence of a stimulus of the renal ganglia. "The same statement applies to the changes in the vessels and tissues in other organs of the body, and when they in their turn are affected the ganglia which preside over them as centres most probably have been acted upon in a similar manner as the ganglia already mentioned."

Dr. Robert Saundby[1] has examined the semilunar ganglia in fifteen cases of Bright's disease and admits the accuracy of the observations of Da Costa and Longstreth, and the importance of their contribution to the data of Bright's disease, but dissents from their conclusions. He regards the ganglionic changes as the results or at most the concomitants of the renal disease, the vaso-motor centers being affected immediately and it is possible the structural alterations take place in the ganglia as early as in the inflamed part.

For a description of the *retinal changes* which occur most frequently in this form of Bright's disease, see the following Section X., by my colleague, Dr. George E. de Schweinitz.

Symptoms.

The degree of uncertainty as to the origin of a large majority of cases of contracted kidney is only equalled by that of the insidiousness of their approach. The beginning of the disease is certainly not marked by any distinctive symptoms; and its progress is not rarely unmarked by any, until those of uremia, as manifested by the unexpected convulsion, drowsiness, or stupor, mark the beginning of the end. The attention of the physician being thus directed to the urine, albuminuria and casts are discovered and confirm the condition. To the observing physician, a hypertrophy of the left ventricle with accentuation of the second sound without valvular disease, a high tension pulse or throbbing or palpitation, or slow convalescence from acute disease or accident may suggest an examination of the urine; or the more tangible symptom of a slight swelling of the feet or ankles, recognizable only at night or through the unexpected tightness of a boot, may lead to the same examination.

I see no better place than this to call attention to what Sir Andrew

[1] Changes in the Renal Ganglia in Bright's Disease, British Medical Journal, January 13, 1883, p. 50.

Clark first called *renal inadequacy* and which may sometimes be a forerunner of this form of Bright's disease. In it he said: Though "there is no alteration of structure that the eye can detect, it can, nevertheless not produce a perfectly healthy urine. It is a urine low in density and deficient in solid constituent, principally in urea and its congeners." Persons possessed of it, he continues, are characterized by an inability to repair damages done to them either by accident or disease, by a peculiar vulnerability to the causes of disease and an uncertainty of recovery from an ordinary surgical operation. Such attributes are not limited to the condition of renal inadequacy but should always invite a study of the urine.

Attention being called to the *urine* in the actual presence of the disease, it will be found to present characters which are more or less distinctive, and commonly even in the absence of other symptoms, alluded to as so characteristic, lead easily to a diagnosis. It is, when freshly passed, acid in reaction, copious, often exceeding the normal amount, never scanty except in the last stages of the disease. The quantity may reach 2,700 c.c. (90 oz.), but this rarely. More frequently it is 60 to 70 oz. (1,800 to 2,100 c.c.). The patient very commonly has to rise at night, probably not more than once or twice, to pass his water. As a result of its increased quantity, the urine is light in color and of low specific gravity,—1,010–1,015,—and contains a trifling or moderate flocculent sediment. It is *generally albuminous,* but the albumin is small in amount, and may be temporarily absent, or it may be absent before a meal, and present after it. Later, however, it becomes constant. It seldom exceeds one tenth the bulk of fluid tested, and is very constantly a good deal less, showing a delicate line of white by Heller's nitric acid test.

Tube-casts are present, but not usually numerous. They are almost solely hyaline, and pale granular. Some of the hyaline casts are delicately so, requiring nice illumination for their detection; others are distinct and sharply cut; others, still, contain two or three glistening oil-drops. Casts may at times be absent and again reappear, as is the case with albumin. The urine often contains some white, and more rarely a few red discs. Occasionally the amount of blood is sufficient to discolor the urine. See three very interesting cases related by Dr. Samuel West, *Lancet,* July 18, 1885.

The hemorrhage in these cases is probably due to an atheromatous degeneration of the blood-vessels of the kidney. Towards the termination of cases of interstitial nephritis the urine diminishes in quantity, the specific gravity increases, and the casts become much more numerous, and include among them highly granular or dark granular, and occasionally even blood-casts, in addition to those alluded to. In a case which recently terminated under my observation, the specific gravity of the urine rose to 1,030, and the quantity fell to about 25 c.c. (8 oz.). The low specific gravity in the early stages is largely the result of the increased quantity.

The *urea* is also diminished sooner or later, and in this manner the lower specific gravity is contributed to. This diminution becomes marked towards the close, accounting for the uremic symptoms which sometimes first announce the disease. It may be as low as 1 gram (15 grs.), and may be anything between this and the normal 24 hours' quantity, which may be put down at from 20 to 40 grams in an adult.

All the remaining normal constituents may be said in general terms to be diminished.

As to the other symptoms which were alluded to as suggesting an examination of the urine, a feeling of unaccountable *weakness* or *of being tired* was mentioned. This is very often present, but it is a symptom which is present in many conditions, and should only be considered as suggestive.

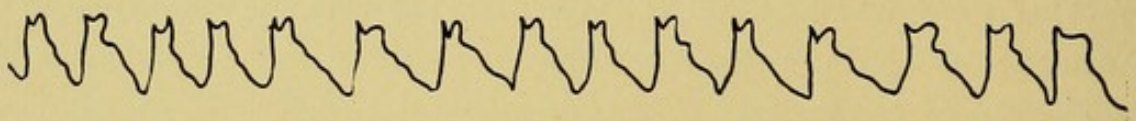
Slight edema about the feet and ankles is often present, being so slight as to escape detection, or is discovered accidentally. When present it is significant, but it is often entirely wanting. We have the explanation of this slight edema or its entire absence, in the free secretion of water, which is such a decided symptom of the early stages of this disease.

Hypertrophy of the left ventricle of the heart is so constant that it may be properly considered as a symptom rather than a sequel, which it strictly is. No case of interstitial nephritis has existed for any length of time without the presence of this condition, and as few cases are discovered until they have existed a good while, few are found without hypertrophy, although it is not always marked. In about one-half the cases, however, the hypertrophy is evident.

Corresponding to this, the pulse has a peculiar tense and bounding character. These two symptoms have, therefore, a diagnostic value. I have already alluded to the cause of this hypertrophy,—the increased effort of the heart to propel the blood through vessels narrowed by inflammatory and degenerative changes. Often there are no symptoms of this enlargement except the increased percussion area, accentuation of the aortic second sound and the peculiarity of the pulse. Occasionally, however, there are symptoms of cardiac distress, dyspnea, and palpitation, together with reduplication of the first sound. The latter is probably due to a want of synchronism in the systole of the two ventricles.[1] There is usually no murmur because there is no valvular disease. The latter may be present, however, in one of two ways. The patient may have had valvular disease prior to the renal malady, or the latter itself, by its long continuance, may have produced endocarditis and atheroma which are among its results, particularly in those who have passed middle life, thus increasing the natural tendency of age to this condition.

Increased arterial tension is another symptom, which is the direct result of the hypertrophy of the left ventricle. This con-

FIG. 40.



Prolonged High Tension Pulse in Chronic Interstitial Nephritis.

tinues as long as the power of the heart lasts. When the latter begins to fail, the blood-pressure diminishes, and with it begin a train of symptoms, among which diminished secretion of urine and dropsy are the most conspicuous. It occasionally happens that, although this hypertrophy is a compensating measure, it is the cause of inconvenience, manifested by the cardiac distress, dyspnea, palpitation, and dizziness, alluded to as sometimes present. A very unpleasant pulsation in the head is a symptom thus caused.

The atheroma and the increased arterial blood-pressure are the causes of another symptom which frequently determines the mode

[1] Sibson, British Medical Journal, April 1, 1871, p. 238.

of death,—rupture of a blood-vessel in the brain; in a word, *apoplexy*. As stated, this accident occurs generally late in life, but Dickinson reports a case in which cerebral hemorrhage occurred in a girl of twelve. The proportion of cases of recognized interstitial nephritis in which this occurs is not large, but many cases of apoplexy are directly traceable by autopsy to unsuspected renal cirrhosis and Dickinson goes so far as to say that of fatal cases of apoplexy one half are preceded by this disease.

Hemorrhages in other situations are referable to this same altered state of the blood-vessels, as into the retina, from the nose, and even into the stomach. Obstinate nose-bleed in elderly persons must always excite suspicion of the presence of chronic interstitial nephritis. In consequence of hemorrhage into the retina *sudden blindness,* as well as dimness of vision due to retinitis albuminurica, is a symptom which often presents itself.

The latter symptom, *dimness of vision due to retinitis albuminurica,* is a grave one. The pathological alteration in the retina which causes it presents itself usually only at an advanced stage of the renal disease, and is but little remediable. The condition itself I deem of such importance as to demand separate consideration by an ophthalmologist. Accordingly, my friend Dr. George E. de Schweinitz has kindly furnished an article on the *Retinitis of Bright's Disease,* which will follow this section.

The termination by *uremia* occurs more frequently in this than any other form of Bright's disease. Bartels says that nearly all the patients he has seen die in the extreme stage of atrophied kidneys, sank under the symptom of chronic uremia. I can say the same of my own experience as to uremia, but acute uremia has been as frequent as chronic. As already stated, it is frequently the first intimation of the existence of any derangement, and manifests itself in any one or more of the forms already described under acute nephritis. Headache, drowsiness, convulsions, stupor, delirium, maniacal excitement, renal asthma, restlessness, nausea, vomiting, any one of these symptoms may usher in the dreadful train which is so apt to be fatal. But coma or a partial coma is here more frequent than convulsions. Drowsiness and severe headache are also frequent be-

ginnings. Dr. E. C. Seguin has called attention to *occipital* headache as a symptom of uremia.[1] It occurs frequently, however, from other causes, not always easily determined. In a case which terminated fatally under my observation, in which delirium, coma, and maniacal symptoms were present, but interrupted by active treatment, the *temperature* was very high, ranging from 102° to 105°, and rose to 107° immediately before death. Usually, however, the temperature in uremia though somewhat elevated is not high.

A most interesting group of symptoms of uremia are hemiplegia with or without unconsciousness and aphasia—in a word all the symptoms of a true apoplexy without the rupture of a blood-vessel. These symptoms are the more interesting because apoplexy with all its typical symptoms often occurs in chronic interstitial nephritis. The proof that these symptoms are due to uremia is found in the fact that they may recur a number of times in succession and disappear completely. Even tumor of the brain has been simulated by the nervous symptoms of chronic interstitial nephritis as well as the retinal changes.

Dyspeptic symptoms with obstinate vomiting, particularly in the morning before eating, are apt to usher in a chronic uremia. Diarrhea is less common, but also sometimes occurs towards the close, when it may be very difficult to control. Diphtheritic enteritis is then sometimes found at necropsy.

The duration of this form of renal disease is indefinite. Always a chronic process, it may last for years undiscovered, and when discovered before it is too far advanced, the knowledge of its presence will suggest measures of precaution and treatment, which may so prolong life that it need only be determined by its natural limit or some other disease. Many patients live five, ten and even twenty years. When complicated with retinitis the duration is much shorter. Complete recovery from well-established interstitial nephritis is probably unknown.

Complications.

These are, in addition to what have already been considered as symptoms, but of which some might with propriety be classed among

[1] Archives of Medicine, Vol. IV., No. 1. New York, August, 1880.

complications, bronchitis, pericarditis, pleurisy, pneumonia; and, more rarely, endocarditis, peritonitis, intertubular gastritis, and even inflammation and ulceration of the bowels. But all inflammatory complications except bronchitis, pleurisy and pericarditis are less common than in acute nephritis. Bronchitis is said to be the most frequent complication, while pericarditis is the most dangerous, being almost invariably fatal. The former occurs in about 33 per cent. Pleurisy and pneumonia are also of tolerably frequent occurrence, Grainger Stewart finding the former in 15 per cent. of his cases and pneumonia in 7 per cent. The latter author found pericarditis also in only 7 per cent., while Dickinson found recent pericarditis in nearly 25 per cent. My own experience finds no such large percentage, but accords rather with that of Stewart. Acute endocarditis and peritonitis occur but very seldom. It is possible that the obstinate vomiting in some cases may be due to intertubular gastritis, the occasional presence of which is asserted by Drs. Fenwick and Wilson Fox, as distinguished from the follicular inflammation found in acute nephritis. Three cases of ulceration of the ileum are mentioned by Dr. Dickinson, and one by Dr. Bartels. The occasional obstinate diarrhea may be due to this cause.

The cause of this tendency to inflammation attending contracted kidneys is probably the irritating state of the blood, poisoned with the retained excretions which the damaged kidney is unable to remove.

Diagnosis.

The diagnosis of an interstitial nephritis is usually easy, if by any means an examination of the urine is suggested. The increased, or at least undiminished quantity, the low specific gravity, small albuminuria, delicate hyaline, and pale granular casts, in the absence of other symptoms, are sufficiently distinctive. The conditions which should suggest such an examination are a feeling of constant weariness, slight swelling of the feet, drowsiness, intense headache, confused intellect, dyspeptic symptoms, obstinate nausea, delirium, coma, and convulsions. Hypertrophy of the left ventricle without valvular disease should always suggest examination of the urine. Sclerosis of the radial arteries is similarly suggestive. Gradual failure of vision

should also invite a study of the urine. The ophthalmologist is often the first to recognize chronic interstitial nephritis by his retinal examination.

Prognosis.

The prognosis is unfavorable as to complete recovery, but favorable as to prolongation of life if the diagnosis be made sufficiently early. If it is not made previous to the setting in of uremic symptoms, little may be expected. But even at this stage energetic treatment may still avail to avert the immediate danger and prolong the patient's life. The possible sudden occurrence of convulsions and coma, and of death therefrom, should always be remembered and impressed upon the relatives of the patient. Some ophthalmologists say life is rarely prolonged more than a year after well-developed neuritis, but I have had many patients live longer.

The following by de Schweinitz[1] probably presents as nearly as possible the actual facts as they stand to-day:

"The prognosis *quoad vitam* is bad. In Bull's list more than fifty per cent. of the cases died within the first year, and in general terms it may be stated that it is exceedingly uncommon for patients with albuminuric retinitis to live longer than two years. Of course I know there are exceptions to this rule, that patients have lived five, seven and even greater number of years after the retinal lesions have developed. In this particular there is a marked difference between hospital and private patients. Naturally, those who can afford the best treatment, climatic, as well as dietetic and therapeutic, have the best chance for prolonging their lives. Belt's statistics are interesting in this particular. He collected 155 cases from private practice, of which 62 per cent. died within one year, 85 per cent. in two years, and 14 per cent. lived more than two years. He collected 75 cases from hospital practice, and of these 85 per cent. died within one year, 93 per cent. within two years, and 6 per cent. lived more than two years.

"That the prognosis of retinitis associated with the albuminuria of pregnancy and scarlatinal nephritis is much more favorable than the retinitis of chronic Bright's disease is well known."

[1] The Ocular Manifestations in Chronic Bright's Disease. Reprint from Medicine, December, 1902.

For a fuller consideration of this subject see the section in this volume on Albuminuric Retinitis by George E. de Schweinitz.

Treatment.

From what has been said under prognosis, it is evident that the most hopeful result to be expected from treatment is the protection of the patient from the consequences of his malady rather than the restoration of the kidney to its normal condition. Our power in the former respect depends largely upon the stage at which the disease is discovered. But let us first suppose that it is detected, as it often is, at a period in which the urine is tolerably abundant, the albuminuria small, the casts are few, and there is no edema. Here, again, the indications are, *first,* to maintain the integrity of the blood, chiefly by preventing the accumulation of urea and its allied compounds, and by compensating for the loss of albumin, which is at first not great; and, *second,* to treat as they arise, the accidents and complications which are often so dangerous to the patient.

The first of these is best accomplished by dietetic and hygienic measures, aided by the use of a few remedies.

First, as to *food,* all that was said under chronic parenchymatous nephritis is more than applicable to interstitial nephritis, because the appetite is still good and a suitable selection can be exercised.

As there stated, it is now generally recognized that the urea found in the blood and eliminated by the kidneys in health, has its chief source in the proteid elements of food, and that the more of this food we consume, the larger is the accumulation of urea in the blood, and the greater the work thrown upon the kidneys. Now while it is not possible nor desirable to exclude all nitrogenous food, it must be of advantage in this disease to reduce it to a moderate amount. This is accomplished by the substitution of all, or perhaps preferably, of a part of animal flesh by milk and cream, while drawing the elements of a mixed food from the vegetable kingdom. The so-called vegetarians have proved conclusively that it is possible to live and maintain good health upon milk and an otherwise exclusively vegetable diet. And while this diet may not be compatible with the highest mental and physical development, the resulting life is perfect enough for all its objects, and will doubtless be acceptable

to those who prefer to live. On such a system I have known the patient with contracted kidney to maintain apparently perfect health for many years.

Fruits are eminently suitable for persons with contracted kidney, and although they may not contain a large amount of nutriment the fruit juices are a suitable addition to the blood, while the very considerable amount of sugar they contain contributes to their nutritive value. Among them may be included oranges, grapes, peaches, apples, bananas and small fruits. Due regard must of course be had to the ability of the patient to digest the fruit desired. Cooked fruit is more easily digested than raw fruit.

With regard to *beverages,* there is no doubt that the use of strong alcoholic drinks should be avoided, and brandy, whiskey, and strong sherries and ports should be prohibited. The light wines, and especially the red wines, and lighter alcoholic drinks, as lager beer, porter, etc., may be used moderately.

What was said of *clothing, fresh air,* and *exercise,* in connection with chronic parenchymatous nephritis, is even more applicable to interstitial nephritis. Warmth of the body, maintained by *woollen garments next the skin* to encourage its action, and the *avoidance of damp and cold* which check it, are peremptory. The wetting of the body by rain, or of the feet alone, has frequently been the exciting cause of a uremic attack which was fatal. Rubber overshoes should be worn in all damp weather.

In this connection *sea-bathing* requires to be alluded to. It is well known that sea-bathing sometimes induces albuminuria in persons perfectly healthy, or at least in those at other times free from albuminuria. This may be due to a temporary congestion of the kidney, the result of an introversion of blood from the skin, kept up by the length of the bath. Still more harmful, therefore, must be prolonged sea-bathing upon one whose kidneys are already damaged and incompetent. I am confident that one case of latent contracted kidney under my observation was hastened to its fatal termination by this cause, the patient in this instance remaining in the water two or three hours at a time. Sea-bathing, therefore, or indeed any form of cold bathing should be interdicted to the patient with contracted kidney. Sea-bathing is especially mentioned because

it is otherwise so healthful, and involves remaining in the water so much longer at a time. On the other hand the warm bath, and especially an occasional Turkish bath is advantageous.

For the same reason *residence in a warm equable climate* is often of signal service in interstitial nephritis; and cases are reported where the albumin has disappeared and apparent recovery taken place during such residence, where the previous duration was such as to make recovery at least improbable. I recall the instance of a lady past middle life who had granular kidneys, and who had already begun to suffer the numerous inconveniences of advanced renal disease. She went abroad, and, during a residence in southern Germany, was entirely relieved of all unpleasant symptoms. She described herself as feeling during that period like a young girl. She had no sooner reached Liverpool, on her return, than all of these symptoms returned, and she died in a few months after reaching home. I have no precise knowledge of the frequency of Bright's disease in the southern part of the United States, but I seldom hear of cases originating there.

Prolonged bodily or mental fatigue should also be avoided by these cases, as they may be the exciting cause of uremia and death. The patient should live a life as easy and as free from any of these causes which have been considered, as his circumstances will permit.

As to *drugs,* they are of limited utility. Tonics, including the simple bitters as stomachics, also quinin and strychnin, are useful and may be necessary to combat the tendency to anemia and weakness, which sooner or later supervene in this disease. Iron should, however, be used cautiously. It has become so much the habit to prescribe iron in Bright's disease and especially Basham's mixture that some have come to regard it as more or less a specific. On the other hand, I am sure much harm is often done by the indiscriminate use of iron. Its tendency to constipate and lock up secretions generally is often responsible for headache and throbbing, which are so often annoying symptoms in advanced stages of this disease. Only when anemia is present is iron indicated. It should then be given in moderate doses well diluted. Preparations should be given which are least disposed to constipate. The acetate of iron in the form of Basham's mixture,

the formula for which is given on p. 150, has always been a favorite, as stated above. It is commonly regarded as a diuretic, but I am doubtful whether it is one unless it be through the water with which it is commonly diluted when administered. The dose should not exceed f℥ss of the preparation of the U. S. Pharmacopeia, which contains 5½ minims. The vegetable salts of iron, such as the citrates, malates and tartrates, are less disposed to constipate. These are given in doses of three to five grains.

The sense of weariness or weakness which is sometimes such a marked symptom in cases of chronic interstitial nephritis, is not always an indication of actual weakness. I am inclined to think it may be the result of accumulation in the muscles and nerves of effete matters which it is the office of the kidneys to eliminate just as the same sensation in diabetes mellitus may be due to glucose in the tissues, the oxidation of which relieves the sense of fatigue. In that event the weary feeling would be more likely to be relieved by elimination by the bowels and perhaps by the skin, as the kidneys are crippled in their function. This may be accomplished by the hot bath at bed time, and especially the hot air bath, a convenient form of which is a cabinet now much in use in families and figured in the text.

It is conveniently kept in the bath room and may be used once, twice or three times a week just before retiring. Continued at first only a few minutes, after sweating begins it may be prolonged to twenty minutes. The patient should be well rubbed down after the bath and go immediately to bed. The Turkish bath answers a similar purpose but has the disadvantage that the patient must be exposed more or less in returning home.

A gentle diuretic, as the sweet spirit of niter, or solution of acetate of ammonium, with tonics and chalybeates, brisk exercise in the open air, and proper precautions against subsequent exposure while perspiring—these, alternated with sufficient rest, all tend to supplement the action of the kidneys and avert the consequences of their incompetency.

Diuretics are not indicated in the early stage, because the secretion of urine is already free and not likely to be much increased by diuretics. The *bowels* should be kept *regular* by the use of the

natural aperient waters, the Hunyadi, Friedrichshalle, and Rakoczy, or an occasional blue pill, but there is no need of decided purgation. If there is anemia the aperient may be combined with iron, and for this purpose sulphate of magnesium (epsum salt) is useful. An ounce of the former, ten grains of sulphate of iron, and a drachm of aromatic sulphuric acid may be added to a pint of water, and of this a wineglassful taken before breakfast. Of course, later in the disease, when the urine is again scanty, both diuretics and purgatives may be desirable to avert the calamity of uremia. The same principles are to govern us in using them as have been laid down under acute nephritis.

The second indication mentioned, the *treatment of the complications and accidents* incident to the condition, resolves itself into the treatment of the bronchitis, the pericarditis, the pleurisy, pneumonia, endocarditis, gastric and intestinal disorders which have been named as occurring, and especially of the most serious calamity of all, uremia. The treatment of the complications is that of the same conditions under other circumstances. Prompt restorative and even stimulating measures are, however, here earlier called for than in these same conditions uncomplicated, and when to these is added counter-irritation, the chief indications for the thoracic troubles are fulfilled. Paracentesis is a measure which is often of signal service in effusions into the chest, and occasionally of the pericardium.

Opium should be cautiously employed, not only in complicating gastro-intestinal troubles, but under all circumstances, as it undoubtedly increases the dangers of uremia. This has been abundantly proven. It need not be discarded altogether, for there is indeed no substitute for it in most bowel affections and conditions of severe pain, but it should be given in smaller doses than usual, and its effects watched. In like manner hypnotic, sedative, and antispasmodic effects, when desired, should be produced by *chloral, chloralose, chloralamid, somnose* and *bromids* if possible.

Dyspeptic symptoms are best treated with pepsin and acids. I have found full doses of the wine of pepsin, f℥ij to f℥ss, with 5 to 10 drops of dilute nitromuriatic acid, and $\frac{1}{30}$ to $\frac{1}{20}$ of a grain of sulphate of strychnin, here, as elsewhere, among the most efficient remedies for indigestion. Or the powdered pepsin in 8 to 10 grain

doses may be dissolved in an aqueous acid solution. Flatulence must be controlled by antiferments, such as salol and sulphocarbolate of sodium in moderate doses. The bichlorid of mercury in doses of $\frac{1}{50}$ to $\frac{1}{20}$ grain is an admirable remedy in combination with extract of nux vomica. The salicylates should be avoided, as they are positively irritating to the kidneys.

Finally, as to the treatment of *uremia,* when it occurs, the immediate indication is, of course, increased elimination of a decided character. This is accomplished by sudorifics, purgatives, and diuretics. The degree to which these should be pushed will of course depend upon the urgency of the symptoms. If there be simple drowsiness, headache, or gastric derangement, a brisk purge by $\frac{1}{6}$ to $\frac{1}{4}$ of a grain of elaterium, or 2 drops of croton oil, or a saline, followed by full doses of infusion of digitalis, with acetate or citrate of potash, may suffice to avert the danger. Or, a drachm of jaborandi-leaves may be infused in six ounces of hot water, and a tablespoonful administered to an adult, and repeated if necessary until a sufficient diaphoresis results. If it be desired to counteract any depressing effect, which can hardly exist with so moderate a dose, a drachm of solution of acetate of ammonium, which is also diuretic, may be added to the mixture. The fluid extract of jaborandi, which I have not found so reliable as the freshly prepared infusion, may be given for the same purpose in 20-drop doses. If there is headache, full doses of bromid of potassium and phenacetin are indicated.

Usually, however, when the symptoms of uremia appear in this disease, they are urgent, and require more active treatment. Coma is very frequently present, and the administration of remedies by the mouth is difficult or impossible. Then $\frac{1}{4}$ or $\frac{1}{3}$ a grain of *muriate of pilocarpin* may be given hypodermically, in solution. If the remedy acts, profuse sweating, with or without salivation and diuresis, will take place within half an hour, and this is often attended with a prompt return to consciousness. Effect follows more promptly if the patient is surrounded simultaneously by hot applications. If this is done $\frac{1}{4}$ grain will often have the effect of $\frac{1}{2}$ a grain unassociated with these measures. It may be repeated in half an hour. If pilocarpin is not at hand, half of the above-directed infusion may be thrown into the rectum, and the remainder in half an

hour, if sweating does not result. But while waiting for this effect, the patient may be dry-cupped over the loins and at the back of the neck, and, if necessary, a couple of the cups at the neck may be cut. At the same time a couple of drops of croton oil, diluted with plain oil or glycerin, may be dropped into the mouth, or $\frac{1}{4}$ of a grain of elaterium dissolved in a little water and introduced into the fauces. These latter remedies under the most favorable circumstances are apt to require several hours before they operate, but they are useful in keeping up the effect. Hot-air- or vapor- or hot-baths may be used when neither pilocarpin nor jaborandi are available or efficient. Diuretics may also be resumed with return to consciousness. Digitalis is the best, but other remedies may be substituted or alternated with it. The infusion of scoparius (broom tea) is a favorite remedy. Its active principle, spartein, in $\frac{1}{4}$ to $\frac{1}{2}$ grain doses often acts when digitalis fails. Trousseau's diuretic wine, containing juniper, squill, digitalis, and acetate of potash, is an efficient diuretic. Squill alone I have never found to have diuretic properties. Compound tincture of juniper or gin may be used, especially where stimulants are indicated, and to meet the popular demand for them.

If *convulsions* are present, alternating with or to the exclusion of coma, *chloral* should be given. A drachm of chloral hydrate may be given to an adult by enema, often with the most promptly satisfactory results. General bloodletting should not be forgotten. The same indications which make it the best remedy in puerperal convulsions call for it here; and while it is less efficient than in puerperal eclampsia, it still may be used, with due regard to the strength of the patient. It should be associated with hypodermoclysis or transfusion.

The *asthmatic attacks,* which are a part of the uremic condition, will be relieved by the same class of remedies, but the antispasmodics, chloral, the bromids, Hoffman's anodyne, and inhalations of ether may be used as adjuvants.

Apoplexy, which is not an infrequent termination of the disease, in consequence of diseased blood-vessel walls, is recognized by the paralysis, general or partial,—most frequently hemiplegia,—which accompanies the unconsciousness. Remedies are here generally futile, but such may be used as are indicated for apoplexy elsewhere. Bleeding, counter-irritation, and, if the patient survives the immediate accident, iodid of potassium, with a view to

promoting absorption of the extravasated clot, may be used. It should not be forgotten, however, that all the signs of apoplexy, including unconsciousness, hemiplegia and even aphasia, may form a part of the symptoms of uremia without rupture of any vessel. These symptoms are especially prone to appear in the uremia of chronic interstitial nephritis.

Hemorrhages in other situations, as from the nose or alimentary canal, are treated by the same measures as when they occur under other circumstances.

As to *specific treatment,* or treatment directed to the removal of the interstitial overgrowth in the kidney, there are two remedies which theoretically could be expected to be of service, and they are iodid of potassium and bichlorid of mercury. Unfortunately the peculiar requirements of their administration, viz., the length of time during which the patient must take them before any results may be expected, and the consequent difficulty in accumulating a sufficient number of cases, are such that it is almost impossible to determine how far they can be of any service.

Bartels says of his experience with the iodids: "The patients whom I treated upon this principle before the occurrence of any threatening symptoms—before their exhibiting any trace of dropsy or uremia, withdrew themselves from my observation too early, so that I cannot, as yet, venture to form an estimate of the ultimate results of this method of treatment." He states, moreover, that he gives the iodid in solution to the extent of 1.5 to 2 grams (20 to 30 grains daily) for an indefinite period, and has seen no prejudicial effects from its use uninterruptedly for many months. I have long been convinced that the iodid of potassium in moderate doses is harmless for an indefinite period. Recently I have used it more frequently in this disease. If it is useless in removing the interstitial tissue, as I fear it is, it is useful in dilating the blood-vessels and acting as a diuretic. It is to be remembered that nothing is to be expected unless its use is begun in the earliest stages, before dropsy, uremia, or defects of vision have made their appearance. It is best given fasting.[1] Smaller doses thus suffice, and there is less

[1] The value of this method of administration, also recommended by Bartels, is well illustrated in an excellent paper published in the Philadelphia Medical Times, Vol. X., 1880, p. 445, by Dr. John Guitéras, on the therapeutic advantages of administering iodid of potassium during fasting, with some remarks upon interstitial hepatitis with enlargement of the liver.

interference with the administration of food and other remedies required. From 10 to 20 grains a day thus administered may be continued indefinitely. I prefer to begin with small doses not exceeding three grains and increase very cautiously. At present I am using the iodid of sodium rather than potassium. The bichlorid of mercury also appears to do good in some cases, and has at times an effect in improving the vision in albuminuric retinitis.

Nitroglycerin is a remedy which is sometimes useful in relieving the unpleasant symptoms of high tension and throbbing in interstitial nephritis. It may be given in doses from $\frac{1}{100}$ to $\frac{1}{25}$ grain repeated often enough to produce the desired effect. As it is a remedy whose effect does not last long it is best given in moderate doses repeated at short intervals rather than large doses at longer intervals. It is not curative. Nitrite of sodium and potassium are reputed to have a more permanent effect, said to extend over three to four hours and would seem on this account to be preferable. They are given in doses of from three to five grains every four hours.

Recently my attention has been called by Dr. William H. Thomson of New York to the value of tincture of aconite for this same purpose of relieving arterial tension. He recommends $2\frac{1}{2}$ minims or 5 drops every three hours kept up for some time. Chlorid of gold and sodium were urged a number of years ago as curative for interstitial nephritis by the late Dr. Roberts Bartholow.[1] I used it for a time without satisfactory results and I believe it has fallen into disuse.

[1] Medical News, January 19, 1884.

SECTION X.

Dietetic Treatment of Bright's Disease.

The important rôle so long assumed by the dietetic treatment of Bright's disease justifies a separate section, though it may involve some repetition of statements already made. It is not too much to say that in certain cases, if not in certain varieties of Bright's disease the importance of the dietetic equals, if it does not exceed that of the therapeutic treatment.

Two objects may be said to be covered by the dietetic treatment —*first,* the protection of the organ from an exercise of function calculated to increase the damage to a kidney already crippled; and, *second,* to prevent the accumulation in the blood of toxic substances generated in the metamorphosis of certain foods, and more or less difficult of excretion, which add to the dangers of the disease.

The importance of the dietetic treatment differs, too, in the acute and chronic forms of the disease, since the period over which it must extend is necessarily much longer in the chronic than in acute forms. In the latter, therefore, we may avail ourselves of all the advantages of a dietetic treatment without any of the disadvantages which grow out of a too long continuation of a monotonous diet.

Dietetic Treatment of Acute Nephritis.—As already stated, the conditions of treatment of acute nephritis are much simpler, more readily arrived at and more easily met. In acute nephritis, for example, we may measure the severity of the disease by the quantity of albumin excreted, variations corresponding, as a rule, with differences of severity, while in chronic nephritis there are often large variations which bear no relation to seriousness, and which take place quite independently of any treatment whatever.

Both purposes of the dietetic treatment, viz., saving the kidney and guarding the blood against the accumulation of toxic substances, are accomplished in acute nephritis by avoiding meats, meat extracts and broths, because these are rich not only in proteids and urea-forming substances, but also in kreatin, whence comes kreatinin, a

substance both poisonous and difficult of excretion. This is present in traces only, in the white and yolk of eggs and milk and not at all in vegetables. On the other hand, milk and eggs both contain a considerable quantity of albumin. We must not, therefore, suppose that when we are giving a pure milk diet, we are giving a minimum of proteid. Nor is it desirable to eliminate proteids altogether from the food, since the body cannot be perfectly nourished on a diet of pure carbohydrates and hydrocarbons, though proteid admits of considerable reduction compatible with health. The required quantity of proteid for a healthy man weighing 140 pounds was originally set by v. Voit at 2,700 grains per diem, but these figures have been very much reduced, as low as 1,200 to 1,700 grains *per diem,* women requiring rather less than men, while even a smaller quantity, say, 900 grains, may suffice for a short time. A quart of milk contains five hundred to six hundred grains of proteid, so that it is evident three pints of milk will contain this permissible amount of proteid and a larger quantity, say, six pints, would contain 1,500 to 1,800, furnishing too large a quantity to be excreted by the damaged kidney. Even three pints of milk per day will sustain life for a time if the patient is at rest in bed, but the nutrient quality of the milk may be increased by adding a quantity of cream which contains very little proteid and is almost pure fat. The addition of 12 ounces of cream to three pints of milk furnishes a mixture which will support, in fair condition during acute illness, an adult patient who remains in bed. Such a reduced quantity of nourishment has other advantages. The stomach and bowels are kept from being overloaded and deranged in function, the tendency to such derangement being increased by the feeble digestion of the nephritic patient. Such limited ingestion of liquid favors also the reabsorption of edematous infiltration when present. The proportion of albumin in the yellow as well as in the white of eggs is much larger than in milk, and egg can, therefore, not be regarded any more than meat as a suitable constituent of the food of acute nephritis.

Some regard must be paid to the habit of large eaters who may regard this quantity of food insufficient. To these thin soups and farinaceous preparations, sugared ices, natural fruit juices and the like may be permitted. An additional quantity of water may also

be allowed where thirst is complained of. With a return of the secretion of urine we may reasonably infer that the power of the kidney to excrete urea has returned, permitting also a more liberal allowance of the milk and cream mixture, to which the farinacea and succulent vegetables like peas, string beans and cooked fruit may be added, though the proteids should be kept below the allowance of health until all signs of nephritis have passed away. Even meat and eggs may be allowed at this stage, provided we restrict the proteid to the quantity laid down as permissible.

Dietetic Treatment of Chronic Nephritis, including Contracted Kidney.—Two important differences characterize the conditions in the dietetic treatment of chronic nephritis as contrasted with acute nephritis. In the first place, as already intimated, the difficulties in interpreting the results of treatment are very much greater because more marked variations occur in the symptoms quite independently of treatment. Thus we have seen that in acute nephritis the albuminuria may be fairly regarded as a measure of the severity of the disease, while in chronic nephritis such variations cannot always be so interpreted. The same is true of other symptoms. Hence less reliance can be placed on changes which may succeed upon any treatment, be it dietetic or medicinal. Moreover, because of the chronicity of the disease, the dietetic treatment must extend over a considerable period, becoming often so tiresome and distasteful to the patient that he rebels against it; while the very repulsiveness of diet, whatever the reason for it, can scarcely be else than harmful if continued.

In a general way, the indications are the same as in the acute form, viz., to spare the kidney and prevent the accumulation of toxic substances in the blood. These indications are fulfilled theoretically by the milk diet laid down on p. 164, which has indeed been very popular. But while such a diet is preëminently suited to the acute exacerbations in the course of chronic nephritis, it is not suited for prolonged use and has been persisted in at times to the disadvantage of the patient.

Another disadvantage of a milk diet not often thought of and to which attention has been called by Von Noorden, especially bearing on the treatment of chronic nephritis, is found in the fact that milk

contributes to the blood a large amount of phosphoric acid, reaching at times 45 to 60 grains *per diem,* whose excretion severely taxes the kidney. Von Noorden has, however, also shown that a portion of the phosphoric acid contained in the food can be prevented from passing through the kidney by administering a small quantity of calcium carbonate daily. The calcium unites with a portion of the phosphoric acid, causing it to remain in the intestine, or after circulating through the body to pass with the intestinal excretion into the lower intestine and out with the feces.

But while these objections just cited tend to remove the pure milk diet from the high pinnacle which it once occupied in the dietetic treatment of chronic nephritis, it may still form a large part of that treatment, and I still quite often adopt it for a short time, as when a case of chronic nephritis first comes under observation as well as in one of the acute exacerbations referred to.

Turning to other foods which are regarded as harmful to the victim of chronic nephritis, we come first to meat. Very erroneous and ill-founded notions have arisen in the minds of some of the laity and, I am sorry to say, among a few physicians also, with regard to meats, and especially as to the difference between white meats and red meats. So emphatic has been the preference in favor of white meats as against red meats that some have acquired the idea that white meat is not meat at all. It frequently happens to me to be consulted by patients who say they are not eating meat, when it will transpire that they are eating large quantities of the white meat of chicken and fish and veal. I have known a well-to-do family quite inconvenienced by the expense of buying large quantities of poultry to supply a want of this kind.

Now it ought to be unnecessary to say that white meat is meat, and that the quantity of proteid in white meat is little less than in red meat, and that to eat a half a pound of white meat is taking in much more proteid than to eat a quarter of a pound of red meat. Yet not a few have expressed surprise at this information. The truth is borne out not only by general chemical principles, but also by the results of actual analyses made with a view to settling the question. It will be remembered that the objection to dark meat is based on the supposition that it contains considerably more nitrogenous extrac-

tives injurious to the kidneys. With a view to settling this question, Offer and Rosenquist, pupils of Von Noorden,[1] made, at the latter's suggestion, some observation, in the course of which it was found that nitrogenous extractives were at times more abundant in dark and at others in white meat, while certain kinds of white meat (as poultry and hare) were found to be even richer in extractives, on an average, than beef. Moreover, it was ascertained that any differences in rare meats may disappear completely on cooking.

Reasoning from the above, it goes without saying that some meat may be allowed patients with chronic nephritis. This is in direct opposition to former teaching. Von Noorden even holds that some meat is *necessary* in cases of contracted kidney in order to maintain the highest degree of bodily vigor, having learned by experience that patients subjected to a prolonged low proteid diet are weak, delicate and incapable of performing any real muscular work, while as soon as they are given a greater variety of food and proteids, with the free use of dark meats, they recover rapidly.

For some years I have been insisting upon the fallacy of the older doctrine and have advised patients with chronic nephritis to limit their consumption of all meats rather than of any one kind and I am much gratified to have the support of so able an authority as Von Noorden. Thus is escaped the inevitable disgust which comes of any single article of food to which one may be restricted.

As to the quantities allowable, Von Noorden says:

"Basing on the assumption that a patient with contracted kidneys takes on an average one and a half pints of milk (with about four hundred grains of albumin) a day, and two eggs (with about two hundred grains of albumin) a day, and that about thirty grains of nitrogenous material are ingested with vegetable food (bread, vegetables, etc.), the following values remain for meat:

"In men from one to two ounces of albumin, equal to seven to ten ounces of meat (weighed raw); in women two thirds to one and a third ounces of albumin, equal to five to eight ounces of meat (weighed raw). After cooking this amount of raw meat would weigh about thirty per cent. less if prepared with the juice, about

[1] Von Noorden, Clinical Treatises on the Pathology and Therapy of Disorders of Metabolism and Nutrition, Part II., Nephritis, New York, E. B. Treat & Co., 1903.

forty per cent. less prepared in some dry manner. This quantity of albumin, on the one hand, or of meat on the other, is, as a rule, sufficient, and we may always be certain that we are giving the patient sufficient albumin to maintain his strength."

I have not felt justified in going quite as far as the above implies, but for some years I have been in the habit of allowing my cases of chronic nephritis very small quantities of meat of any kind once a day, adding also a single egg at breakfast, with very satisfactory results, in addition to milk, white bread cereals and succulent vegetables. I desire to emphasize, however, the statement already made that in acute exacerbations during chronic nephritis, as well as acute nephritis, the proteids must be more energetically reduced, in fact to a minimum.

Another article of diet to which modern teaching assigns a modified rôle is water. We have heretofore taught that in all forms of chronic nephritis, and especially contracted kidney, the free ingestion of water should be encouraged as calculated to diminish the elimination of albumin and increase that of urea. That the former is an erroneous interpretation has always been recognized by the ordinarily thoughtful physician. For it is evident that from reduced percentage we dare not infer absolute diminution of albumin. As to urea, it did seem reasonable that an increased flow of urine should be associated with an increased excretion of urea. From Von Noorden again comes the criticism. He says that, as a rule, increased diuresis in contracted kidney following the use of much mineral water causes nothing more than a dilution of the urine and that " the flooding of the vascular system with water overtaxes the heart to an extraordinary degree and ultimately damages the organ. The water that is absorbed from the intestine can only be excreted by the kidney if the blood pressure is increased. It is difficult to demonstrate directly that the heart is damaged by excessive water drinking; but indirectly this can be shown, for many cases of weak heart are on record that give a history of having indulged in abundant water drinking for long periods of time. In cases of this kind improvement may be frequently witnessed if the amount of water is limited."[1]

A case recently under my care strikingly confirms the dictum of

[1] Von Noorden, op. citat., p. 96.

Von Noorden. A gentleman 62 years old who proved to have interstitial nephritis had been in the habit for some time of drinking at his dinner a quart of red wine and a quart of water, in addition to eating a large meal. At the remaining two meals he was also accustomed to drinking large quantities of liquid. He quite suddenly acquired a dropsy which invaded the scrotum and abdominal cavity. The heart was dilated and there were stenocardiac attacks which compelled him to rise at night to get his breath. Gradually the excessive ingestion of liquid was withdrawn, and under the use of diuretics the secretion of urine was largely increased and cardiac distress disappeared completely with a reduction in the size of the heart. While it is certainly satisfactory to see cases of chronic nephritis passing plenty of urine, I have no doubt that the matter of water ingestion can be overdone, as I believe is shown by this case and others reported by Von Noorden.

Finally turning our attention to articles of food that are directly prejudicial in chronic nephritis, there can be no doubt as to beef essences, strong meat extracts, and spoiled or "high" meats. These contain toxic substances especially prejudicial, while more than moderate quantities of meat of any kind are harmful.

Alcohol preëminently should be avoided even more rigorously than in acute nephritis, although at times a couple of ounces of red or white wine may be permitted at dinner, constituting as it does a stimulus to digestion and a tonic to the heart. The same is true of a tablespoonful, seldom more, of whiskey taken diluted with water at a meal. Nor need tea or coffee or smoking tobacco be totally forbidden, the practical difficulty being that when these substances are allowed at all they are taken in excessive quantity. Their action on the heart is more to be feared than on the kidney.

A class of accessory foods which should be totally forbidden are condiments, including curry, pepper, mustard and radish, especially horse radish, and stimulating sauces like Worcestershire sauce.

Asparagus is usually regarded as irritating to the kidney, and when ingested in large quantities probably is so, but in moderate quantity I do not regard it as harmful. Only recently a case of anurea under my observation was rapidly substituted by free secretion after administering a small quantity of asparagus. Hence I

see no reason why asparagus in moderate amount should not be included in the vegetable diet of a nephritic subject. Celery should also be classed with asparagus among those vegetables which may irritate the kidney. Of remaining vegetables I know of none sufficiently irritating to preclude their use on any ground except digestibility. Especially suitable are the succulent vegetables like rice, potato, peas, beans, spinach, tomato and the like.

The cereals, especially hominy grits and the whole wheat products, are allowable in small amounts with milk or cream and, moderately, sugar.

SECTION XI.

THE OCULAR MANIFESTATIONS OF BRIGHT'S DISEASE.

By G. E. de SCHWEINITZ, A.M., M.D.,

Professor of Ophthalmology in the University of Pennsylvania.

The following ocular manifestations may be associated with or caused by various forms of Bright's disease:

1. Complete blindness without ophthalmoscopic lesions, or at least, without the presence of lesions more or less suggestive of disease of the kidney, generally called uremic amaurosis and most often seen in acute nephritis, but also in acute exacerbations of chronic renal disease.

2. Various types of retinitis, neuroretinitis and neuritis, to which the descriptive term "albuminuric" is commonly applied, and which are most often seen in association with chronic forms of kidney disease.

3. Alterations in the caliber and relation of the retinal vessels owing to sclerotic changes in their walls, with or without hemorrhages and exudates in the retina, seen in association with all forms of chronic renal disease, but particularly with those in which vascular changes are evident elsewhere in the body.

4. Alterations in the uveal tract, particularly in the choroid and iris.

5. Certain varieties of cataract.

6. Paresis and paralysis of the external ocular muscles.

7. Recurring subconjunctival hemorrhages and recurring subcutaneous palpebral ecchymoses.

Uremic Amaurosis.—In this condition the loss of sight is often sudden, bilateral and complete, so that even the perception of light is lacking; occasionally first one eye becomes blind, to be followed by a similar blindness in the second eye a day or two later. In other instances light perception is not wanting and never entirely

disappears, the visual disturbance coming on gradually and requiring some time for its development. A hemianopic defect of vision has been recorded by Jessop and Pick and an amblyopia by Babinski, which is difficult to diagnosticate, especially in children. The condition of the pupils varies. Sometimes they are dilated and motionless, that is, irresponsive to light stimulus; at other times they react to the light impulses and are normal in size.

Ophthalmoscopic examination may be negative, which is the case in the majority of the instances of this affection, unless there has been preëxisting retinal disease. Sometimes there is a general edema of the retina, or an edema located particularly around the optic nerve with fulness and tortuosity of the retinal veins. A form of choked disc remaining during the amaurosis and disappearing afterwards has been reported.

Occurrence.—Uremic amaurosis, to quote a sentence of J. B. Lawford, "may occur in any of the various forms of renal disease in which there is sufficient interference with the excretion by the kidneys to load the blood with those poisonous materials, whatever their exact nature may be, which induce the uremic condition." It is more common in the acute nephritis of the eruptive fevers, especially scarlet fever, and of pregnancy than in other forms of renal disease, and has been found in nephritis due to exposure to cold, and in acute exacerbations of chronic renal disease.

Pathology.—Retention of the pupillary reflex with absolute blindness would indicate that the lesion in this condition resides in the visual tract beyond the primary optic centers. In those cases with failure of the pupillary light reflex, it is probable that the toxic action affects the central and peripheral parts of the visual tract, and it is possible that the retinal elements themselves may be intoxicated, just as the ganglion cells are influenced by other toxic agents, for example, those developed in diabetes and certain intestinal fermentations.

Prognosis.—The blindness may last from a few hours to a day or even longer. I have seen it remain unchanged for nearly two days in scarlet fever-nephritis. The return of sight is usually comparatively sudden and all traces of the visual defect may have disappeared by the end of the third day. According to Groenouw, permanent

blindness from pure uremic amaurosis does not occur, that is, in cases unassociated with preëxisting retinitis, although, according to Leber, in rare instances it may be the cause of optic nerve atrophy which develops some time after its subsidence. Prolongation of the attack or frequent repetition of it renders the prognosis less favorable. Retention of the pupil reflex is an encouraging sign.

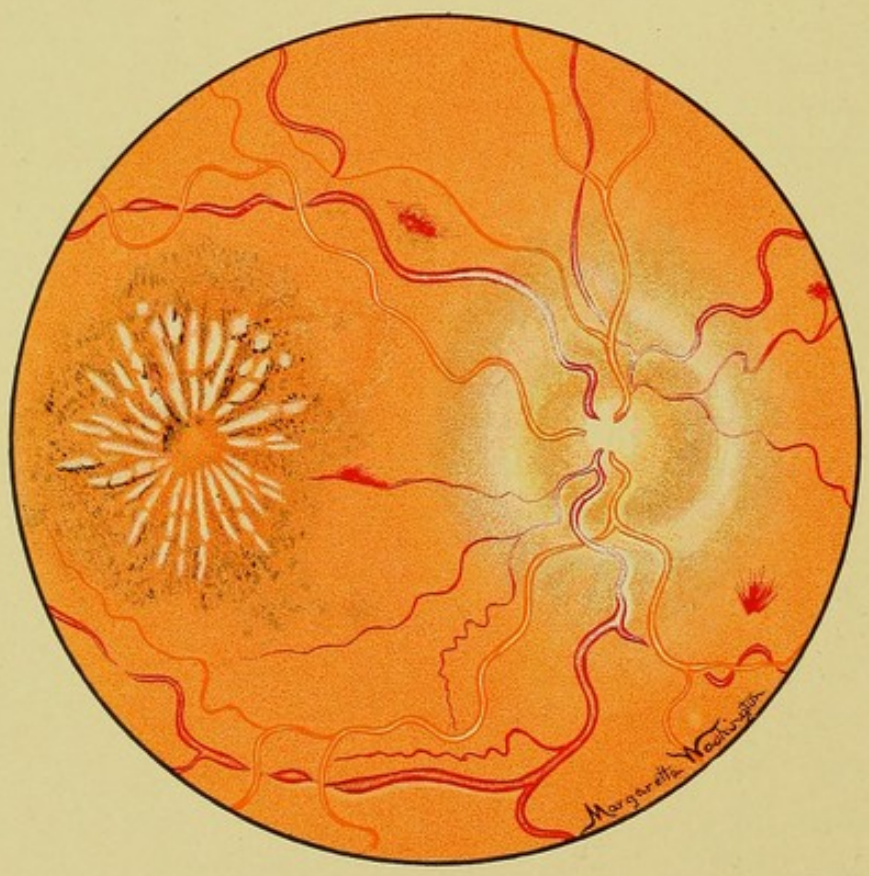
Treatment.—This demands measures which are elsewhere described for the relief of uremia (see page 132).

Retinitis. *History.*—In the first edition of this book the late Dr. William F. Norris, referring to the history of the discovery of ocular manifestations in connection with Bright's disease, wrote as follows:

"The occasional occurrence of amblyopia in the course of Bright's disease has been observed ever since this malady has been diagnosticated and studied, and although Bright himself in his first paper on the subject[1] (1827) gave no eye symptoms beyond edema of the eyelids, he in 1836[2] recorded eleven cases, 'illustrating some of the more insidious attacks which attend a fatal termination,' in four of which failure of vision coming on at a period varying from six weeks to six days before the fatal termination, was one of the prominent symptoms. In 1840[3] the same author published twenty-four cases, with defective vision in three of them, and in 1843[4] Bright and Barlow reported thirty-seven cases of the disease accompanied by uremic poisoning, with five cases of defective vision among them. It was not, however, till Türck[5] in 1850 demonstrated the occurrence of splotches of fatty degeneration in the retina, that the anatomical changes accompanying it were known; and six years later we find a more exhaustive study of the same subject by Virchow.[6] The first ophthalmoscopic description of these changes was published by Heymann[7] in 1856—just five years after the discovery of the ophthalmoscope by Helmholtz, and in 1859 Liebreich[8] added still further to

[1] Reports of Medical Cases, by Richard Bright, M.D., F.R.S.I., London, 1827.
[2] Guy's Hospital Reports, 1836, pp. 338, 380.
[3] *Ibid.*, 1840.
[4] *Ibid.*, 1843.
[5] Zeitschrift der Gesellschaft der Wiener Aertze, 1850.
[6] Virchow's Archiv, Vol. X., pp. 170–193.
[7] Archiv f. Ophthalmologie, Bd. II., part 2, pp. 137–150.
[8] *Ibid.*, Bd. V., part 2, pp. 265–268.

PLATE VI



TYPICAL ALBUMINURIC RETINITIS (DE SCHWEINITZ)

our knowledge of the subject, illustrating his description with a colored lithographic plate."

Varieties.—Systematic writers have divided the various types of retinitis and neuroretinitis associated with kidney disease as follows: Typical albuminuric retinitis, degenerative albuminuric retinitis, hemorrhagic albuminuric retinitis, albuminuric neuroretinitis and albuminuric papillitis.[1]

(*a*) *Typical Albuminuric Retinitis.*—Variously shaped and placed white spots, at first only minute foci, appear in the macula or in its immediate neighborhood. Sometimes they are discrete and sharply separated, but later and under other circumstances they form a star-shaped arrangement, the rays of which may completely or partly surround the fovea forming the so-called "macular figure." Near the papilla, and often encircling it, large, yellowish white areas appear, so that there is a ring-shaped zone around the nerve-head, forming a striking white region to which the name "snow bank of the retina" has sometimes been applied. Linear, flame-shaped or round hemorrhages are scattered over the fundus. They are especially noteworthy in the fiber layer of the retina, on or in the neighborhood of the optic papilla, along the blood-vessels and commonly in the macular region. The blood-vessels may be partly buried in the white exudate, or pass over it. The veins are frequently dark, tortuous and distended, the arteries either unchanged in size or smaller than normal and striped with white lines. The nerve head may be hyperemic, actually swollen, and sometimes exhibits the appearances of a decided neuritis. Since Leber's description three stages have been recognized in this so-called typical variety of the disease, namely, the hyperemic, the degenerative and the atrophic, names which sufficiently characterize the appearances of each stage.

(*b*) *Degenerative Albuminuric Retinitis.*—The lesions consist of white spots, sometimes small and separated by nearly normal areas; hemorrhages, but less conspicuous than in the type just described, and confined to the fiber layer of the retina; and dark and tortuous veins, the arteries showing a sclerotic condition of their walls. The disc is red, and its margins indistinct, but there is no white area or

[1] Joseph Schoebl: Diseases of the Retina. A System of Diseases of the Eye, edited by Norris and Oliver, Vol. III., p. 516.

peripapillary zone to be noted, and either the star-shaped figure is wanting in the macular region where the white spots previously referred to are dotted, or it is irregularly and imperfectly developed. Sometimes in later stages of this degenerative type larger white plaques form and the retina becomes diffusely opaque, partly hiding the blood-vessels. In the final stage of the affection the disc becomes dirty white or yellowish-white in color, the blood-vessels grow narrower and more sclerotic, and alterations in the retinal elements are associated with the formation of pigment deposits.

(*c*) *Hemorrhagic Albuminuric Retinitis.*—This term has been applied to those varieties of the disease in which the most conspicuous features are hemorrhages, and in which, in the earlier stages at least, the nerve head and the retina, except where hemorrhagically involved, are comparatively unaffected. The hemorrhages may be linear, fusiform, or flame-shaped, and large hemorrhages of various shapes may develop in the deeper layers. After absorption white areas take the places of the hemorrhages, sometimes bordered with pigment.

(*d*) *Albuminuric Neuroretinitis and Papillitis.*—These terms have been applied to types of retinal disease connected with nephritis in which, on the one hand, there has been a decided involvement of both the retina and optic nerve with marked exudations, hemorrhages and inflammatory signs, in short, an exudative neuroretinitis, and, on the other hand, in which the entire process seems to have spent itself in the development of a typical papillitis or choked disc, the rest of the retina being comparatively unaffected.

In general terms, it is true that these varieties are recognizable, but often seem to shade one into the other or they exist in combination, and therefore for practical purposes it is sufficient to recognize two varieties, usually termed inflammatory or exudative, and degenerative.

It is a matter of some importance, if possible, to determine what are the earliest appearances of renal retinitis, which, indeed, may not develop into any of the varieties previously described, or may perhaps be their prodromes. Small, comparatively insignificant white dots, or small, fluffy exudates with here and there a hemorrhage, may be the first signs of the retinal lesions of nephritis, or with these appearances there may be associated vascular and peri-

vascular changes presently to be described. My experience coincides with that of Edward Jackson[1] that amongst the earliest signs of renal retinitis changes in the capillary circulation and in the smallest arteries and veins, especially dilatation and tortuosity of the small veins around the macula, are noted, while the optic disc assumes a dirty, or brick-red discoloration. These appearances belong to the stage of high arterial tension and may antedate noticeable alteration in the urine.

Symptoms.—In addition to the ophthalmoscopic signs of the retinitis of Bright's disease already sufficiently detailed, it is necessary to consider certain subjective symptoms. Depreciation of vision may vary from a slight and gradual impairment to complete blindness, although the last named condition in pure albuminuric retinitis must be extremely rare. It should be remembered that the disturbance of sight may be very slight and not at all in proportion to the ophthalmoscopic signs of the disease, and be more marked in one eye than the other. Indeed, normal visual acuity, so far as test-letters are concerned, is not at all incompatible with very decided retinal lesions, if these have not destroyed or impaired the percipient elements in the macular region, and it is a well-known fact that Bright's disease is often discovered by an ophthalmoscopic examination, the patient being unaware that he is the subject of a serious organic malady.

Except when certain complications presently to be described exist, peripheral vision is generally good, although, naturally, the visual field may be altered in accordance with the situation and gravity of the retinal lesions. Scotomas, and particularly blue-blind areas have been described, and H. F. Hansell,[1] who has reported a color scotoma in retinitis albuminurica, the patient dying six weeks after the condition was discovered, suggests that an observation of this character might be important in prognosis. Generally central scotomas depend upon changes in the macula. It is possible that they may be due to the action of a toxin in the blood. There is not much alteration of light-sense according to Förster, and usually this is stated to be the case with color-sense, unless, of course, there should

[1] Medical News, Vol. LXXX., I., 1902, p. 307.
[2] Philadelphia Polyclinic, V., 1896, p. 462.

be such a color scotoma as has just been referred to. Schnabel, however, has described blue-yellow-blindness, and Simon[1] maintains that violet-blindness is not uncommon in connection with albuminuric retinitis. He even suggests that it may be characteristic of the disease. The blue-blindness which was described by Gerhardt as a sign of contracted kidney is also to be mentioned.

Two complications of albuminuric retinitis should be referred to, namely, detachment of the retina and hemorrhagic glaucoma. The former is probably more frequent than has been supposed and would necessarily increase the visual disabilities and be indicated by corresponding defects in the visual field. Hemorrhagic glaucoma is a secondary glaucoma, occurring in the same manner as this does after ordinary retinal hemorrhages.

Other complications are embolism of the central artery of the retina, or perhaps more accurately, thrombosis; retrobulbar neuritis; and hemorrhage into the sheath of the optic nerve. Diffuse retinitis and extensive perivasculitis have also been described.

Varieties of Renal Disease which Produce Retinal Lesions.— Although ocular lesions may occur with any form of nephritis, it is chronic interstitial nephritis, that is, renal sclerosis, whether this is an independent primary affection, or whether it is a sequel of arteriosclerosis, which is most frequently associated with the various types of retinitis. Retinal lesions may also be symptoms of chronic parenchymatous nephritis, and some observers, notably Samuel West[2] maintain that a sharp distinction should be made between the degenerative and exudative forms of albuminuric retinitis, believing that the former is indicative of chronic granular nephritis, and that the degenerative changes depend upon vascular alterations, while the latter indicates a chronic parenchymatous nephritis and depends upon an inflammatory or toxic influence. Naturally, the secondary contracted kidney, which is a sequence of the large white kidney, may be associated with retinitis, and this is also true of amyloid disease of the kidney, because there is no reason why lardaceous degeneration of the kidneys, which is not a separate disease but an event in the course of Bright's disease most frequently occurring in parenchymatous nephri-

[1] Centralbl. f. prakt. Augenheilk., August, 1894.

[2] Lancet, Vol. II., 1899, p. 483.

tis of cachectic origin, should not produce this ocular complication. Uremic amaurosis, ordinarily a symptom of acute forms of Bright's disease, may occur during the course of a retinitis caused by chronic kidney lesions, for example, during an exacerbation.

Date of Occurrence of the Retinal Lesions.—At one time it was supposed that the retinal lesions of renal disease began at the same period that cardiac hypertrophy was manifest, but this certainly is not a constant association. In general terms it is probable that the renal disease must be present for some months before the retinal lesions appear, but the very fact that retinitis may be the first sign of kidney disease, indeed, as already noted, the means by which it is discovered, renders an authoritative statement on this subject all the more difficult. There has been a good deal of discussion as to the existence of the so-called *pre-albuminuric retinitis* and a number of cases have been recorded; that is, the retinitis, retinal hemorrhages, exudates, etc., have been found to precede the albuminuria by a considerable length of time. Dr. Sutton suggests that these are examples of granular kidney in which albumin is absent, or only present to a very small amount until a later stage of the kidney affection. In other words, it is conceivable that the patient with retinal lesions might consult the physician, as Groenouw suggests, during a period when albumin was lacking, and that therefore these lesions might be ascribed to a pre-albuminuric period, although really they appeared during a period when albumin is temporarily absent. On the other hand, lesions especially located in the blood-vessels, particularly various types of perivasculitis and of "silver-wire arteries," producing compression upon under- and overlying veins, are often present for long periods before nephritis is manifest, or at least before other signs of renal disease are fully established, that is, albumin and casts. To this condition fuller reference is made in subsequent pages.

Age at which Retinal Lesions Occur.—Inasmuch as chronic interstitial nephritis is a rare disease before the twenty-fifth year, its percentage rising between that age and forty and growing still greater between forty and sixty, the retinal lesions are likely to appear at the same periods. According to Nettleship,[1] the age varies from thirty

[1] British Medical Journal, September 26, 1903.

to sixty, the most prolific single decade being from fifty to sixty. Children, however, are not exempt. In other words, the disease may occur at any age. Reference is not now made to uremic amaurosis, for example, in scarlatinal nephritis, but to so-called typical albuminuric retinitis. The youngest case recorded by Bull in his analysis of 103 cases of exudative neuro-retinitis associated with chronic Bright's disease, was five years of age. Arnold Lawson and G. A. Sutherland have observed this affection in a patient twelve years old, and I have seen one case in a child of nine.

About twice as many cases of renal retinitis occur in men as in women, and it is stated that when decided hyaline thickening of the retinal arteries is evident to the ophthalmoscope, an early stage of granular kidney may be suspected, especially if the patient is comparatively young (Nettleship).

Frequency of Retinal Lesions in Chronic Bright's Disease.—To ascertain accurately the exact proportion of renal disease in which retinitis occurs is difficult, and the recorded percentage has varied from nine to thirty-three. Groenouw[1] has collected from the literature 935 cases of kidney disease, among which there were 209 examples of retinal lesions, namely, 22.4 per cent. According to William F. Norris, fully 25 per cent. of the cases of chronic Bright's disease as they occurred in general hospitals, are affected by various forms of retinitis. My own experience yields an equally great if not greater percentage, and if one includes not alone the cases in which there are more or less typical forms of retinitis and retinal lesions, but also those in which the ophthalmoscopic signs are comparatively insignificant, consisting chiefly of alterations in the walls of the retinal vessels, this percentage will rise much higher. It is interesting and important that Litten among 33 cases of chronic parenchymatous nephritis six times noted albuminuric retinitis.

Course and Prognosis.—Some reference to the course of typical renal retinitis has already been made. It is customary to divide it into the stage of hyperemia of the papilla, opacity of the retina and hemorrhages; the stage of fatty degeneration; and the stage of retrograde metamorphosis and atrophy. While the white spots may

[1] Graefe-Saemisch, Handbuch der Gesamten Augenheilk., Zweite Auflage, 26 u. 27 Lieferung, 1901, p. 97.

subside; they rarely disappear entirely, and the macular changes are most permanent. Discoloration and atrophy of the papilla, contraction of the vessels, the formation of white tissue along their walls and pigment changes in the retina may finally result. As complications already noted are detachment of the retina, hemorrhage into the vitreous, thrombosis of the retinal vessels, secondary glaucoma and extravasations into the choroid.

The prognosis *quoad visum* depends largely upon the character and situation of the exudates and hemorrhages; in other words, upon the amount of destruction of the percipient elements of the retina, and also upon the sequential changes. In some of the exudative varieties with great involvement of the macula, vision is markedly depreciated, although, curiously enough, at times very florid types of albuminuric retinitis clear up more decidedly and more rapidly than less pronounced varieties of the disease. Even when improvement in vision occurs (and indeed, sight may sometimes rise to the normal standard) there is rarely, if ever, entire disappearance of the stellate exudate in the macula, and this is true even when albuminuric retinitis is caused by a syphilitic affection of the kidney, although appropriate treatment may be followed by complete restoration of vision in so far as the test-types are concerned. Naturally, the development of any of the complications previously described, namely, detachment of the retina, atrophy of the optic nerve, retrobulbar neuritis, hemorrhages into the optic nerve sheath and secondary glaucoma, would produce great depreciation of vision.

The prognosis *quoad vitam* is bad if one is to base an opinion on the elaborate statistical material available for this purpose. In general terms, it may be stated that it is uncommon for patients with albuminuric retinitis to live longer than two years after its detection, and a very considerable per cent. of them die within the first year of its development. There are many exceptions to this rule, and the records show that patients have lived five, seven and even a greater number of years after the retinal lesions have appeared. In this particular there is a marked difference between hospital and private patients. Naturally, those who can afford the best treatment, climatic, dietetic and therapeutic, have the best chance for prolonging their lives. This is well shown in the Baroness Possaner's

statistics,[1] and is interestingly developed by Belt, who collected 155 cases from private practice, of which 62 per cent. died within one year, 85 per cent. in two years, and 14 per cent. lived more than two years. Of the 75 cases collected from hospital practice, 85 per cent. died within one year, 93 per cent. within two years, and 6 per cent. lived more than two years. An important fact is brought out by Miley's[2] investigations, who found among 164 patients with acute or chronic renal affection, 105 with unaffected eyes, and 51 with retinitis albuminurica. The death rate of the patients with sound eyes was 27 per cent.; of those with eyes showing retinitis 53 per cent., or about double.

I am inclined to think that while the prognosis of albuminuric retinitis will always remain exceedingly grave, statistics gathered some years hence will show an improvement in so far as the duration of life is concerned as compared with those to which reference has been made.[3] This naturally will be the result of improved methods in therapeutics. Finally, it should be remembered that ophthalmologists frequently see the lesions of renal retinitis late, that is to say, in all likelihood the lesions have existed for some time before their detection, and therefore it is not entirely correct to say that the majority of patients die within two years after the appearance of the retinal changes of Bright's disease, but only that they are apt to die within two years after these changes have been discovered.

Pathology.—In general terms, to use the language of Robert Saundby, the various types of so-called renal retinitis must depend upon an altered condition of the blood, degenerative changes in the blood-vessel walls and excessive pressure of blood within these vessels. The immediate pathological changes include thickening of the retina by the presence of inflammatory edema, together with hypertrophy of its nervous and supporting tissue. Fatty degeneration of the exudate and of the retinal elements accounts for the white spots in the macular region, while their star-shaped arrangement depends upon an oblique direction of the cone fibers. Within the nuclear layers there may be fatty and granular cells and coagu-

[1] Deutschmann's Beiträge zur Augenheilk., Vol. XV., 1894, p. 22.

[2] Trans. Ophth. Soc. U. K., 1898.

[3] Those interested in a complete analysis of these statistics should consult Groenouw, loc. cit.

lated fibrin. Hemorrhages are present in any of the layers of the retina, but need not be a pronounced feature. In almost any stage of renal retinitis vascular changes are to be noted: alteration in the adventitia, hyaline change, and proliferation of the lining endothelium. Although the term "inflammatory edema" has been used, it is proper to emphasize the fact that inflammatory phenomena, even in very decided so-called albuminuric retinitis, are comparatively not in evidence, as has been well shown by Weeks and confirmed by Greeff. The alterations in the vessels are the important factors in the pathological changes. Formerly it was believed that the retinal changes were secondary to a kidney lesion which was regarded as the primary disease. Investigations of Von Michel, Karl Theodor, Weeks, Greeff and others all go to show, however, that the process in the retina and in the kidneys has the same origin. In other words, the same causes which originate disease of the blood-vessels of the kidney originate also the alterations in the retinal vessels, and to these alterations the chief rôle must be ascribed in causing the various types of retinal lesions which have been discussed. Von Michel has gone even further and stated that the ophthalmoscopic picture of so-called retinitis albuminurica is entirely the outcome of disturbances in the circulation and of lesions of the retina brought into existence by a primary disease of the vessel system of the central retinal artery and vein, that is, of arterio- and phlebo-sclerosis with their sequelæ. It is interesting that a number of observers have noted sclerotic changes in the vessels of the choroid analogous to those which are found in the retina.

Diagnosis.—It is frequently stated that the appearance of the retina to which has been applied the term typical albuminuric retinitis is characteristic of kidney-affection, and that ocular examination under these circumstances is more satisfactory than a urine-analysis. This belief is still widespread, but is not entirely accurate. It has been known since the observations of Von Graefe, Schmidt and Wegner, more than thirty years ago, that appearances exactly simulating those seen in retinitis albuminurica, particularly the so-called macular figure may be found in brain tumor. Moreover, the star-shaped macular figure is seen in syphilitic retinitis, in retinal hemorrhages especially as they occur in young

people, and in some forms of retinal disease connected with anemia. As Haab well puts it, this figure is simply a representative of an intense vascular disease with interference of the retinal circulation, and is caused by the accumulation of fatty granules in the cone fibers of the macular region, and is not due, as is often taught, to fatty degeneration of the ends of Müller's fibers. Nevertheless when the appearances described as typical albuminuric retinitis in the earlier portion of this article are present and are bilateral, they are strongly suggestive of chronic renal disease, provided the exceptions to which reference has been made are borne in mind.

Usually both eyes are affected in albuminuric retinitis, although it is common to find more extensive lesions in one eye than in the other. A certain number of cases of unilateral albuminuric retinitis, however, have been reported, and to quote Knies's expression, this unilateral character is not a rarity. It should be remembered, as was forcibly brought out by De Wecker long ago, that there are certain forms of retinitis attending nephritis which may be classed as hemorrhagic retinitis and that these may be unilateral, or at least, that the second eye is attacked only very late, while the true albuminuric retinitis is bilateral. In other words, as I have elsewhere stated, a certain proportion of cases maintain monocular retinal lesions until death. In another large percentage of cases the unilateral character of the affection continues for a certain period of time and ultimately becomes bilateral.[1]

It is a mistake to suppose, when looking for the lesions in the retina which indicate chronic nephritis or are associated with it, that the picture must be a typical one. In point of fact, the so-called typical cases are not nearly as frequent as the cases in which the lesions are not so evident, but none the less significant, namely, the types with scattered hemorrhages, with or without white exudates, certain types of perivasculitis, early changes in the nerve head with tortuosity of the macular vessels, and particularly the alterations in the caliber of the vessels of the retina to which reference will be made later.

[1] Those interested in the literature of this subject may consult Marple, Medical Record, March 11, 1893; de Schweinitz, Medical News, December 19, 1896; and W. L. Pyle, Philadelphia Medical Journal, November 19, 1898.

PLATE VII

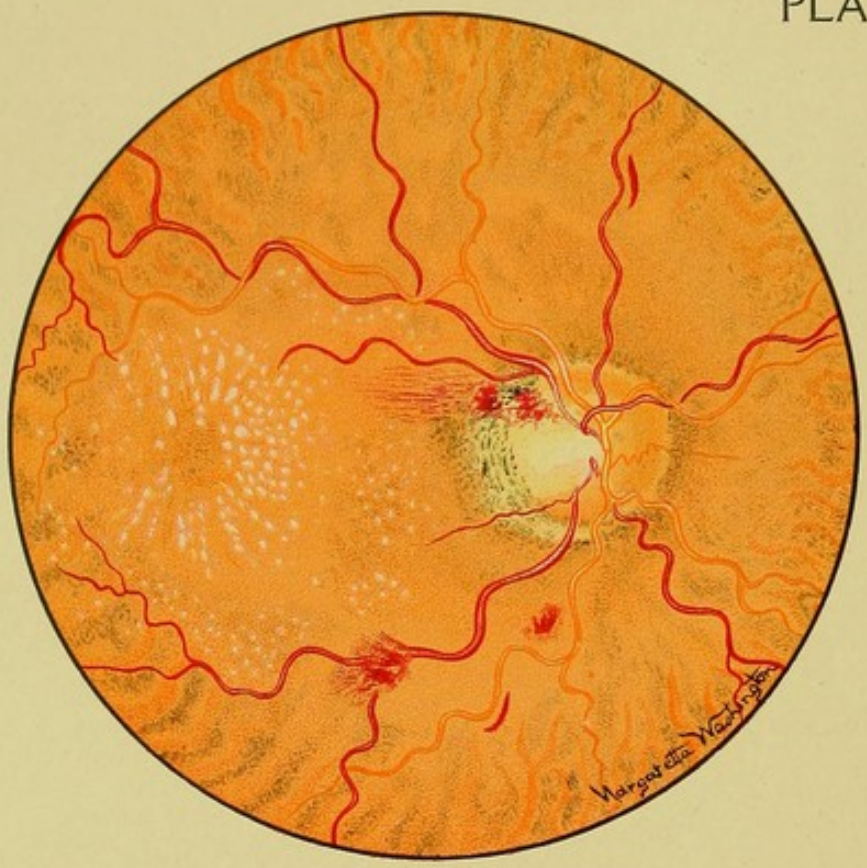


FIGURE 1

RETINAL LESIONS IN CHRONIC INTERSTITIAL NEPHRITIS
(DE SCHWEINITZ)

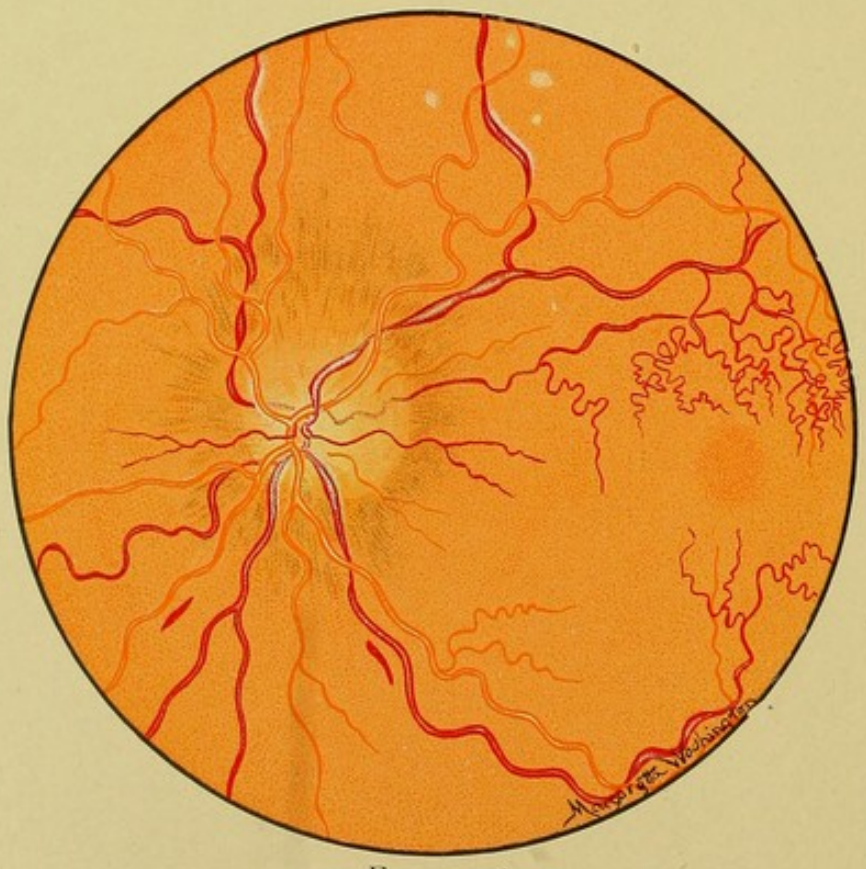


FIGURE 2

RETINAL LESIONS OF ARTERIO-SCLEROSIS (DE SCHWEINITZ)

Treatment.—Local measures are practically of no avail unless there should be a tendency to rise of intraocular tension, when the myotics will be indicated. Each case should be managed on the general principles suited to the form of kidney disease which is present. Frequently the best results follow the administration of iron in the form of the tincture, of bichlorid of mercury, of iodid of sodium and the iodids generally in small doses, and when indicated by the tension of the vessels, nitroglycerin.

Alterations in the Caliber and Relation of the Retinal Vessels as a Sign of So-called Bright's Disease.—Following Marcus Gunn's[1] admirable classification, the ophthalmoscopic signs which may be encountered in general arterio-sclerosis, and therefore in many cases of chronic renal disease, are the following:

1. Alterations in the course and caliber of the retinal arteries, manifesting themselves as (*a*) undue tortuosity, which is not significant unless, to quote the words of Mr. Gunn, it is associated with other evidence of disease; (*b*) alterations in the size and breadth of the retinal arteries, consisting of general contraction of one or more branches, or more suggestively, of alternate contractions and widenings, where, for example, a vessel may proceed with practically normal caliber for a certain distance, then suddenly narrow almost to a thread, again fill out, and again narrow, thus presenting, as it were, a beaded appearance.

2. Alterations in the reflections from, and the translucency of, the walls of the retinal arteries, manifesting themselves (*a*) in increased distinctness of the central light streak on the retinal vessel and an unusually light color of the entire breadth of the artery. The vessels, as Mr. Gunn points out, give the impression not only of increased brightness of the central light streak, but of an unusual reflection from the arterial coat and have been named "silver-wire arteries." (*b*) Loss of translucency, so that it is impossible to see, as is possible in the normal state, through the artery an underlying vein at the point of crossing; (*c*) positive changes in the arterial walls, consisting of whitish stripes, indicating degeneration of the walls, or infiltration of the perivascular lymph sheaths.

3. Alterations in the course and caliber of the veins, together with

[1] Trans. Ophth. Soc. U. K., Vol. XVIII., 1898, p. 356.

signs of mechanical pressure, manifesting themselves (*a*) in undue tortuosity, which, as in the case of the arteries, is not significant except in the presence of other disease; (*b*) alternate contractions and dilatations; (*c*) an impeded venous circulation where a diseased artery crosses it. This is the sign which Mr. Gunn particularly dwells upon, and which, in my experience, is of the utmost importance. Ordinarily, as an artery crosses the vein, as may be seen by an examination of the normal eyeground, there is no sign of pressure, and the translucent artery permits a view of the vein beneath it. If the walls of the artery are thickened by disease, then it presses upon the vein, pushes it aside, or directly contracts its caliber, so that beyond the point of crossing there is an ampulliform dilatation. So, also, where the vein overlies the artery there may be a similar contraction of the venous caliber and dilatation on either side of the spot of crossing and the vein seems, contrary to the normal, semitranslucent. (*d*) Changes in the venous walls, precisely as they occur in the arteries, so that whitish stripes border the vessel, and are indications of degeneration in its walls. Often associated with this one may see varicosities, as has been pointed out by Raehlmann.

4. Edema of the retina, manifesting itself as a grayish opacity, which may be present in the immediate neighborhood of the papilla, or in spots over the eyeground and along the course of the vessels, looking like a fine gray haze, or in little fluffy islands far out in the periphery.

5. Hemorrhages, manifesting themselves as linear extravasations along the course of the vessels, roundish infiltrations scattered over the fundus, or sometimes, when extensive, in drop-like form, especially in the macular region, forming the so-called subhyaloid hemorrhages. As a result of hemorrhages there are frequently scattered through the eyeground yellowish and whitish-yellow spots bordered with pigment, indicating the atrophy of the elements that has taken place during the course of the absorption of hemorrhages.

Significance of Changes in the Retinal Vessels.—It has been known for a long time that alterations in the size of the retinal arteries unassociated with albuminuric retinitis are apt to be present in chronic renal disease. For example, Gowers[1] has described in some

[1] Medical Ophthalmoscopy, Second Edition, p. 180, and British Medical Journal, December 9, 1876.

cases of chronic renal disease, especially the granular form, a distinct diminution in the size of the retinal arteries independently of any special retinal disease, and has further noted that the veins in such cases are not larger than normal, but the arteries are not more than one half or even one third the diameter of the veins. This alteration in the caliber is coincident with high tension pulse. In recent times this subject has been greatly developed and much attention has been paid to ophthalmoscopic alterations in the retinal vessels, and as a result the lesions described in the preceding paragraphs are well known. Special mention should be made of the observations in this respect of Hirschberg, Raehlmann, Friedenwald, Marcus Gunn and Ole Bull.[1]

These retinal vessel changes in general terms are indicative of arterio-sclerosis and especially of endarterial disease in the cerebrum, but they are most interesting in the study of chronic nephritis and are important from the diagnostic standpoint because, as has been well stated, they are often obvious in cases in which the usual retinitis has not developed. In other words, they are part of the symptomatology of arterio-sclerosis which may be associated with or eventuate in renal sclerosis. More than this, they may be evident where the usual retinitis will not supervene because they are significant of a process which may terminate fatally before the development of a fully established nephritis.

Diseases of the Uveal Tract in Chronic Nephritis.—In many cases of retinitis albuminurica the underlying choroid is also affected, but the choroidal lesions are not evident to the ophthalmoscope and can be seen only on microscopic examination. Special forms of choroidal disease, however, somewhat resembling pigment degeneration of the retina have been described, also disseminated choroiditis and choroidal hemorrhage ending in atrophy. Iritis is occasionally observed. According to Knies, in the absence of any other cause, an

[1] Those interested in the literature are referred to the author's address before the Medical and Chirurgical Faculty of Maryland, Apr. 26, 1900, Maryland Medical Journal, June, 1900, and "The Ocular Manifestations in Chronic Bright's Disease," Transactions of the Philadelphia County Medical Society, October 8, 1902, and to Raehlmann's article, "Ueber die Ophthalmoscopischen Diagnose sclerotischer Erkrankungen der Netzhautgefässe," Zeitschr. f. Augenheilk., VII., 1902, p. 427.

iritis or iridocyclitis may be attributed to albuminuria because the latter is often associated with extensive disease of the iris vessels, and therefore this membrane will be susceptible to those causes which readily excite iritis. In the Philadelphia Hospital I have on a number of occasions found albumin in the urine of patients suffering from iritis, but I have never been able to establish a causal relationship because there were too many other likely and well known etiological factors that could not be eliminated with certainty.

Nephritic Cataract.—The various types of Bright's disease have been brought into connection with the formation of cataract, particularly by Deutschmann. In his last communication on this subject he reported the examination of 230 patients with uncomplicated cataract, among whom 5 per cent. were undoubtedly nephritic and 11 per cent. probably affected with Bright's disease. Most elaborate examinations to determine this point and to test the trustworthiness of Deutschmann's albuminuria theory have been made by Evetzky, whose results indicate that albumin does not mean nephritis, that nephritis and cataract may combine, that in young nephritics there is no cataract, and in old ones not more, usually, than in those who are without the signs of Bright's disease. In other words, a causal relationship between nephritis and cataract has never been established.

Ocular Muscle Palsies Due to Nephritis.—These must be rare, or perhaps are only rarely reported. Knies has particularly called attention to them, and has recorded abducens paralysis, superior oblique paralysis, and external ophthalmoplegia. To this list may be added a good report of paralysis of the superior oblique in nephritis by H. F. Hansell. One point is of importance from the prognostic standpoint, namely, as Knies points out, these muscular palsies may be terminal symptoms of albuminuria. They are indicative of changes in the cerebral vessels similar to those which are found in the retina and elsewhere in the body. Paresis of the ciliary muscle has often been observed.

Recurring Subconjunctival Hemorrhages and Subcutaneous Palpebral Hemorrhages.—In general terms it is well known that recurring subconjunctival hemorrhages may be a sign of chronic renal disease, but I am inclined to think that this manifestation has

not received the place it deserves among the ocular signs of nephritis. To be sure, a number of writers—for example, Talko, Hirschberg, D. B. St. John Roosa, Frank Ring, Charles Stedman Bull, and myself—have called attention to this matter, but more commonly text-books when describing nephritis are silent with reference to this symptom, although other hemorrhagic phenomena, epistaxis, purpura, retinal extravasations, etc., are recorded. In my experience these subconjunctival ecchymoses have occurred in persons past forty, and usually during sleep, the patient being surprised on waking in the morning to find a more or less extensive subconjunctival extravasation, most frequently, I think, in the left eye. In one case they may occur at comparatively short intervals; in another the periods between the attacks may comprise several weeks or even months. What the relative frequency of these subconjunctival hemorrhages is compared with other more commonly described ocular manifestations of nephritic origin is not apparent, owing to insufficient data. Sometimes they may be associated with the ordinary retinitis of nephritis; again they may precede it and finally they may be the only ocular sign of the disease.

Hemorrhages of this character occurring in elderly people are indicative of ordinary angiosclerosis, and are only one of the many signs of this condition, but they are not confined to the eyes of old persons, but may be seen in those not much over forty, and in subjects, moreover, in apparently perfectly vigorous health, and when signs of arterial degeneration are not evident in the radial or temporal arteries.

An exactly analogous condition may appear in the delicate skin of the lower eyelid, and should, therefore, be designated recurring subcutaneous ecchymosis. The spots are only a few millimeters in length, of a slightly purplish hue, resembling a small bruised area, and, like their congeners in the conjunctiva, they come and disappear quickly. They undoubtedly have the same significance. Indeed, in one case I have seen the subconjunctival and subcutaneous ecchymoses alternate. Hemorrhage in Tenon's capsule causing exophthalmos has been reported. Edema of the eyelids is a common manifestation in Bright's disease; sometimes it is intermittent, especially in children, and may be designated a recurring edema or swelling of the lids.

Albuminuric Retinitis in Pregnancy.—While the occurrence of albuminuria during pregnancy is not uncommon, varying according to the statistical reports, from 2 to 20 per cent., involvement of the optic nerve and retina in the form of a neuro-retinitis, to which the term albuminuric retinitis of pregnancy is usually applied, is much less frequent. It occurs, however, in a sufficient number of cases to render a brief word in regard to it important.

Date of Occurrence.—The true retinitis of this condition may gradually develop, occurs most frequently in primipara, and generally in the second half of pregnancy, exceptionally at an earlier period. The ophthalmoscopic signs of this retinitis may not differ from those which are caused by other forms of Bright's disease, and in general terms, there is a widespread neuro-retinitis with exudates and hemorrhages.

Silex has described an early symptom of this condition, namely, an alteration in the central reflex of the vessels, but as this is also present in arterio-sclerosis, it is not, as Silex himself remarks, characteristic. Uremic amaurosis, without ophthalmoscopic change, as already noted, may occur.

Cause.—The retinitis of pregnancy is most frequently the result of the nephritis which is brought about by this condition, essentially a fatty degeneration of the kidney epithelium. It, however, may also be caused, as Groenouw points out, by an acute nephritis which has developed during the pregnant period, or by an exacerbation of a preëxisting chronic nephritis during the same period.

Prognosis.—This in so far as life is concerned is much less grave than in the retinitis of interstitial nephritis, unless there has been a preëxisting nephritis of this character, when of course the same gravity in prognosis arises. In general terms it may be stated that the prognosis in regard to vision depends upon the period at which the retinitis begins. Touching this point, Lucien Howe[1] has said: "Where vision begins to be impaired only in the last two weeks of pregnancy, recovery follows almost invariably. When retinitis begins in the eighth month or thereabouts, not one half of the cases recover, and a certain number do not materially improve. Finally, when the retinitis begins earlier, for example, the middle of the

[1] American Journal of Ophthalmology, 2, 1885, p. 116.

seventh month, and when nature does not interfere by bringing on a miscarriage, and when the patient escapes with her life, it is only to remain blind." Interesting statistics on this point have also been gathered by Culbertson[1] and Silex.[2] The former's records are as follows: Blindness 24.99 per cent.; partial recovery of sight 58.31 per cent.; recovery of sight 16.66 per cent. For comparison Silex's percentages are given: Blindness 25 per cent.; partial recovery of sight 47 per cent.; recovery of sight 29 per cent. Even when recovery takes place, remnants of the retinitis, in the form of white spots and pigment disturbances, are usually discoverable. The blindness is generally caused by atrophy of the optic nerve and degeneration of the retina and choroid; detachment of the retina may occur. Although it is true that if a patient has partially recovered sight after the subsidence of a pregnancy retinitis, a subsequent pregnancy may cause blindness, this is by no means an invariable rule.

Treatment.—The most important question to decide is the propriety of terminating pregnancy for the relief of the retinal disease, and much difference of opinion has existed in regard to this matter. Each case must be decided on its own merits and it would be extremely difficult to lay down hard and fast rules. It seems to me, however, that Randolph[3] has summarized this matter in the most satisfactory manner and issued safe rules for practice as follows: Naturally, the later the renal retinitis makes its appearance, the more favorable the prognosis in regard to sight, and we know that if it appears during the last two weeks of pregnancy recovery of sight follows almost invariably. Therefore nature should be allowed to take its course, aided by whatever proper general regimen is necessary. Even when the retinal trouble manifests itself during the last seven weeks of pregnancy the prognosis is comparatively favorable unless the retinal lesions are very pronounced and the quantity of albumin great. Therefore there should be hesitation before the advice is given to induce premature labor. On the other hand, if the visual disturbances appear during the first six months of pregnancy, especially when they are associated with violent headaches and the retinal lesions are distinct, there should be no hesitancy, if sight is to be saved, in advising the induction of premature labor.

[1] American Journal of Ophthalmology, 2, 1894, 133.

[2] Münch. med. Wochenschr., 1895, p. 106; quoted by Groenouw, loc. cit.

[3] The Significance of Albuminuric Retinitis in Pregnancy, Bulletin of the Johns Hopkins Hospital, Vol. V., No. 41, 1894, p. 69.

SECTION XII.

SUPPURATIVE INTERSTITIAL NEPHRITIS.

Synonyms.—Suppurative nephritis, septic and pyemic nephritis, pyelo-nephritis, renal abscess.

SUPPURATIVE INTERSTITIAL NEPHRITIS IS THAT FORM OF NEPHRITIS WHICH RESULTS IN THE FORMATION OF ABSCESSES RANGING IN SIZE FROM THAT OF A MERE POINT TO THAT IN WHICH THE ENTIRE KIDNEY IS CONVERTED INTO A SINGLE PURULENT SAC.

THE term interstitial is used for this condition because the inflammation which results in these abscesses always begins in the interstitial tissue of the kidney. In contradistinction, the contracted or cirrhotic kidney is characterized by a slow *non*-suppurative overgrowth of connective tissue. Most frequently suppurative nephritis starts in the pelvis of the kidney, as a pyelitis, and thence extends along the interstitial tissue of the organ into its parenchyma. Hence the term pyelo-nephritis is often appropriately applied to this condition. It may happen too that the nephritis does not start from the pelvis, but in the interstitial tissue of the substance of the organ, when it may be caused by an infectious embolus or traumatic cause, or obstruction of the tubules by concretion. I do not consider it necessary on this account to make two divisions of the subject, as some authors do, who apply the term pyelo-nephritis to that variety beginning in the pelvis of the kidney, and suppurative nephritis to that beginning in the substance of the organ. The processes are essentially the same.

Etiology.

Probably the most frequent cause of suppurative nephritis is *retention of decomposed urine* through the infectious bacteria it contains. Such retention and decomposition are the result of long-continued obstruction to the descent of the urine from any cause, as stone in the bladder, inflammation of the bladder whether due to stone impacted in the ureter or pelvis of the kidney, or to stricture of the urethra.

Calculous concretions in the substance of the kidney are another frequent cause, producing most of the cases not the result of the backing of retained urine on the pelvis of the kidney. It is plain how these may act as irritants to the interstitial tissue, and excite suppuration.

Infectious emboli cause a small number of cases of suppurative nephritis. These emboli are usually derived from the valves of the heart in cases of ulcerative endocarditis, but they may also arise in putrid wounds, stumps, or other seats of putrid inflammation. The abscesses found in the kidney in common with other organs in pyemia are thus produced.

Traumatism by blows, kicks, or penetrating wounds in the neighborhood of the kidney, or falls upon the sharp edge of a fence or similar object, may also cause suppurative nephritis. These agencies, however, rarely cause the condition, because if extremely severe, rupture of the kidney and peritonitis generally cause death before suppuration sets in, and if less serious a transient hematuria, followed by recovery in a few days, is the only issue.

The *tubercle bacillus* is a frequent cause and *pathogenic bacteria* are probably an indispensable prerequisite in all cases. Until modern aseptic methods came into general use suppurative nephritis was often caused by the careless use of unclean catheters and even at the present day a cystitis and later suppurative nephritis are sometimes thus caused.

Suppurative nephritis may occur at any age subject to the operation of the cause. The youngest patient I have met is the boy, whose case is related on p. 218. Suppurative nephritis was undoubtedly here present when the boy was two years old.

Morbid Anatomy.

The appearances vary necessarily with the stage of the disease, and also somewhat with the cause.

In the earlier stage, as most frequently caused, by retained ammoniacal urine, the organ is enlarged and vascular. The capsule strips off easily, but in places drags shreds of the renal substance with it. The shreds are often found to correspond with little punc-

tate abscesses about a millimeter in diameter, on the surface of the kidney, which are thus ruptured. Others are noticed scattered over the reddened surface of the organ. They may be isolated or arranged in groups of from three to six. At this stage, too, they will be found scattered over one or more areas, each corresponding to the base of a single Malpighian pyramid, while other pyramids may be entirely free. Each abscess is surrounded by an intensely red border. On principal section of the kidney, these little abscesses appear as yellow striæ running in the direction of the tubules, between which they are found on minute examination to be placed. The striæ converge a variable distance into the medulla, becoming, as they do so, more closely aggregated, and extending occasionally as far as the papillæ. In the medulla they accompany the connective tissue about the vasa recta, and in the cortex the interfascicular veins, the beginning of which on the surface of the kidney corresponds with the punctate abscess, the latter being, as it were, the outer end of the streak. In addition to pus-corpuscles, they contain also various pathogenic organisms, especially those of suppuration and tuberculosis.

At a later stage, these little collections of pus unite to form larger ones, these again to form others still larger, destroying the tubular structure of the kidney as they encroach upon it; and it is at this stage that cases of pyelo-nephritis not unfrequently terminate unfavorably, and the specimens come under observation. At first each of the abscesses thus formed is confined to the region of a single pyramid, and it not unfrequently happens that a kidney is partitioned off in the manner shown in Fig. 33, drawn from one of the author's specimens. Before this occurs, however, the abscess bursts through the papilla and calyx into the pelvis of the kidney. The pelvic end of the papilla is then bounded by an uneven ulcer, which gradually enlarges and deepens until the entire pyramid is destroyed, with more or less of the cortex corresponding to it. If the case lasts long enough even the partitions referred to may be eroded, and thus it occasionally happens that the entire kidney is converted into a huge purulent sac. This of course may occur with one kidney only, while the other is, in a measure, able to continue its function of secretion, although the two kidneys are sometimes so far altered that it seems

incredible that death from uremia should not have occurred much earlier in the course of the disease.

More rarely, it happens that the abscess ruptures through the capsule and leads to the formation of subperitoneal abscesses, which may open posteriorly or gravitate towards the pelvis and open under Poupart's ligament.

Renal *tuberculosis* is also a frequent cause of abscess of the kidney. The tubercle bacillus may invade the kidney by two channels, first by the genito-urinary passages and second from the systemic circulation. In the latter instance it more frequently begins in the bladder and extends upwards through the ureters to the pelvis of the kidney and thence to the substance of the organ. When the bacillus enters the kidney by the renal artery it is deposited in more or less numerous foci scattered throughout the organ. These may increase in size, unite, become cheesy, break down and form large abscess cavities, destroying more or less extensive areas of kidney substance.

The pelvis of the kidney is always dilated, and the seat of a purulent catarrh, the product of which passes down the ureter with the urine into the bladder. Often, the ureter is similarly dilated, being sometimes converted into an intestine-like tube. This is more particularly the case when it is impacted with calculi, as in the drawing presented, or there is some decided obstruction to the passage of the urine from the ureter into the bladder. The pelvis of the kidney itself is even more frequently impacted with calculi than the ureter, when the latter, unless it at the same time contains stones or is also obstructed at its outlet, is less dilated. According to the degree of obstruction, the pelvis and ureter also contain more or less decomposing and stinking urine, mixed with pus and swarming with bacteria.

Almost invariably fatal as these cases are, a complete arrest of the process is not impossible, followed by inspissation, caseation, calcareous metamorphosis, encapsulation, and recovery, with a kidney, however, always more a less impaired in its function.

Klebs[1] and Ebstein[2] describe a still earlier stage of pyelo-nephritis

[1] Klebs, Dr. E., Handbuch der Path. Anat., dritte Lieferung, Berlin, 1870.

[2] Ziemssen's Cyclopædia of Med., Vol. XV., William Wood & Co., New York, 1877.

than that of the punctate abscesses described. In this, the kidney is enlarged and vascular and the capsule non-adherent. They say that at this stage there are no *inter*tubular changes whatever; that the tubules themselves are broad, their epithelium cloudy, sometimes fatty; their lumen is widened and *filled with bacteria.*

Where the abscess is *embolic* in origin its seat is at first occupied by an area of intense hyperemia, resulting in hemorrhagic extravasation, which takes place also into the tubules, causing bloody urine. To this succeeds suppuration. The size of the abscess depends upon that of the plug obstructing the blood-vessel, which is usually one of the interlobular arteries or a vas afferens. The embolic abscesses may also be multiple in consequence of the breaking of the embolus into a number of minute fragments.

Where the cause is *traumatic* the process is not so easily defined. Circumscribed abscesses may occur, or the kidney may be converted into a soft pulpy mass, a mixture of pus, blood, and broken-down renal substance.

Symptoms.

The symptoms of this condition are not numerous, and, apart from the characters of the urine, are not very distinctive. *Pain and tenderness* are the most constant, but it has occurred that considerable inroads have been made upon the structure of the kidney without pain resulting. On the other hand, the pain is often of a very severe character, while the tenderness over the region of the kidney affected is also evident. Most frequently, but not always, the severest pain is in the region of the kidney itself, whence it radiates towards the front of the abdomen and the groin, and is accompanied often by retraction of the testicles. Where the condition is the result of impacted calculus, the seat of the impaction is the seat of pain. Thus, in the little patient whose case affords a typical illustration of one due to impacted calculi, and which is therefore narrated at the end of this section, the region between the umbilicus and the pubis was the seat of numerous and severe paroxysms of pain, and the post-mortem examination revealed that both ureters, in that part of their tract corresponding to this region,—on the lumbar vertebræ,—were thoroughly impacted with calculi. The pain is always intermittent as

to degree, sometimes totally so, but generally there is more or less constant pain of a less degree, which is paroxysmally increased. Various positions are assumed by the patient with a view to easing the pain, among which that on the face is not infrequent.

A distinct *tumor* can sometimes be recognized in the region of the kidney by palpation and percussion. This implies an enlargement of the organ, due either to its complete conversion into a purulent sac, or to distention of its pelvis with pus or calculi or both. In the case to be narrated a distinct tumor could be felt below the umbilicus, which was found, at the post-mortem examination, to be a mass of calculi impacted in both ureters.

Fever is also an intermittent symptom. Possibly in a very few latent cases it may be altogether absent, but except in these there is always slight frequency of pulse and slight elevation of temperature. These latter at times become decided, and in advanced stages the fever is sometimes hectic, being followed by profuse sweats and preceded by chills. In acute cases the beginning of suppuration is often marked by a *chill* or succession of chills, but in most instances it is quite impossible to recognize the beginning of the suppurative stage.

The *characters of the urine,* as intimated, are more distinctive. This secretion, except in acute infectious cases, almost invariably contains *pus* sooner or later, and unless pus appears no certain diagnosis can be made. *Blood* is also a very constant constituent of the urine in suppurative nephritis, but while such urine is scarcely ever examined by the microscope without discovering a few blood-disks, the quantity is not often large enough to be recognizable by the naked eye. The quantity of pus is also very variable. While it may be so copious as to produce a heavy white opaque deposit, equalling one sixth to one fifth the bulk of urine, it may be represented by little more than the normal proportion of leucocytes. This variation will also occur at different times in the same case. Pus from the kidney and its pelvis is distinguished from that formed in the bladder by the absence of that glairy property so characteristic of the latter, due to admixture with mucus and the alteration in the pus itself due to the action of the carbonate of ammonium formed out of urea during decomposition. Pus from the pelvis of the kidney is

also occasionally prone to decomposition, fetid, and swarming with bacteria, but rarely as compared with pus from the bladder.

Tube casts, on the other hand, are not often met in this form of kidney disease.

The *urine* is also *diminished* in quantity, the degree of diminution depending upon the proportion of kidney structure destroyed in the suppurative process. Complete suppression is not uncommon towards the close of bad cases. Notwithstanding such reduction, the color is pale and the specific gravity low, owing to the small proportion of solids present. I have known the range of specific gravity in a single case to be from 1003 to 1016. In *reaction* the urine is faintly acid, neutral, or alkaline, and, as already stated, is often prone to rapid decomposition, and therefore to become rapidly alkaline even when faintly acid when passed.

It *is always albuminous,* but the quantity of albumin is never excessive, and varies generally *pari passu* with the quantity of pus and blood. The ratio, however, varies surprisingly at times. Thus there is in some cases a large amount of albumin associated with a small amount of pus, and at other times, a quite large bulk of pus with but a trace of albumin. The cases with large albuminuria are commonly more serious. It sometimes happens that there is a sudden increase in the quantity of pus in the urine, followed by a gradual diminution, or the urine previously clear may suddenly become loaded with pus. Such occurrences indicate the probable period of rupture of an abscess through a papilla, and a pouring out of its contents into the pelvis of the kidney. Accumulations and sudden evacuations of this kind may also be due to temporary obstructions to the descent of the pus. It rarely happens that a small portion of the substance of the kidney is thus discharged with the urine, when it may be recognized by the microscope, which will discover the tubules and Malpighian bodies of the kidney. Two instances of this are related by Ebstein.[1]

Occasionally, also, the abscess, instead of rupturing into the pelvis of the kidney, perforates into the perinephric tissue, burrowing in different directions and producing fistulous openings. Perforations may thus take place posteriorly in the lumbar region, or anteriorly at the groin, especially into the colon, and more rarely into the lungs and liver, and even peritoneal sac.

[1] Ziemssen's Cyclopædia of Medicine, New York, 1877, Vol. XV., p. 557.

The *course* and *duration* of suppurative nephritis are very various. Traumatic cases are comparatively rapid, either to recovery or death. Pyemic cases may run their course in forty-eight hours, and are invariably fatal.[1] But cases due to impacted calculus, to stone in the bladder, cystitis, or other cause of obstruction to the descent of urine from the kidney, may be prolonged indefinitely, while some terminate without being discovered. Sooner or later the patient succumbs to exhaustion, but even in youth, life may be sustained for years with paroxysms of the severest suffering and a surprising degree of destruction of the kidneys. The greatest danger to those thus affected is intercurrent illness, which is always more serious and much more apt to terminate unfavorably. It is well known that the operation for stone is more apt to be followed by a fatal result when the subject happens to have a surgical kidney, a very prominent instance of which is that of the ill-fated Napoleon III., late Emperor of the French. The operation is, however, not necessarily fatal, even when there is suppurative nephritis of both kidneys, as is shown by the appended highly interesting and illustrative case:

On April 21, 1877, when 3 years and 10 months old, W. H. was cut for stone by the late Professor D. Hayes Agnew, who removed an oval, smooth phosphatic calculus, 3.5 cm. long by 2.2 cm. in its longer, conjugate diameter; on section, also white, loose in the texture of its central portion, and without a nucleus. It was of the same composition throughout. The cut made by the operation was very slow in healing, the latter not being completed until October 1. At least two years before the operation—that is, when less than two years old—he began to complain of bladder symptoms; previous to this he had been delicate. He came under my care about May 1, 1878, one year after the operation for stone. He was then suffering with the symptoms of cystitis, such as are present with a calculus in the bladder, but usually subside soon after the removal of the stone. There was frequent micturition, a small amount of pus, and a very small albuminuria, while the urine was either alkaline when passed, or became so very soon afterwards. He was subject, in addition, to paroxysms of extreme pain, which was confined almost exclusively to the region of the navel. The attacks occurred about once a week, and succeeded upon days on which he felt unusually well, played a good deal, and tired himself thereby; they

[1] In an able experimental thesis, presented to the Medical Faculty of the University of Pennsylvania, March, 1881, Dr. Louis Brose has shown that interstitial changes may make their appearance in 22 hours, and abscess of the kidney at the end of six days after injecting tincture of cantharides.

lasted until paregoric sufficient to relieve them had been given. He was very pale, anemic, and appeared a very delicate child.

I put him on benzoic acid, which was to be given until the urine was distinctly acid, and at the end of two weeks he was greatly better. The paroxysms were less frequent; there was less pus in the urine. To the benzoic acid treatment was added sandalwood oil, and the two were continued, more or less constantly, either together or alternately, as the condition of the urine and other symptoms suggested, throughout the entire summer. This was spent at the seaside. Iron and quinin were also given as tonics when required. It was considered that during this time there was a gradual abatement of his severer symptoms.

About September 10 he had a decided return of his symptoms, this time accompanied with great pain over the bladder and frequent micturition, during which he seized his penis in his hands; he passed water from three to six times in a night. His general health, I thought, at this time greatly improved. The urine was very pale, almost colorless, acid, specific gravity 1003, and contained a few leucocytes and a small quantity of albumin. By the middle of October he was again relieved of the painful symptoms, the specific gravity of the urine increased to 1007, but the albumin had increased decidedly to half the bulk of urine tested. No tube-casts could be found, nor were any ever found in the entire course of the sickness, at least while he was under my observation.

By the middle of January, 1879, the albumin had again become very small in quantity, there was a scanty sediment of leucocytes, and the urine had attained a specific gravity of 1016,—the highest it ever was while he was under my care. The special treatment during this time was sandalwood oil directed to the cystitis, and benzoic acid, to influence the reaction of the urine, as required.

On February 3, 1879, he had a hemorrhage from the bladder accompanied by great pain. It was, however, at a single act of micturition, and what I examined by the microscope, eight hours later, contained no blood-corpuscles but one half its bulk of albumin. The hemorrhage did not recur.

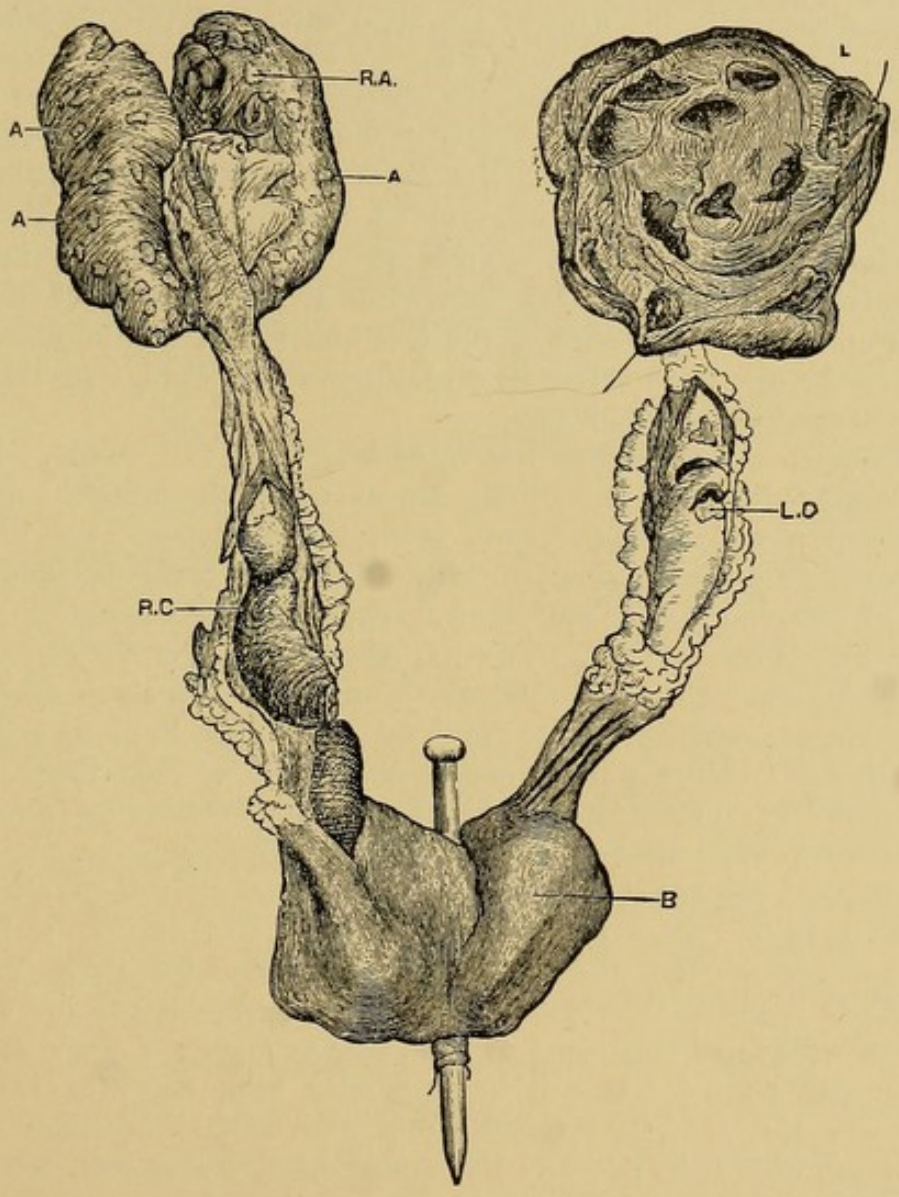
February 12, Professor Agnew sounded for stone successfully. On March 11 he operated, and, after some difficulty, removed the second stone. This was much smaller than the first, being also oval, 2 cm. long by .6 cm. wide. More than half the external surface was white, the remainder brown, and projecting from the former were a number of spicules, by which it was supposed it was imbedded in corresponding depressions in the bladder, whence the difficulty in extracting it. On section, the external concentric laminæ were white, but in the center was a brown, oval nucleus, 1 cm. long and .5 cm. wide. Portions of this nucleus almost totally disappeared on incineration, but the residue reponded to the murexid test. It, therefore, contained some uric acid.

He was kept in bed six weeks, until April 30, when he was allowed to get get up, although the wound was not quite healed. Until April 15 there was a good deal of pus and some blood in the urine, but upon that date we returned to the treatment by sandalwood oil, after which they rapidly diminished. He had some pain on passing water, which continued until April 15, when

this too disappeared. Immediately after getting up the urine dribbled through the opening in considerable amount, but this gradually diminished until it was scarcely sufficient to soil a napkin during the entire day. On May 10 the urine contained a mere trace of albumin, a small sediment composed of pus and earthy phosphates, was faintly acid when passed, but became alkaline soon thereafter, and had a specific gravity of 1005. Soon after this he went to the seashore.

On August 14 the little patient's mother called upon me to report his con-

FIG. 41.



dition. She said that for as much as two weeks at a time there was no dribbling of urine from the wound; then an attack of pain was succeeded by dribbling for a time. He was very well in every other respect, although thin. He ate heartily and played all day long. He continued taking the sandalwood oil, and for a time the benzoic acid.

Early in September the boy returned from the seaside. He was very thin, but his wound had entirely healed. His mother reported that soon after his

return he took cold two or three times in rapid succession, his stomach became deranged, his appetite was poor, and he became weak and emaciated. I saw him September 20, the first time since his return, and was much struck by his emaciated and cachectic appearance. The urine presented about the same characters as when last examined. He was immediately put to bed, placed on roborant treatment, and for a time seemed to grow stronger; but, as though in consequence of the absence of treatment especially directed to the urine, the latter contained much more mucus and became alkaline, and these characters continued until the benzoic acid was re-ordered, when they partially disappeared.

The improvement in his general condition was, however, only temporary, and early in November it was evident he was again declining. He emaciated, grew weaker day by day, and died on the afternoon of November 15, 1879, although he was out in his coach two days before. On the day before his death he had to be catheterized, but there was considerable urine in his bladder, and there was no reason to suppose there was suppression of the secretion. He also suffered a great deal of abdominal pain for two or three days before he died. Very interesting in connection with the results of the post-mortem examination is the fact that his father, while feeling his abdomen on the afternoon before he died, discovered a hard, irregular mass in the neighborhood of the umbilicus.

The *post-mortem examination* was made fifty hours after death. The body was extremely emaciated, but all the organs were found normal except the kidneys, ureters, and bladder. Both kidneys were cystic, each being converted into a multilocular cyst, of which the loculi were distended with a mixture of pus and urine, the former apparently predominating, as there was very little urinous odor. The left kidney was the larger, measuring 10.5 cm. by 5.5 cm. Its surface contained numerous white tubercles (see A, A in the figure), ranging in size from that of a pin's head to a pea. The *pelvis* of this *left kidney* was distended with the same fluid which filled the loculi, and the left ureter—dilated throughout its extent—was almost completely occluded by a single calculus of most peculiar shape. It was spirally twisted and somewhat spindle-shaped, much constricted near its middle, and 5.5 cm. long by 1.5 cm. in its thickest part.

The *right kidney* was smaller, measuring 8.5 cm. by 4 cm., but in all other respects similar. The pelvis and ureter were dilated, and the latter was packed with three fragments of what was originally a single stone, constricted at two points, where it had probably been fractured in removal, making three pieces. The original stone was arcuate in shape, 10.5 cm. long and 1 cm. wide at its middle. The same tubercles were scattered throughout the cortex of this kidney.

The *bladder* contained a small stone, which had evidently descended since the last operation, and was apparently a fragment of one of the stones remaining in the ureter, the fracture having taken place at a point of constriction. This stone was about 2.5 cm. long, and varied in diameter from .5 to .75 cm. The bladder was thickened, as also its mucous membrane, and no traces of the cut made at the time of the operation were discoverable.

The pediculation observed on the stone removed at the last operation,

which was believed to have occurred during its presence in the bladder, most probably did not occur there, as the stones found in the ureter exhibited the same peculiarities, although these pedicels were probably the means of its attachment to the bladder.

This case was a rarely interesting one, not only in its unique morbid anatomy, and as showing the rapidity and extent of sedimentary processes in the urine, but also in suggesting a possible explanation of certain recurrences of stone in the bladder; while from the therapeutic aspect it is not without its suggestions.

It is evident that the hard mass felt through the abdominal walls just before death was made up by the calculi, which, although contained in separate ureters, united to form a single confused mass in the median line just above the sacrum. How long before death this could have been felt I do not know, for I had not examined the abdomen for some time. There is every reason to believe, however, that it might have been recognized at any time subsequent to the emaciation, which began during his absence from the city, in the summer, and which so impressed me when I first saw him, some time after his return. The practical hint to be deduced from it is that frequent examinations of the abdomen should be made in cases of suspected impacted calculus.

There are no *complications* peculiar to suppurative interstitial nephritis other than those mentioned as causing it or as resulting from unusual accidents of rupture, of abscess, and perforation of neighboring organs.

Diagnosis.

The diagnosis of suppurative nephritis may be easy or difficult. It is easy when there is the history of a traumatic cause followed by hematuria, and later, purulent urine, with tenderness and pain over the region of the kidney. On the other hand, while persistent inflammation of the bladder, stone in the bladder or kidney, or other cause of decomposition of urine and of obstruction to its descent, are always reasonable ground for suspicion that suppurative nephritis exists, they afford no positive proof of its presence. If, however, the urine contains pus which by its characters is known to come from a source above the bladder, and there are symptoms of any one of the conditions named as causing suppurative nephritis, its existence may be averred with tolerable certainty. And if, moreover, there is tenderness over the region of the kidney, and especially if a tumor may be mapped out, there is less doubt.

A most important practical question, one which if correctly

answered would be of infinite service in diagnosis, is the following: How long can an obstructed ureter and pelvis of the kidney exist before producing suppurative nephritis? Unfortunately there are no precise data on which to base an answer to this question. In the case of the boy Willie, whose case is related on pages 227–231, I have no doubt the condition was present when he came under my care one year after the first operation for stone. The stone was in the bladder two years before it was removed, so that the suppurative process was present within three years after impaction set in, and probably sooner. I think, however, it may be safely stated that *where obstruction of the ureter or pelvis have existed for three years, the corresponding kidney or kidneys are probably the seat of suppurative nephritis, and partially cystic.*

Pyemic abscesses of the kidney can only be suspected to be present as a part of the pyemic process, which is recognized in surgical cases presenting conditions favorable for its causation, by the occurrence of chill and other symptoms peculiar to it.

Prognosis.

The prognosis so far as recovery is concerned is unfavorable. Traumatic cases may recover if the injury is not too extensive, while very grave injuries are usually rapidly fatal. That the kidney possesses extraordinary reparative power under certain conditions is proven by the result of modern surgery wherein a kidney is often split in the search for a stone and recovers completely after the two surfaces are reapposed. Cases due to obstruction of the ureters cannot get well as long as the obstruction and irritation continue, and as their removal is often impossible such cases gradually grow worse. It is often a matter of surprise and wonder, on viewing the post-mortem appearances of cystic purulent kidneys, that the patient has lived as long with the extreme structural changes which are found to exist, the barest remnant of secreting structure being sometimes found. It is impossible to say how extensive a lesion of the kidney thus produced might be repaired, after removal of the cause. While it is not likely that the essential structure of the kidney can be reproduced to any extent, there is scarcely a limit to the supple-

mental function of the remaining remnant. While there is no positive evidence to prove that any one has recovered either partially or completely from a suppurating cystic kidney, there are numerous instances in which the victims of this disease have lived for many years, sometimes even unconscious of ill-health. It is scarcely necessary to say that such persons are in imminent danger from any cause, such as cold or acute disease, which tends to suppress the action of kidneys already crippled in their function. The following case illustrates my meaning:

The patient was a man, forty-three years of age, whose business was farming and the purchase and sale of cattle, on account of which he made frequent fatiguing journeys to the West. He first consulted me in May, 1878, and stated that his first illness was in 1864. It was evidently nephritic colic. Severe lumbar and abdominal pain continued to recur, more particularly after exposure to cold, until 1865, when he passed a small calculus. He was relieved for three years, having then another attack, during which he passed a sediment which he described as "steel-colored," and, finally, another small calculus, also "steel-colored." There was again an interval of relief until 1873, when there occurred a long series of attacks, in the last of which, in 1874, he passed quite a large stone, three-quarters of an inch long and one-third wide, which he described as having a white coating (phosphatic?). From this time up to the date of his visit, there had been more or less dull pain. His urine, which for some time previous had been dark-hued, had lately assumed a lighter hue, and while brick-dust sediment formerly was observed it had lately disappeared. Pus was first observed in his urine in 1875, by Professor Reamy, of Cincinnati. He had had no acute attack during the year 1878, up to the date of his visit to me. He had been sounded for stone in the bladder four times—twice in 1864, once in 1865, and once in 1875—with negative result.

At the time of his visit to me he was rising at night to pass water from four to eight times, and during the day could not retain it longer than one hour and a half. His urine was pale amber in hue, and had a specific gravity of 1012, and deposited a considerable amount of pus. There was also a small amount of albumin, not more than a line by Heller's acid test. The bladder symptoms were very much relieved by sandalwood oil, but he continued to have attacks of lumbar pain, always after exposure to reduced temperature, especially if he happened to be overheated at the time.

On the evening of January 15, one week after his return from a trip to the West, during an extremely cold season, he was seized with one of his attacks, the pain being chiefly on the left side. The attack was one of unusual severity, but he was relieved by a hypodermic injection of half a grain of sulphate of morphia by his physician, Dr. W. H. Barr, of Middletown, Del. The relief was complete, but he remarked to Dr. Barr, on the morning of the 17th (about thirty-six hours after the attack), that he had not passed water since two o'clock of the 15th, and had no desire to pass any.

I saw him on the 18th, reaching Middletown at two o'clock, just seventy-two hours after he had passed water. The bladder was empty, as shown by the use of the catheter. He was entirely free from pain, but was suffering a good deal from nausea, which had made its appearance the day previous. He was slightly drowsy, but he was so far conscious that he could pass the catheter on himself, as was occasionally his custom. The drowsiness, however, increased during the four hours I spent with him. He was cupped over the loins, and the cupping followed by hot cataplasms, and, in the course of the next nine hours was freely purged by elaterium, and sweated by jaborandi. The treatment availed nothing, however, in relieving the suppression. The drowsiness increased, and he died at noon of the 20th, one hundred and eighteen hours (within two hours of exactly *five* days) after he last passed water.

The *autopsy* was made by Dr. Barr, fifty-six hours after death. The bladder appeared not to have been examined, but all the other organs in the abdomen except the kidneys were normal. The latter I presented to the Pathological Society of Philadelphia. The left one had lost almost entirely the appearance which made them, in conjunction, among the most striking specimens I have ever seen. The *right* was sacculated, the cysts ranging from half an inch to one and a half inch in diameter, and were round and oval; in one of them was imbedded a calculus as large as a pea. The others were filled with a yellowish and odorless fluid containing albumin. They were not lined with an epithelium. The kidney was also somewhat enlarged, weighing six and a half ounces. The capsule was strongly adherent. *Microscopic examinations* of thin sections exhibited the appearances of interstitial nephritis, and the condition was evidently one of long standing, the result of the constant hyperemia caused by the calculi which have from time to time formed, and all of which seem to have escaped except the one still shown in position. In the parenchyma numerous infarctions of blood were seen, and the epithelium was fatty in places. The *left* kidney exhibited a great and most interesting contrast to the right. It was throughout of a bright-scarlet color, weighed seven ounces, and was hard in consistence. The capsule was only slightly adherent; surface smooth. On section, it presented a homogeneous, very bright-red color. There were no cysts. The pelvis was somewhat dilated. Microscopic examination showed large, swollen tufts, the epithelium of the tubules largely swollen and desquamated, the blood-vessels normal but overdistended by blood, with other features of a parenchymatous nephritis.

Treatment.

There is no curative treatment for suppurative nephritis without a removal of its cause, of late this has become quite a frequent event growing out of the advances in modern surgery. To the surgeon therefore most cases must be relegated. So far as the physician is concerned treatment is mainly palliative. One of the most frequent

indications is the *relief of pain* often so severe as to call for powerful anodyne measures,—*opium* and its alkaloids being absolutely essential. Hypodermic injections of the salts of morphin, in doses of $\frac{1}{8}$ to $\frac{1}{3}$ of a grain, repeated, if necessary, are favorite and effectual methods of relieving the pain, which is often due, not so much to the inflammatory process as the obstruction. Suppositories of $\frac{1}{2}$ to 2 grains of the extract of opium may be substituted. Hot fomentations are also valuable adjuvants.

The *catarrhal process* which is constant in the kidney itself, in its pelvis, and the ureter, and also in the bladder, requires treatment, and, although in consequence of the persistent operation of the cause is incurable, is nevertheless capable of decided improvement. Until recently the balsams and benzoic acid were the only remedies of any value for this purpose. Recently, however, a very efficient remedy has been added and that is *urotropin,* of which the active part is the well-known antiseptic formaldehyde. It is given in doses of from three to ten grains, three or four times a day. My usual dose is five grains four times a day, after each meal and at bedtime. Pus, when present in large quantity, is promptly diminished and when present in only small amount as promptly disappears. The glairy tenacious matter so often present in the urine in these cases is cleared away and the urine assumes its normal acid reaction. *Uriform* which is also composed of urotropin in combination with some of the balsams is also an excellent remedy given in fluidram doses three and four times a day. Resorcin and naphthalin are sometimes prescribed for a like antiseptic purpose.

Heretofore the only efficient remedies have been benzoic acid and sandalwood oil. Of these I prefer *sandalwood oil,* because it is better borne by the stomach. Given in gelatin capsules, each containing 10 drops, of which one or two may be taken three or four times a day, it will be found to have a decided effect upon the catarrhal inflammation, seen in a diminution of the amount of pus in the urine.

Benzoic acid fulfils another indication, that of securing an acid reaction of the urine, which is very often either alkaline or so faintly acid that it rapidly becomes alkaline, and thus predisposes to decomposition. The benzoic acid may be given in the form of compressed pills or perhaps better in capsules. For an adult three or four 5-

grain capsules daily are usually sufficient to keep the urine acid. Larger doses than these may be given. It may be given either alone or in conjunction with the sandalwood oil, the former being given before and the latter after a meal. To children smaller doses may be given. I usually begin with one grain three times a day and increase it. To the boy Willie, whose case is related on p. 227, I gave five grains three times a day. I have never found the careful administration of these remedies to produce derangement of the stomach, and by their use have greatly ameliorated the symptoms. Benzoic acid is sometimes advantageously combined with opiates.

The comparatively recent remedy, *methylen blue,* is an excellent one, especially for the catarrhal inflammation. Given in one- to three-grain doses I have been much surprised at its effect in diminishing the pus. It is advantageously combined with sandalwood oil and copaiba oil in a gelatin capsule.

The various vegetable diuretics, as buchu, pareira brava, etc., I have never found of any use in these affections, suppurative nephritis and pyelitis.

The constant and inevitable tendency in these cases to run down in general health, in consequence of the drain and wear and tear to which they are subjected, renders due attention to restorative measures essential, and the use of quinin, iron, milk, and other nutritious articles of diet is constantly indicated; while the dangers to which the patient is subjected from exposure require constant precautions to be observed against cold and dampness, which, by inducing acute nephritis, may lead to a rapidly fatal issue, as illustrated by the case just related.

Too much time should not be occupied in medical treatment. The advice of a surgeon should be early sought, as cure often lies in operative procedure.

SECTION XIII.

CYANOTIC INDURATION OF THE KIDNEY.

Synonym.—Passive congestion of the kidney.

CYANOTIC INDURATION IS AN INDURATED STATE OF THE KIDNEY DUE TO A SIMPLE HYPERPLASIA OF ITS INTERSTITIAL TISSUE, SUCCEEDING ON LONG-CONTINUED PASSIVE CONGESTION.

Etiology and Pathogeny.

WHILE any agency which obstructs the movement of the blood through the kidney may become a cause of cyanotic induration, the only ones encountered in actual practice are valvular disease of the heart and chronic pulmonary diseases involving considerable areas of the lung, such as emphysema, phthisis, or pleurisy, with extensive effusion, or marked adhesions.

In either event the mechanism of its production is the same. The blood is crowded into the venous side of the vascular system. In mitral insufficiency the blood is regurgitated from the left ventricle into the corresponding auricle, and thence into the lungs; the latter organs become engorged, and again resist the entrance of blood from the right side of the heart, whence it is backed into the valveless vena cava. The smaller veins of the extremities at first resist it by means of the valves with which they are provided. But the veins of the abdominal organs, including the liver and the kidneys, are without valves, and are the first, therefore, to receive the brunt of the stagnation. They become gorged with blood, and it is as though a string were tied around the renal vein, preventing the exit of the blood. What is the consequence? The connective tissue so abundantly present in the liver—and although sparsely present in the kidney, still there in sufficient quantity to become the starting-point of new formations—becomes infiltrated with *leucocytes* and *liquor sanguinis*, the natural pabulum of the tissues. Thus supplied with food, the connective tissue corpuscles proliferate. Others are formed by the

proliferation and fixation of the white corpuscles, whose outwandering is favored by a stagnated circulation. These new cells are differentiated into connective tissue fiber. The condition is really that of a true interstitial nephritis, for the process starts in the interstitial tissue, while in the so-called interstitial nephritis of the controlled kidney the process is secondary and substitutive.

In pulmonary or pleural disease the obstruction begins in the lungs instead of the heart, but the mechanism is the same.

Morbid Anatomy.

The kidney of cyanotic induration or passive congestion is hard, firm, and bluish-red as to its external surface. In the earlier stages it is enlarged simply by distension with blood. The stellate veins are unusually distinct. The capsule strips off easily, and on section the enlargement is found to involve the cortex but the veins of both cortex and medulla are engorged, the distension of the straight veins causing the medulla to appear darker in hue than the cortex. The glomerules, on the other hand, are not always engorged. The cut surface of the kidney is moist and succulent, but the microscope reveals no further changes, either in the cortex or the medulla, the epithelium being unchanged.

But the kidney is not often seen in this stage. When found at autopsies of cases of heart disease, the enlargement referred to has nearly or quite disappeared, and the kidney is slightly, if at all larger than the normal organ, though rarely, if at all smaller. The other superficial characters of hardness, smoothness, and bluish-red color, however, remain. Sometimes there appears a slight tendency to lobulation, or even a slight disposition to unevenness, by reason of certain shallow superficial depressions, but very seldom anything like a granular appearance of the surface of the organ stripped of its capsule. In this event the capsule may not strip off quite as easily as usual, but may drag small portions of the parenchyma with it.

On section the relations of the cortex and medulla are not much altered, but the succulency of the parenchyma which characterized the early stage has been replaced by a uniform hardness. The capillaries are less turgid, and contribute less of their hue to the

cortex, which is therefore paler, although the Malpighian bodies may be relatively more distinct from distension with blood. The microscope explains the cause of the induration in a moderate overgrowth of formed connective tissue. This tends slightly to contract and compress the capillaries, interfering thus with the nutrition of the parenchyma, resulting in destruction of portions of it; whence the superficial depressions of the surface alluded to.

The condition is also to be distinguished from a preëxisting granular kidney, upon which cardiac disease may have been ingrafted secondarily.

Symptoms.

The symptoms are primarily those of the disease of which it is the consequence, which I will not repeat.

They include, however, generally a dropsy, scanty urine of high specific gravity, containing usually a small amount of albumin and at times a few small hyaline casts.

The *dropsy* is always of the lower extremities, in the area drained by the inferior vena cava, while it will be remembered that that of renal disease more frequently at first involves the face and upper extremities. There also occur, however, effusions into the pleural sacs and into the peritoneum, and the hands and arms may be involved.

The *urine,* as stated, is scanty, and of high specific gravity, often 1030, and even higher. It is turbid with urates, depositing a copious sediment of them and of uric acid. The *albumin* is usually small in quantity, but may become larger if the obstruction to the movement of the blood is great. The *casts* are small, transparent, or faintly granular, and not numerous, indeed often absent. Fatty casts are also occasionally present.

Further, a kidney thus constantly engorged is more liable to attacks of acute inflammation than one which is in the normal state. Hence in such cases the urine may become suddenly bloody, highly albuminous, and contain epithelial and blood-casts, even after slight exposure, such as would be without effect upon a healthy individual. In the intervals between such attacks the blood-casts disappear entirely, while the epithelial and granular casts become much less numerous, and often disappear.

Diagnosis.

The supervention of this state of the kidney upon cardiac disease may be suspected when all the symptoms of the latter become aggravated, when the dropsy becomes peculiarly persistent, and the urine is scanty. The high specific gravity of the urine, and the presence of albumin and casts, confirm the suspicion.

Prognosis.

With the supervention of the renal involvement, the inconveniences and annoyances of cardiac disease become many times greater, while the difficulties in the way of improvement are nearly proportionately increased. Yet the results which sometimes follow appropriate and energetic treatment, and the substitution of favorable for unfavorable hygienic surroundings, such as succeed the admission of a neglected outcast to the wards of a hospital, are often astonishing. Under these circumstances it is not unusual for the dropsy to decline, the albumin and casts to disappear, and the patient to be restored to comparative comfort.

Treatment.

As intimated under prognosis, the substitution of favorable for unfavorable hygienic surroundings is the primary requisite. Shelter, warmth, rest, good food are indispensable. After this *digitalis* is our most powerful lever, and for evident reasons. We have here to deal with a dilated, weak, failing heart, unable to drive the blood forward. Its power must be increased, and we have a remedy capable of this in digitalis. But sufficient doses must be given, whether of the tincture, powder, or infusion. The infusion, freshly prepared, used to be the most reliable preparation, although much of its efficiency was due to the fact that it is given in larger doses than the other preparations, as explained on p. 129. Less than fifteen drops, or eight minims, of the tincture—equivalent to about one grain of the powder—is too small a dose for an adult. Twenty drops may be given every four hours, equivalent to about a fluiddram in the twenty-four hours. Under such doses, if the cardiac disease is not too advanced, the urine may increase, become clear, its albumin and

casts grow less, and with these also the dropsy, dyspnea, and restless, sleepless nights. Strophanthus may be substituted for digitalis, and citrate of caffein in three-grain doses every four hours may be added.

Due attention must also be paid to the bowels, for the sake of securing prompt action of the diuretics as well as the elimination which their free action secures. Even the hydragogue cathartics, such as elaterium and the salines, may be used with advantage. In these cases calomel often acts admirably. I prefer to give it in doses of three grains every three hours until twelve or fifteen grains are taken. Or the time-honored combination of digitalis one grain, squills one grain and calomel one grain may be given every three hours. It is often followed by copious diuresis.

The appended case illustrates so fully the cause, symptoms, effects of treatment, and morbid anatomy of this condition that I cannot but think it will form an appropriate and useful conclusion to this section:

Mary K., 39 years of age, married, was admitted to my wards in the Philadelphia Hospital on November 15, 1873. Both of her parents suffered from rheumatism and subsequent cardiac disease, and her mother died with dropsy, which came on after confinement. The patient herself had several attacks of rheumatism, but in other respects enjoyed fair health until about five months before admission, when she began to notice shortness of breath on exertion, together with edema of the legs and ascites. At that time she was five months advanced in pregnancy. These symptoms grew slowly worse up to the time of her confinement, after which they continued to increase even more rapidly. Her labor was quite normal, and took place five weeks before her admission to the hospital. At admission her abdomen was enormously distended, with effusions; the lower portion of the abdomen rested upon the thighs, and the friction of the opposed surfaces had caused extensive excoriation. The legs, from the feet upwards, were edematous, and there was also some edema of the hands and arms. The dyspnea was so great that she could not lie down in bed; the respirations, when she was sitting up, numbered sixty per minute.

There was no evidence of any disease of the lungs or pleura. The area of cardiac dulness was increased, and a double mitral murmur, with an aortic systolic murmur, could be distinctly heard. The pulse was feeble and frequent, beating one hundred and fifteen times a minute. The urine was diminished in quantity, high-colored and acid in reaction, and contained a large quantity of albumin, the precipitate by acid and heat being equal to at least three fourths of the bulk of the fluid tested. There were numerous *hyaline* and *fatty* casts. She was much reduced, appetite was gone, and her bowels were constipated.

She was ordered half an ounce of Basham's mixture three times daily,

twenty drops of tincture of digitalis, repeated according to its action on the pulse, small doses of elaterium to relieve the constipation, and a nutritious diet, with a small quantity of whiskey (f℥ij in twenty-four hours). Under this treatment the abdomen became somewhat less tense, a larger quantity of urine was passed, and the breathing rate fell to thirty per minute, but the pulse remained frequent, seemingly unaffected by the digitalis, although it was pushed to the limit of safety.

This improvement was but temporary, and on November 20, paracentesis of the abdomen was done. Six pints of a highly albuminous fluid were allowed to flow, when the canula was withdrawn and the aperture allowed to remain open. Two hours after the operation, the pulse, which had been beating one hundred and twenty per minute, fell to fifty, then to forty-six, and became dicrotic. The patient was, however, in every respect better; indeed, felt quite comfortable.

November 24, the pulse was seventy-two, somewhat irregular, and entirely free from dicrotism; the respiratory movements were reduced to twenty-six, and were much deeper, while the edema was greatly diminished. She passed, on an average, three pints of urine each day, which contained at this date a *few hyaline casts;* the amount of albumin was reduced to one sixth of the bulk of the urine tested. Since the operation a large quantity of fluid had trickled from the orifice in the abdomen. Quinin was added to the treatment.

Notwithstanding the continued use of diuretics (bitartrate of potash and infusion of juniper, infusion of scoparius, and free doses of digitalis), the ascites slowly increased, and on December 12 she was again tapped by Dr. Bruen, the resident physician, and one hundred and thirty ounces of fluid were removed. This was again followed by amendment, the edema continuing to diminish. By December 22 the opening of paracentesis was closed, the *urine was free from albumin, and no casts were found after prolonged and careful examination.*

On December 24, after exposure to cold, she became much worse, and by December 25, the legs were again swollen almost to bursting, and had assumed an erysipelatous hue. The respirations were hurried, the skin was hot and dry, and the urine was so charged with albumin that it became almost solid on the application of heat and nitric acid. Paracentesis was performed for the third time, fifty ounces of fluid being removed. No relief was experienced from this operation; in fact, the dyspnea steadily increased, and the pulse became so feeble that it could scarcely be counted at the wrist.

At 3 P. M. on December 27, the pulse at the wrist was extinct and no cardiac impulse could be felt, but on auscultation the heart was found to be beating one hundred and thirty-nine times a minute. Upon extending the examination to the other parts of the chest, the physical signs of pleuritic effusion were detected on the right side. At 6 P. M., as a last resort, this side of the chest was tapped, and twenty-eight ounces of liquid removed; immediately afterwards the patient felt easier, but soon began to sink, and died at 9.30 P. M.

The general plan of treatment remained the same as that already mentioned throughout the course of the illness, although, as the indications varied from time to time, the quantity of digitalis used, as well as the form

of its administration, was changed; other diuretic preparations, such as acetate of potash, juniper, sweet spirit of niter, etc., were also tried.

At the *autopsy,* which was made twenty-four hours after death, eighteen ounces of fluid were found in the right pleural cavity, and the upper part of the parietal and visceral was covered by a moderately thick layer of fresh lymph. The right lung was congested and somewhat compressed, but not at all inflamed. There was nothing abnormal in the left lung or pleura. The *heart* weighed fifteen and a half ounces. The left ventricle was dilated and hypertrophied. The leaflets of the aortic valve were thickened; most marked along the edges of the leaflets and in the corpora aurantii; the latter were increased in size, being about as large as a split pea. Both leaflets of the mitral valve were thickened, and they were fused along their edges so as to form a funnel-shaped projection into the cavity of the left ventricle, with only a slit-like opening, through which the end of the thumb could scarcely be passed; in the valve thus coalesced were calcareous deposits. The right ventricle was also moderately dilated and hypertrophied; the pulmonary and tricuspid valves were healthy.

The *liver* weighed ninety-seven ounces, and was very fatty. The *kidneys* were lobulated, and weighed, together, fourteen ounces; they were, therefore, somewhat enlarged, and also congested; but in other respects they appeared normal to the naked eye. On microscopical examination, the renal tubules were in part lined with healthy epithelium, or with epithelium which was only slightly granular; in other portions, however, the epithelium was highly fatty. There was also slight increase in the interstitial fibrillar tissue. No trace of amyloid degeneration could be detected by the iodin test.

SECTION XIV.

LARDACEOUS DISEASE OF THE KIDNEY.

Synonyms.—Amyloid disease, albuminoid disease, waxy kidney, depurative disease.

LARDACEOUS DISEASE IS THAT FORM OF CHRONIC BRIGHT'S DISEASE IN WHICH THE TISSUES OF THE KIDNEY ARE MORE OR LESS INFILTRATED WITH A PECULIAR ALBUMINOID SUBSTANCE, RESEMBLING MOLTEN WAX OR BOILED STARCH, BEST RECOGNIZED BY ITS STRIKING A DEEP MAHOGANY-RED INSTEAD OF THE ORDINARY YELLOW COLOR, WITH A SOLUTION OF IODIN.[1]

Etiology.

The dependence of amyloid disease upon cachectic states was early pointed out by the eminent Viennese pioneer pathological anatomist Rokitansky. The most frequent cause of lardaceous disease is acknowledged to be profuse and long-continued suppurative discharge, such as occurs in chronic bone disease, whatever its cause; or such discharge as constitutes the expectoration in cases of chronic phthisis and chronic bronchitis with bronchiectasia. Syphilis, independently of the tertiary conditions which it produces, is a frequent cause of lardaceous disease. Chronic dysentery, ulceration of the bowels, chronic albuminuria itself, may all become the causes of this condition. Bad forms of malarial disease, carcinoma, in fact, any

[1] I do not consider it necessary to discuss the nature of the lardaceous or waxy material. Its albuminous composition is now everywhere acknowledged, its formula being C 53.58, H 7, N 15.04, S + O 24.38 (Kekulé and Friedreich), while that of albumin is C 52.7 to 54.5, H 6.9 to 7.3, N 15.4 to 16.5, O 20.9 to 23.5, S .8 to 2 (Gorup-Besanez). The question as to whether the deposit is a metamorphosis or an infiltration is not so definitely settled, but it seems to deport itself altogether like the infiltrations, and unlike the metamorphoses; I shall therefore include it among the former until some good reason is found for altering this position. I retain the term *lardaceous disease* because it defines the physical characters of the deposit better than any other, although not the chemical; further, because it is the term adopted in the revised nomenclature of the Royal College of Physicians of London.

diseases capable of developing a cachexia have been held responsible for amyloid disease. Amyloid disease is not limited to the kidneys and in its more advanced stages at least invades simultaneously the liver, spleen, and alimentary canal.

Age and Sex.—The sexes are equally subject to lardaceous disease, but as men are more frequently exposed to its causes, it is in them rather more common. Very young children are rarely affected, for evident reasons. Dr. Dickinson has known a case to be fatal at five years of age, and refers to a case of Dr. Gee, in which the lardaceous change was found in the spleen but not in the kidneys of a boy two and a half years old who had had a profusely discharging abscess of the thigh. The following table from Dickinson shows the distribution as to age of sixty-one cases:

Age.	No. of Cases
0 to 10	3
11 to 20	11
21 to 30	21
31 to 40	10
41 to 50	10
51 to 60	3
61 to 70	3
Over 70	None

Morbid Anatomy.

The incipient stages seldom present alterations recognizable by the naked eye unaided by reagents. But if, after section of the kidney, the cortex be treated by a solution of iodin and iodid of potassium,[1]

[1] *The Test Solutions.*—The best test solution for macroscopic purposes is one made by dissolving .161 grams iodin by the aid of .321 grams of iodid of potassium in 30 c.c. of water (2½ grains iodin, 5 grains iodid of potassium to a f℥ of water). The solution contains about one half per cent. of iodin. For microscopic preparations a solution weaker than the above, or a one fourth per cent. of iodin dissolved by twice the quantity of iodid of potassium, is more suitable, and sometimes a solution containing as much iodin as water alone will take up answers best. There is a decided difference of opinion as to the effect of the subsequent addition of sulphuric acid to preparations treated with iodin. Virchow[1] originally announced that a blue or violet color was assumed by the amyloid tissues thus treated. In this he is sustained by all subsequent German pathologists, including the most recent. Most English writers, on the other hand, either deny this reaction

[1] Virchow's Archiv, Bd. vi.

altogether, or speak of it as uncertain and unreliable. Thus Dickinson[1] says: "This appears to be an error of observation, partly arising from the fact that when sulphuric acid acts upon iodid of potassium—a salt generally present in the test solutions used—a precipitaton of iodin takes place, which usually blackens the tissue." So, also, a Russian writer, Morochowetz,[2] says the reagent is useless because sulphuric acid produces with iodin solutions alone, a violet or blue coloration by a precipitation of iodin crystals. The discrepancy is undoubtedly due to methods of manipulation. Boettcher[3] and Kyber,[4] whose papers are among the most careful and practical, both declare that a delicacy is obtained by the use of the sulphuric acid which far exceeds that of any other test. Both ascribe the want of success to the use of too concentrated sulphuric acid. Kyber recommended an iodin and iodid of potassium solution of the above strength for macroscopic work, and watery solutions of iodin for the most part for microscopic preparations; and sulphuric acid *diluted* fifteen to twenty times with water. Boettcher advised the solution of iodin and iodid of potassium, above given, for both macroscopic and microscopic work, and 7 to 8 c.c. of sulphuric acid to 100 c.c. of water. Kyber also says that in the treatment of sections by the iodin solution, the normal tissues should not be allowed to assume a deeper tint than a pure yellow. If they are *browned* the section is worthless for further treatment, and should be thrown away.

The Anilin-violet Solution.—Jürgens[5] and Heschl[6] in Germany and Cornil[7] in France were the first to call attention to anilin-violet as a test for the lardaceous substance, although the late Dr. Bennett, of Edinburgh, had previously called attention to the fact that carmine and magenta produce distinct coloration. The anilin-violet, of which a 1 per cent. solution is suitable, strikes a red or pink color with the amyloid material, which contrasts with the violet staining of the normal tissues, and beautiful preparations for the microscope may be thus obtained. Eberth[8] and Fürbringer[9] prefer this test solution, which the former says is decidedly to be preferred to the iodo-sulphuric acid test to demonstrate the first beginnings of the amyloid change, and Fürbringer also says it is a more delicate test. Kyber says it is this very stage which is best shown by the iodo-sulphuric test. Eberth also says that the anilin-stained microscopic preparations also keep the longest, which is probably true. The blue tint received by the normal tissues, however, rapidly fades, so that the contrast is not maintained.

[1] Op. citat., p. 231.

[2] St. Petersburg Med. Weekly, vol. iii, 1878, p. 75.

[3] Boettcher, Arthur, Beobachtungen über die amyloide Degeneration der Leber, Virchow's Archiv, Bd. 72, 1878, s. 506.

[4] Kyber, Eduard, Weitere Untersuchungen über die amyloide Degeneration, Virchow's Archiv, Bd. 81, 1880, s. 1.

[5] Eine Neue Reaction auf Amyloidkörper, Virchow's Archiv, Bd. 65, 1875, s. 189.

[6] Sitzb. d. Wiener Akad., iii. Abth., Oct., 1876.

[7] Archiv de Physiol. Norm. et Path., t. vii, p. 673, Paris, 1875.

[8] Eberth, C. J., Die amyloide Entartung, Virchow's Archiv, Bd. 80, 1880, s. 138. An excellent paper.

[9] Fürbringer, Paul, Zur Diagnose der amyloiden Entartung der Nieren, Virchow's Archiv, Bd. 71, 1877, s. 400.

numerous mahogany-red points make their appearance; or if by a solution of violet-anilin, as many red or pink points. These are the Malpighian bodies, whose capillary tufts are the first to be affected by the change. The kidney in this early stage is normal in size, or very slightly enlarged. Its capsule strips off readily, leaving an organ which exhibits no peculiarities, or presents a paleness or translucency which readily escapes notice, though the translucency may be more easily recognized at the edges of a thin section. Very often too, these changes are completely overshadowed by others, which are apt to be associated with these slight degrees of lardaceous disease. Thus the large white kidney of chronic parenchymatous nephritis may exhibit this amount of lardaceous change, which may altogether escape notice unless iodin be used. Hence *the iodin reaction should be tried upon all kidneys* whose morbid anatomy we may be investigating. Under the microscope, however, thin sections exhibit a transparency which does not require iodin to secure its recognition, while distinct demonstration results from its addition to such preparations.

In a more advanced stage of lardaceous change the kidneys are both enlarged, usually symmetrically, but the extreme degrees of enlargement are usually associated with fatty degeneration of the renal epithelium. Such organs were a pair weighing 23 ounces, which came under Dr. Dickinson's[1] notice. Dr. Johnson[2] refers to a case in which the two kidneys weighed 28 ounces. Rindfleisch[3] has seen a single instance of that very rare condition, *complete* lardaceous infiltration, in which the basement membrane of the uriniferous tubes, as well as the capillaries, were infiltrated, the kidney being enlarged to nearly twice its normal size. In the uncomplicated forms of advanced lardaceous disease the capsule is not adherent, but if interstitial changes exist to any extent it is. The surface of the kidney after the capsule is removed is pale and anemic; occasionally the stellate veins are conspicuous. The characteristic translucency may even be recognized in the organ in bulk, but in sections is more striking. When the change is present in high degree the edges of a thin sec-

In my own experience I have found the simple iodin reaction without the use of sulphuric acid sufficiently distinctive for practical purposes.

[1] Dickinson, op. citat., p. 249.

[2] Johnson, op. citat., p. 104.

[3] Rindfleisch, Path. Histology, New Syd. Soc. Trans., 1873, Vol. II., p. 167.

tion are almost as translucent as a similar section of bacon. On bisection the cortex is seen to be enlarged; it is pale, anemic, waxy, firm, and resisting. The pyramids are normal in hue and extent. The iodin solution added to such a kidney produces its peculiar coloration, not merely in the Malpighian capillaries, but also in the afferent and efferent vessels and the vasa recta of the pyramids.

In a still later stage, that of *atrophy,* the kidney becomes contracted, diminished in size, rough, and even distorted in shape. The capsule is adherent, and on section the cortex is found narrowed, sometimes as much so as in the contracted kidney of interstitial nephritis.

The most diverse views as to the cause of this *contracted* lardaceous kidney are held by authors. Thus Dr. Grainger Stewart and Dr. Johnson ascribed it to a wasting and destruction of the epithelium and tubules; Virchow, Klebs, and Bartels to a simultaneous or previously existing contracting disease. Dr. Dickinson believes that it is due to the contraction of a new-formed intertubular tissue, which is the result of an irritant property of the lardaceous material, similar to what occurs in the second stage of parenchymatous nephritis. This, once formed, contracts in accordance with its invariable tendency, and produces the rough granular appearance and diminished size of the organ. Rindfleisch also supposes the amyloid change of the vessels to be primary; that the mechanical obstruction thus resulting induces a collateral hyperemia of the cortex; this produces the conditions favorable to a cellular hyperplasia, which succeeds immediately or upon the addition of some further irritant. It may be that the lardaceous disease is ingrafted on a previous interstitial nephritis.

As to the *histology* of this disease, in the first stage, in which the naked eye often fails to detect anything abnormal without the aid of iodin, a microscopic examination of thin sections reveals a lustrous or waxy appearance of the Malpighian bodies, due to an infiltration of the capillaries by the peculiar lardaceous material. The capillary walls are thus thickened and the glomerule enlarged. At this stage there is no visible alteration in the renal tubules or their epithelium.

In the second stage the larger vessels, the vasa afferentia and efferentia, in the cortex, and also the vasa recta of the cones are invaded

by the amyloid substance. The other capillaries of the cortex are also involved, and an exudation takes place into the tubules of a glistening material which forms casts. I have already discussed these casts on p. 62. Dickinson[1] believes the material to be, occasionally at least, identical with the lardaceous substance, although he admits that it very rarely exhibits the peculiar reaction with iodin. According to Grainger Stewart, it presents neither the peculiar translucency nor the coloration with iodin which are characteristic of the waxy degeneration, but exactly resembles the material of hyaline tube-casts.[2] Cornil has never found them to strike the red reaction with the anilin-violet solution, while Jürgensen obtained the reaction with this solution in several instances. The result of my own efforts in treating these casts with iodin after their extrusion from the tubes into the urine, is shown in the plate opposite p. 62. It is to be remembered, too, that similar casts are found in the tubules in other forms of chronic renal disease.

The *arteriole walls* are thickened by an invasion of both interna and media. This thickening is attended by an extraordinary distinctness of the muscular fiber cells of the circular coat. The middle or muscular coat, since the original announcement by Virchow,[3] has always been considered the first involved. But Cornil[4] held that in every case the lesion is localized in the internal coat of the renal vessels. It is true the interna is sometimes disproportionately changed in the small arteries, but this need not alter the seat of primary deposit. A very distinct demonstration of the thickened muscular walls is obtained by injecting the kidney with a transparent injecting mass, and then examining sections by the microscope, although the injection of such kidneys is very difficult.

As to the involvement of these *tubules* and their *epithelium* there is some difference of opinion. Dr. Johnson[5] insisted that, in the large majority of instances, the changes in the secreting structures are primary, and further that he has not met with a single case in

[1] Op. citat., p. 253.
[2] Op. citat., p. 126.
[3] Cellular Pathology, Chance's Translation. Philadelphia, 1860, p. 417.
[4] Archives de Physiol. Normal. et Pathol., T. VII., 1879.
[5] Op. citat., pp. 104–106.

which thickening of the blood-vessels in any form was unassociated with extensive changes in the secreting structure of the kidney.

Klebs and Rindfleisch hold that the lardaceous change only rarely attacks the basement membrane and epithelium. The latter held that amyloid infiltration of the tubes is found chiefly in the papillæ, where it is accompanied also by similar changes in the vessels, especially the vasa recta; thence it radiates into the pyramids of Ferrein. He had never seen it in the convoluted tubes, though admitting the possibility of its occurrence there, where it is hard to distinguish the diseased tubes from the vessels which are similarly affected.[1] Grainger Stewart has seen the cells present the swollen, dimly translucent appearance, but never the peculiar coloration. He has often found the basement membrane thickened and waxy-looking, without any coloration taking place on the application of iodin, but on a few occasions he has seen that coloration.[2] Bartels[3] says, "a similar change may subsequently affect the tunica propria and epithelium of the tubuli uriniferi." Dickinson describes alterations in the tubules and their lining cells, due to infiltration with lardaceous material, as the result of which "their normal structure is displayed with abnormal distinctness." . . . "Fibrinous casts are abundantly formed and displaced, and yet the epithelial lining of the tube undergoes no disturbance."[4] Axel Key also admitted the involvement of the cells, and held that the waxy casts in the amyloid kidney are the direct result of the fusion of the epithelial cells which have succumbed to the amyloid infiltration. Boettcher[5] describes the change in the renal cells as "decided," and Cornil[6] said they sometimes become the seat of amyloid infiltration, when they are transformed into little glassy blocks which exhibit the characteristic coloration with iodin and sulphuric acid.

The facts appear to be these: The blood-vessels are first involved, for the excellent reason that, whatever is the exact morbid condition,

[1] Rindfleisch, op. citat., p. 145.
[2] Grainger Stewart, op. citat., p. 127.
[3] Bartels, op. citat., p. 519.
[4] Dickinson, op. citat., p. 254.
[5] Boettcher, Virchow's Archiv, Bd. 72, 1878, s. 534.
[6] Manuel d'Histologie Pathologique. Paris, 1876, p. 1017; American Translation, 1880, p. 46.

the source of the infiltrating material is the blood. Naturally, therefore, the walls of the vessel-walls become first invaded. Beyond are the epithelium and basement membrane, which are also capable of the alteration. That the cells of the liver become thus the seat of waxy change all except E. Wagner[1] admit, and reasonably also may those of the kidney, with the basement membrane on which they are seated. We would expect them, however, to be later involved, while the change may be delayed indefinitely. When cells become the subject of the lardaceous change, they acquire a peculiar translucent glassy hue, are enlarged, and lose all distinctness of outline, neighboring cells appearing to be fused together. The basement membrane also becomes thickened and translucent.

It is also very common for the epithelium of the cells to be in a state of fatty degeneration, and the capillary walls to contain aggregations of fat-globules, while the urine in the latter stages contains oil-casts and fatty cells.

From the above considerations it is evident why the kidney in the later stage of amyloid disease is enlarged. The arterioles and capillaries are thickened and occupy more bulk, while the cells are swollen, the basement membrane of the tubules thickened, and the tubes themselves more or less distended with the material of the casts.

In the lardaceous contracted kidney, or as some would have it, the third or contracting stage, minute examination reveals, in addition to the appearances described, the hypernucleated intertubal overgrowth, already referred to. Cysts are occasionally present for the same reason that they are found in the granular contracted kidney of interstitial nephritis, and an approximate rough granulation may also be assumed.

It is not very rare to find at least the Malpighian capsules in the large white kidney the seat of the lardaceous change, but the iodin test is, in my experience, generally necessary to demonstrate it. Dr. Johnson first suggested that it is the direct result of the drain upon the system incident to the large albuminuria which attends parenchymatous nephritis. But Dr. Dickinson[2] says that, while among his earlier observations he thought he found reason to admit

[1] Archiv der Heilkunde, Bd. II., s. 486.

[2] Op. citat., p. 245.

this cause occasionally, later experience has served to show that where the lardaceous condition is associated with one of the other forms of renal disturbance, the former, lardaceous, is usually the primary change. Bartels also calls attention to the very frequent coincidence of amyloid disease of the kidney with other renal affections, and especially with chronic parenchymatous nephritis in both kidneys, of which, he says, both processes are apparently "coeffects of one and the same cause."

Dr. Dickinson's views are certainly not sustained by those cases occasionally met, in which are found, first, in a marked degree, the causes which all acknowledge to be most efficient in producing lardaceous disease; second, copious albuminuria and casts, with extreme dropsy, and, finally, death, with the post-mortem examination revealing the most typical form of large white kidney, in which, however, the iodin solution also reveals amyloid infiltration of the Malpighian tufts only. On the other hand, the fact, which can hardly be controverted, that the same set of causes is capable of producing either disease, makes it reasonable to believe, that when both conditions are present, they are " coeffects of one and the same cause."

Symptoms.

The symptoms of amyloid kidney cannot be said to be distinctive. An individual who has had syphilis, or who has phthisis, chronic bronchitis, bone disease, or other affection in which there is an exhaustive drain, observes that he feels always intensely weary, has no disposition to exertion whatever, or even to rise from his bed. Increased frequency of micturition may be observed at the same time, such that he may have to rise once or twice during the night to micturate. But this symptom may be totally absent. Accidentally, perhaps, a somewhat copious albuminuria is discovered. At first no casts are met, or they are exceedingly scanty, a single one being found in several successive slides, or one or two may be found on a single slide. Those which are noted are hyaline or faintly granular. Later, a slight edema of the feet may make its appearance while the patient is up and about, but disappears during the night while he is in bed. The albuminuria is now copious but still varies,

and casts may be more numerous, or may still be scanty and continue hyaline or faintly granular. The urine is now decidedly increased in quantity, 1,600 to 2,500 c.c. (53 to 80 oz.), its specific gravity low, 1005 to 1015. The patient exhibits a worn and cachectic appearance, which may be present earlier, and is sometimes the first symptom which strikes the attention of the observer. There is sometimes a peculiar fetor of the breath. Still later, all these symptoms increase; the dropsy is persistent, the urine loaded with albumin, and, in addition to the ordinary delicate hyaline casts, may contain the glistening waxy casts. Fatty casts and free fatty epithelium from the tubules of the kidney may be superadded, as well as free oil-drops. Epithelial casts are infrequent. Dropsy now becomes general, involving the arms, trunk, and face, as well as the lower extremities, and even the serous cavities, the peritoneum, pleura, and occasionally also the pericardium. Edema of the lungs may also occur as a serious complication. In general, however, it may be stated that dropsy is seldom as extreme as in parenchymatous nephritis.

Towards the close of the disease, the urine, which had been increased, becomes diminished in quantity, but is seldom suppressed, indeed seldom falls below (600 c.c.) 20 ounces.

Of the solid chemical constituents, it may be said of all, that they are, as a rule, slightly diminished, but not sufficiently to influence the course of the disease. It is in consequence of this that uremia is almost unknown in lardaceous disease, the urea and extractives being eliminated in sufficient amount to avert this evil. Bartels reports a single case in which uremic convulsions were present. In forty-eight cases reported by Dickinson in which there were autopsies, there were three instances of uremic convulsions, two of coma, and one of unnatural drowsiness.

But lardaceous disease of the kidney never occurs alone. It is always accompanied by similar changes in the liver, spleen, and often of the intestinal canal. Hence, evidences of alterations in these organs are more or less marked. Thus the percussion areas of the liver and spleen are almost always enlarged, and the blood-vessels of the stomach and intestines are often involved. In the former event obstinate *vomiting,* and in the latter equally obstinate *diarrhea* results. The latter is far more frequent than the former.

It is by these latter symptoms rather than those pointing to renal disease by which the affection is recognized.

As to *duration,* the disease generally runs a very chronic course, which is limited only by the disease of which it is a complication. As such it is always of shorter duration than interstitial nephritis, and may be shorter than chronic parenchymatous nephritis, although the latter affection and lardaceous disease more closely resemble each other in respect to duration. It is only reasonable, that when superadded to previously existing exhausting disease, the two would hurry an issue more rapidly than either alone. Yet the renal affection is subject to the same improvement to which the general or local one may be subject.

Complications.

So much has already been said of what may be properly called the causal complications of lardaceous disease that they require no further mention than enumeration in this connection. They are tubercular phthisis, syphilis, caries, necrosis, long-continued suppuration from any cause, and long-continued exhaustive drains upon the system, including albuminuria.

As common results of the same causes, rather than as complications, are to be mentioned amyloid disease of the liver and spleen with enlargement, and amyloid disease of the blood-vessels of the gastro-intestinal tract, with the vomiting and diarrhea resulting from these. After these, lardaceous disease is subject to the complications of the other forms of renal disease, but they are less numerous. Bronchitis occurs most frequently. Pleural, pericardial, and peritoneal effusions are very rare, as are also hypertrophy of the heart and retinal changes. Endocarditis, erysipelas, and epistaxis have occurred.

Diagnosis.

There are some instances in which lardaceous disease is easily recognized. In many there are no distinctive signs which point to its presence. If a patient has had syphilis with secondary and tertiary symptoms, or has long been a victim to phthisis, and he is discovered to be edematous, and to have a large albuminuria, with

waxy hyaline and fatty casts, and an enlarged liver and spleen, and obstinate diarrhea, there can be little doubt but that lardaceous disease is present. But where neither of these two general diseases are present, or the phthisis has not existed a very long while, or there is not decided evidence of enlarged liver and spleen, we cannot be certain. While it is never safe to diagnose lardaceous disease without the presence of enlarged liver and spleen, the presence of these enlarged organs along with large albuminuria, and the other symptoms which attend it, do not necessarily imply lardaceous disease. The symptoms and course of the disease, particularly in its latter stages, are so like those of chronic parenchymatous nephritis that it is often impossible to distinguish the two. Further, there is every reason to believe that chronic nephritis is sometimes caused by the same dyscrasic conditions as produce the lardaceous disease. In such cases, therefore, a diagnosis is impossible. Dr. Paul Fürbringer,[1] in an article already alluded to, reported four cases which so admirably illustrate these difficulties that I feel justified in occupying the space necessary to mention them. In all four cases there was chronic phthisis with ulceration of the bowels. In all four he was fortunate enough to be able to watch the appearance of that series of symptoms which are accepted as pointing to the diagnosis of amyloid disease of the kidney. In all four was there splenic and hepatic enlargement, and in all four, autopsies were made. In case one, neither the kidney, liver, nor spleen responded to the iodin test, but the kidney and spleen responded to the anilin-blue test. There was, therefore, amyloid disease, which was uncomplicated by chronic nephritis. In cases two, three, and four, there was no reaction on the part of kidney, liver, or spleen to either test. In case two, there was neither amyloid disease nor chronic parenchymatous nephritis,[2] and cases three and four were well-marked cases of parenchymatous nephritis.

Finally, the two conditions may exist jointly, where a parenchymatous nephritis may be ingrafted on a lardaceous kidney; or the two may result from the same cause, or possibly the lardaceous

[1] Zur Diagnose der amyloiden Entartung der Nieren, Virchow's Archiv, Bd. 71, 1877, p. 400.

[2] Fürbringer does not say what form of kidney disease existed here, but leaves us to suppose that the kidneys were normal.

disease may be the result of the exhaustive albuminuria of a previous chronic nephritis, as originally suggested by Dr. George Johnson. So that in a certain number of cases, also, the separation of the two is impossible.

When these combinations do not exist the urine in lardaceous disease is more abundant and lighter in color, casts are fewer and hyaline, with a few oil-casts, while in parenchymatous nephritis they are more numerous and include every variety. Yet there are cases of parenchymatous nephritis in which the urine presents precisely these characters. Blood-corpuscles are rarely found in the urine of lardaceous disease, while they are occasionally present in that of chronic nephritis. If the original disease, the possible cause of a lardaceous disease, has entirely disappeared before the renal malady was detected, the chances of the latter being lardaceous disease are decidedly fewer.

The only other form of renal disease which it is at all possible to confound with lardaceous disease is interstitial nephritis. But in this we have the almost total absence of dropsy, small albuminuria, and scanty sediment, in which granular and hyaline casts are found. While the quantity of urine is increased in both these forms of chronic Bright's disease, the quantity is larger in interstitial nephritis. Hypertrophy of the left ventricle, an almost invariable symptom in contracted kidney, is very rare in lardaceous disease, while enlargement of the spleen and liver are common, and do not occur in interstitial nephritis.

Contracted kidney may also be associated with lardaceous disease. With regard to this relation, Bartels says he would prefer to consider the gradual cachexia produced by the genuine contracting kidney as the primary mischief and as the cause of the secondary amyloid degeneration of the vessels of the kidney. Why he should admit this, and yet not admit that the same result may be brought about by the cachexia of parenchymatous nephritis, which is so much more marked, I cannot understand. I should prefer to consider the combination an accidental one, or the interstitial disease secondary to the lardaceous disease, the amyloid material acting as an irritant and producing the interstitial hypernucleation and fibrosis in the manner already alluded to. However, all is speculation.

Prognosis.

In the matter of prognosis much depends upon the presence or absence of the original disease causing the lardaceous change in the kidneys. If the former cannot be cured the effect of the latter can only be to hurry on the unfavorable termination, although it is subject to the abatements as well as exacerbations of that affection. If the original disease is curable, and the patient young, there is no limit to the possible improvement, although it is scarcely likely that the diseased structures are ever restored to their normal state. But as it is unlikely that all the renal vessels are involved in the change, and the organ itself, especially before its complete development is attained, is one capable of an extraordinary degree of supplemental function, it is not impossible that there may be a complete restoration of function.

If the patient be past middle life, even if it should happen that the original disease has disappeared, the probabilities of recovery are a minimum, while a decided degree of improvement is not impossible. If the stage of alteration of the blood-vessels of the stomach and intestine, as attested by obstinate vomiting and diarrhea, be reached, the disease is necessarily rapidly fatal.

Treatment.

Of lardaceous disease it may be said with greater emphasis than of any other form of renal disease, "an ounce of prevention is worth a pound of cure." A due appreciation by surgeons and syphilographers of the causes of lardaceous disease would prevent the occurrence of many cases; the timely amputation of a limb, long the seat of suppuration, and the thorough treatment of syphilis being all that is necessary to accomplish this. To this end also frequent examinations of urine should be made by the surgeon in charge of cases of the kind so often referred to, and the slightest indication of albuminuria should be the signal for prompt interference, if such be possible, while the possibility of the occurrence of this renal complication should always be before the surgeon's mind. There is reason to believe that this form of renal disease is growing more infrequent with the prompter treatment of surgical diseases and the practice of antiseptic methods.

In syphilis the faithful and persistent use of remedies for a sufficient time after all symptoms of the primary and secondary affections have disappeared is essential. From a somewhat careful examination of the subject, rather than from personal experience, I am satisfied that the "continuous," rather than the "intermittent," treatment of syphilis, by small doses of mercurials long continued, is the plan most likely to secure the eradication of the disease, and subscribe heartily to the dictum of Dr. E. L. Keyes, announced in his paper read before the International Medical Congress[1] in Philadelphia, so long ago as 1876:

"I think that a case treated from the first symptom should receive mercury continuously *in small doses* for a period not less than two and a half years, or, in any event, until at least six months have passed after the entire disappearance of the clearly syphilitic symptoms." By small doses are meant doses of one fiftieth to one thirty-fifth of a grain of the biniodide. This is practically the older treatment of Ricord, although he would also use iodid of potassium six months after he had discontinued the use of mercury. The experience of syphilographers during the thirty years since Keyes wrote the above has only tended to confirm these views.

With regard to phthisis, a greater stimulus to our efforts both to prevent and cure than already exists is scarcely possible, while the futility of those efforts in the very large number of cases is very well known. In the control of this disease, too, the twenty years which have elapsed since the first edition of this book appeared has furnished encouraging progress, for whether as the result of prophylaxis or treatment there has been a falling off of fully ten per cent. in the ratio of deaths from this as compared with other causes.

If the causing lesion continues to exist, the treatment of the lardaceous disease is the treatment of the former,—if it is syphilis, iodid of potassium and mercurials are indicated; if phthisis, life in high altitudes, cod-liver oil, creosote, creosotal, iodoform, iron, quinin, an abundance of nourishing food, in which milk, cream and eggs should be conspicuous, alcohol and restorative measures generally, together with fresh air and suitable exercise.

[1] E. L. Keyes, Treatment of Syphilis, Transactions of the International Medical Congress. Philadelphia, 1877.

Supposing the original disease to have disappeared, the measures of treatment indicated are precisely those of parenchymatous nephritis and its complications, for the details of which the reader is referred to the chapter on that affection. Of chalybeate preparations the iodid of iron naturally commends itself.

As to special modes of treatment directed to the disease, there is the usual uncertainty. Bartels recommended the use of iodid of potassium as curative, believing he was indebted for the favorable issue of the cases which recovered under his care to that remedy, although he did not claim to know how it acts upon the diseased walls of the vessels. He supported, at the same time, the general nutrition by preparations of iron, vigorous diet (meat and milk), and good wine, and maintaining sufficient action of the skin by baths. Dickinson also recommends iodid of potassium when the disease is of syphilitic origin, directing the remedy to the affection causing the lardaceous condition rather than to the latter. He also endeavors to compensate the loss which the system suffers in exhaustive suppuration, not by general diet alone, but by salines, chiefly potash salts, and has reason to be well satisfied with the results obtained. Senator, Tirard, Saundby and modern authors generally rely mainly on the hygienic restorative and dietetic plan of treatment. Liebig's extract of beef should be especially useful under these circumstances, as it supplies the saline constituents of beef in a concentrated form.

The treatment of complications is in no way peculiar, and has been so fully covered in previous sections that no further allusion is here required.

DIABETES.

SECTION I.

DIABETES MELLITUS—GLYCOSURIA.

NOTWITHSTANDING the numerous and important additions which are constantly being made to our knowledge of glycogenesis, we are still far wanting in that precise information necessary to justify a classification of diseases of which glycemia and glycosuria are essential symptoms. Until such information is acquired we may define diabetes mellitus as AN ABNORMAL CONDITION OF THE ECONOMY CHARACTERIZED BY AN EXCESSIVE SECRETION OF URINE CONTAINING GLUCOSE, DUE TO DERANGEMENT OF THE GLYCOGENIC FUNCTION OF THE LIVER, OR TO DEFECTIVE METABOLISM OF THE NORMALLY PRODUCED GLUCOSE, OR BOTH; ASSOCIATED AT TIMES WITH EVIDENT LESIONS OF THE NERVOUS SYSTEM, AT OTHERS WITH MORBID CHANGES IN THE PANCREAS AND AT OTHERS WITH UNDISCOVERABLE LESION.

Distribution of the Disease—Age and Sex.

Diabetes is not a very common disease anywhere, but there appear to be differences in the frequency of its occurrence in different countries, though its distribution appears to be becoming more equalized as habits of life and customs are becoming similar throughout the world. Thus when the first edition of this book was published the disease seemed more common in England than in the United States. This is apparently not the case at present. Statistics are proverbially unreliable, but in Philadelphia, where we may expect to find a fair combination of the various causes of the disease, together with as much accuracy as can be expected, there were during the past thirty-one years, from 1870 to 1900, inclusive, 1,543 deaths from diabetes out of a total of 620,068, stillborn excluded, or 1 in

402, as will be seen from the following table, compiled from the records of the Philadelphia Board of Health, through the kindness of its presidents, the late Dr. William H. Ford and Mr. Lewis T. Good.

	Years.	Total Deaths, Stillborn Excluded.	Deaths from Diabetes.	Males.	Females.	Ratio.
1	1870	15,317	18	9	9	1 in 850
2	1871	15,485	17	11	6	1 in 910
3	1872	18,987	13	5	8	1 in 1,460
4	1873	15,224	14	10	4	1 in 1,087
5	1874	15,238	11	7	4	1 in 1,385
6	1875	17,805	20	14	6	1 in 890
7	1876	18,892	19	9	10	1 in 994
8	1877	16,004	17	10	7	1 in 941
9	1878	15,743	21	16	5	1 in 749
10	1879	15,743	26	14	12	1 in 605
11	1880	17,711	30	19	11	1 in 590
12	1881	19,515	25	15	10	1 in 781
13	1882	20,059	28	20	8	1 in 1,716
14	1883	20,076	39	21	18	1 in 1,515
15	1884	19,999	29	21	8	1 in 690
16	1885	21,392	48	33	15	1 in 446
17	1886	20,005	42	31	11	1 in 476
18	1887	21,719	49	29	20	1 in 443
19	1888	20,372	52	36	16	1 in 392
20	1889	20,536	64	33	31	1 in 321
21	1890	21,732	55	28	27	1 in 395
22	1891	23,367	64	35	29	1 in 365
23	1892	24,305	84	45	39	1 in 289
24	1893	23,655	72	35	37	1 in 328
25	1894	22,680	92	48	44	1 in 246
26	1895	23,796	92	52	40	1 in 259
27	1896	23,982	92	53	39	1 in 261
28	1897	22,735	80	38	42	1 in 284
29	1898	23,790	107	48	59	1 in 222
30	1899	23,796	114	48	66	1 in 209
31	1900	25,078	109	57	52	1 in 230
	31 years.	620,068	1,543	852	691	1 in 402

The most important fact to be learned from this table is the very rapid increase in the number of cases of diabetes mellitus in Philadelphia during the past 20 years. During the first 13 years from 1870 to 1882 inclusive the ratio of deaths from diabetes to the total number was somewhat irregular, but showed no essential increase at the end of the 13 years. During the last 18 years the ratio increased from one in 850 in 1870 to one in 209 in 1899, falling again to one in 230 for 1900. For the whole 31 years the ratio is one to 402, more than double that of 1870.

Through the kindness of my friend, Dr. Hermann M. Biggs, Health Officer of New York City, I am able to present the

DEATHS AND DEATH RATES FROM DIABETES, OLD CITY OF NEW YORK, 1883–1902 INC.

Years.	Population.	Total Deaths.	Deaths from Diabetes.	Rate per cent. of Total Deaths.	Death Rate from Diabetes per 100,000 of Population.
1883	1,318,264	34,011	68	0.20	5.16
1884	1,356,764	35,034	68	0.19	5.01
1885	1,396,388	35,682	63	0.18	4.51
1886	1,437,170	37,351	82	0.22	5.71
1887	1,479,143	38,933	105	0.27	7.10
1888	1,522,341	40,175	117	0.29	7.69
1889	1,566,801	39,679	118	0.30	7.53
1890	1,612,559	40,103	130	0.32	8.06
1891	1,659,654	43,659	130	0.30	7.83
1892	1,708,128	44,329	123	0.28	7.20
1893	1,758,010	44,486	137	0.31	7.79
1894	1,809,353	41,175	166	0.40	9.17
1895	1,873,201	43,420	203	0.47	10.84
1896	1,906,139	41,622	214	0.51	11.22
1897	1,940,553	38,877	202	0.52	10.41
1898	1,976,572	40,438	238	0.59	12.04
1899	2,014,330	39,912	205	0.51	10.18
1900	2,053,979	43,227	233	0.54	11.34
1901	2,095,686	43,3c7	359	0.83	17.13
1902	2,139,632	41,704	308	0.74	14.40
		GREATER CITY.			
1898	3,272,418	66,294	345	0.52	10.54
1899	3,356,722	65,343	301	0.46	8.96
1900	3,444,675	70,872	357	0.50	10.36
1901	3,536,517	70,720	503	0.71	14.22
1902	3,632,501	68,112	471	0.69	12.96

NOTE.—The sudden and considerable increase in the number of deaths and rates during the year 1901 and 1902 is explained by the adoption of the Bertillon system of classification of causes of death, in which preference is given to diabetes as the cause of death, when it is jointly stated with other causes except deaths from violence.

The total deaths from diabetes in the United States during the census year of 1900 was 4,672, of which 2,650 were males and 2,022 females, and the proportions of deaths from this disease in 1,000 deaths from all known causes was 4.7, while in 1890 the corresponding ratio was but 2.8. Differently put, one death in every 222 in the United States was from diabetes in the census year of 1900. Again the

death rate in 1900 was 9.3 per 100,000 of population; in 1890, it was 5.5; while in old New York City it was 11.34, in New York City it was 8.06. In the city of Chicago for 1890 it was 3. This is in marked contrast with .6 in 1864.

In England and Wales the death rate from diabetes in 1899 was 8.6 per 100,000 of population, nearly the same as in the United States. I have no recent statistics showing the ratio of deaths from diabetes to other deaths in England and Wales, but from R. T. Williamson[1] I learn that the reports of the Registrar-General for the last 45 years show that the number of deaths registered as due to diabetes has steadily increased.

Furthermore, according to W. H. Dickinson, at the time his book was published the disease was more prevalent in the agricultural counties of England and of this the cooler ones, Norfolk, Suffolk, Berkshire, Huntingdon. According to Senator it is prevalent in France, in Normandy; it is particularly rare statistically in Holland, Russia, Brazil and in modern times in Thuringia and Wurtemburg. It is common in certain regions of India, especially Ceylon, and of East Indians the Hindus seem to suffer most and after these, Mahomedans, Christians and other sects.

The following table showing the ratio of deaths from diabetes to the total number of deaths, quoted by Williamson from B. C. Sen,[2] pertains to Calcutta. The mortality from diabetes per 1,000 deaths was as follows:

In 1876.....2.63 or 1 in 374	1884.....2.76 or 1 in 362
1877.....1.73 or 1 in 578	1885.....3.14 or 1 in 318
1878.....1.07 or 1 in 934	1886.....3.84 or 1 in 260
1879.....1.90 or 1 in 526	1887.....3.82 or 1 in 261
1880.....1.96 or 1 in 510	1888.....4.45 or 1 in 224
1881.....2.15 or 1 in 465	1889.....3.25 or 1 in 307
1882.....2.91 or 1 in 343	1890.....3.79 or 1 in 263
1883.....2.63 or 1 in 380	

From this table, too, it appears that there has been irregular but still gradual increase. And thus the world over, from some cause or other diabetes is becoming a more frequent disease.

[1] Diabetes Mellitus and its Treatment, Edinburgh and London, 1898.

[2] Sen, Indian Medical Gazette, Calcutta, July, 1893.

It is generally conceded the disease is more common among Jews than Christians, and my own experience is in accord with this belief. The cause is not evident. Seegen ascribes it to a less stable condition of the Hebrew nervous system. One of my Hebrew friends, a physician, suggested that it is the result of intermarriage among the Jews in association with the acknowledged hereditary tendency to the disease.

The following table by Wallach[1] shows the proportion of deaths from diabetes to the number of deaths from all causes among Jews as compared with other races.

Age.	Deaths from Diabetes per 1,000 amongst the Jews.	Deaths from Diabetes per 1,000 amongst People of Other Faiths.	General Mortality from Diabetes per 1,000 Inhabitants.
0–14 years.	0.02	0.005	0.007
14–19 "	..	0.007	0.005
19–29 "	0.11	0.03	0.04
29–39 "	0.04	0.02	0.02
39–49 "	0.19	0.09	0.10
49–59 "	1.01	0.20	0.38
59–69 "	2.40	0.69	0.92
69–79 "	2.86	0.54	0.94
79–89 "	2.52	0.31	0.75
89–99 "	...	...	...

It is comparatively infrequent in the colored race but does occur among them. The United States Census report gives but 48 cases in this race for the census year 1900, including 28 males and 20 females. I have notes of three cases. The same report finds but two deaths from this cause among Chinamen in the United States, both males, for the census year 1900.

Diabetes most frequently affects adults in middle life, though it is not very rare in children. The United States Census returns for 1900 report 11 cases of deaths under one year, seven girls and four boys; under five years 46, including 24 boys and 22 girls. As all children with diabetes die this may be said to represent the total number of cases under five years for 1900.

The following table from the Fifty-fifth Annual Report of the Registrar-General of England for 1895, taken from Williamson, shows the rarity of the disease among children as well as its gradual increase already alluded to.

[1] Quoted by Williamson from Deut. med. Wochenschrift, Leipzig, 1893, s. 779.

MORTALITY FROM DIABETES MELLITUS PER MILLION LIVING.

The number dying in each sex is compared with a million living of the same sex, and the number of both sexes is the mean of the two sexes.

Year.		All Ages.	0–	5–	10–	15–	20–	25–	35–	45–	55–	65–	Upwards.
1861–70	Persons.	30	3	5	9	17	19	32	42	59	95	117	74
1871–80		38	1	4	10	19	25	37	51	72	132	171	113
1881–90		57	4	7	15	24	30	46	64	107	217	293	238
1861–70	Males.	41	3	5	10	22	24	44	55	83	136	180	120
1871–80		50	1	4	10	24	34	48	68	96	181	247	172
1881–90		69	5	7	14	26	35	58	78	134	282	397	314
1861–70	Females.	20	2	4	8	13	14	22	30	37	58	62	38
1871–80		27	2	4	10	14	18	27	35	50	87	106	67
1881–90		45	3	6	15	22	26	35	51	82	161	206	180

Of 102 cases of diabetes mellitus in children under 16, collected by Wegeli,[1] the distribution was as follows:

Under 1 year	3
1–5 years	26
5–10 years	31
10–16 years	42
	102

Dr. W. H. Dickinson had a case which proved fatal after six months' illness at 6 years. Dr. Bence Jones's youngest patient was $3\frac{1}{2}$ years, Dr. Roberts's was 3. The youngest case I ever treated was a little girl, one year and 10 months old, who lived three months longer. She was prematurely delivered because of nephritis in the mother. Dr. Miles D. Goodyear, of Groton, New York, reported to me the case of a little girl aged two years and two months.

Diabetes insipidus is said to be more common in infancy than is diabetes mellitus.

The disease is much more frequent in males than females. This is apparent from the table on p. 262 but no satisfactory explanation has been offered. In my own practice I have had comparatively few women patients. Senator's[2] statistics show that under the age of 20 more females are affected than males, and this is also in accord with my own experience.

[1] Archiv f. Kinderkrankheiten, Stuttgart, 1895, s. 14.

[2] See Senator's article on Diabetes Mellitus in Ziemssen's Cyclopædia of Medicine, Vol. XVI., p. 866, ad fin.

It has happened to me to have a number of physicians, patients with diabetes, some of whom have been engaged in very laborious country practice. In connection with the well-known fact that anxiety, mental strain and fatigue are admitted causes of diabetes it is not unlikely that the wearisome life of the country physician should make him more liable to the disease. Among my patients, too, have been several hard-working farmers. The disease is far more common among the well-to-do, whence it has been called the rich man's disease. It is, however, by no means confined to the rich.

The observations of N. S. Davis, Jr.,[1] go to show that there is a seasonal variation in the occurrence and recurrence of the disease, being three times as frequent in March, April and November as in January; four times as often in July. He bases conclusions on the number of times glycosuria was found in a given number of examinations per month as compared with its absence. It is less frequent in December, January and February, and notably less common in May than in April and July, less frequent in August, September and October, rising again in November to fall abruptly in December. I do not think much importance dare be attached to such a basis as the appearance and disappearance of sugar from the urine of a patient already diabetic. Dr. Davis also shows that there is no correspondence between the seasonal variation thus determined and variations in mortality from the same disease. In consequence of these facts, however, he warns his patients of the greater danger of exacerbation of this disease in March, April, July, and November.

Pathology and Pathogenesis.

The etiology of diabetes is so intimately blended with its pathology that it is scarcely possible to separate their consideration. What is known, therefore, of its immediate causation will be developed in connection with its pathology, while its more remote causes will be briefly considered in the ensuing section. Inseparably connected also with the pathology of diabetes are the phenomena of sugar formation and sugar consumption in the economy. A brief exposition of these seems, therefore, essential.

[1] Some Statistics of Diabetes Mellitus, read before the Annual Meeting of the Illinois State Medical Society, May 15–17, 1894.

It is very well known that during life there is constantly being produced and stored in the liver of man and the lower animals an *amyloid* substance, which was named by its discoverer, Claude Bernard, *glycogen.*[1] Its formula is $C_6H_{10}O_5$, that of starch, and the term *zoamylin* or animal starch was at one time suggested for it. The glycogen formation takes place whether animal or vegetable food is taken, but it is much more abundant upon a vegetable diet. It used to be held that it does not occur at all with a diet of pure fats, but Salomon[2] showed that it is produced in the livers of rabbits fed on olive oil, and it is now acknowledged that a very small quantity of glucose may thus arise. All physiologists agree that the amyloid substance is derived *mainly* from the starchy and saccharine principles of food, but *partly* also by splitting up and rearrangement of the elements of proteid substances, resulting in urea, a soluble diffusible substance which passes into the blood and is excreted, and *glycogen,* which is stored in the liver-cells. Schultzen has shown that glycosin, leucin and tyrosin are first formed; after these urea. Both the circulating and fixed albumins are capable of this conversion. The muscles are also a store-house for glycogen.

The most important property of glycogen is its ready convertibility at the temperature of the body into *glucose,* dextrose or grape-sugar. For this is required, also, the action of a diastasic ferment contained in the blood, and to a less amount in the liver. The source of this ferment is not known. It may arise in the liver or the pancreas. It is, however, not the pancreatic juice. It is more likely to be an internal secretion like that of the thyroid supplied to the blood by the pancreas. Bernard himself claimed to have isolated such a ferment from the liver, and assumed that it was contained in only a certain number of the liver-cells, while glycogen was found in the others, nervous influence regulating the action of the two on each other. Thus Bernard was the first to isolate an internal secretion.

According to Bernard and his school, the conversion of starch into glucose is constantly taking place *during life,* and there is as constantly being passed into the blood of the hepatic veins, grape-sugar,

[1] Bernard, Nov. Fonc. du Foie, Paris, 1853.
[2] Virchow's Archiv, Bd. 61, Heft 3, 1874, 18.

which is carried through the heart and lungs, and finally oxidized in the capillaries; Bernard claiming that there is less sugar in venous than in arterial blood. The mean difference is put at 0.3 part per 1000. It was at one time thought that the oxidation takes place wholly in the lungs, but at the present day this view is held by none. It is in the peripheral capillaries, generally, and more especially in those of the muscles, that the carbohydrates are utilized with the evolution of latent energy in some form of force.

Dr. Pavy and his school, on the other hand, claim that in health a considerable portion of the carbohydrate ingested is converted by the villi of the intestinal mucous membrane into fat and carried thence by the lacteals to the blood. Another portion is split up, "incorporated with nitrogenous matters and carried away in the form of proteid" by the agency of the same cells of the villi. Dr. Pavy says that the carbohydrates of our food must be appropriated in this way to a far greater extent than has hitherto been supposed.[1] Only the carbohydrate not thus assimilated passes to the liver and is converted into glycogen in the manner described, the cells of the liver picking out the sugar, dehydrating its molecules and condensing the monosaccharid to the polysaccharid state. "The office of the liver," according to Pavy, "is thus supplementary to the assimilative work performed elsewhere. If the latter work is efficiently performed, none is left for the liver to accomplish. It is the sugar that is permitted to reach the portal vein that is taken by the liver, and it may happen that none reaches it in health." At any rate, according to this view there is normally a very slight amount of sugar in the blood, which Pavy's experiments show to be about the same in venous and arterial blood,—0.94 of one part in 1,000. Corresponding to this, also, there is always in health a small quantity of sugar in the urine, 0.5 part per 1,000, too small to be detected by ordinary tests, and therefore of no clinical importance. It is, however, easily recognizable by special chemical methods, as was long ago shown by Brücke.[2]

[1] See Pavy's latest paper "On Experimental Glycosuria," British Medical Journal, October 12, 1901.

[2] Dr. Pavy's results have been confirmed by Schiff, Henzen, Meissner, Jacger, Pflüger, Ritter and McDonnel of Dublin. On the other hand Professor A. Flint, Jr. (New York Med. Jour., January, 1869), of New York, found sugar

In diabetes, according to Pavy,[1] this assimilating action of the cells of the villi and of the liver does not take place, but the glucose absorbed from the intestine, passes directly through the liver into the general circulation, and in the urine in quantities appreciable by the ordinary tests. Pavy says it may be that the conversion into amyloid substance occurs, and that this, through the condition of the blood, is brought back again into sugar. His own language is as follows: "The fact stands, that the sugar from ingestion is not stopped from reaching the general circulation as it ought to be, and I incline to the opinion that a simple passage through the liver occurs."[2] Such a state of affairs may result from an over-ingestion of carbohydrate and thus an alimentary glycosuria result. As might be expected, an over-ingestion of sugar is more active in producing such a glycosuria than an over-ingestion of starch. Indeed, Naunyn considers that in a perfectly healthy subject starchy food may be given to a practically unlimited extent without producing glycosuria, and says that if glycosuria does follow its ingestion it should be considered that assimilative power is below the normal. In measuring the assimilative power it is usual to give the food test in the morning, and, according to Naunyn, 100 grams of dextrose given in solution two hours after a breakfast of roll and butter with coffee ought not to cause glycosuria. Pavy holds also that in the diabetic, sugar may reach the general circulation in part by a true glycogenic action

in the blood of the hepatic vein of a dog within a minute after death, by ligature of the vena cava inferior. Professor Lusk (New York Med. Jour., July, 1870) found that the blood removed during life from the right side of the heart by catheterization through the jugular vein, contained from two to four times more sugar than the blood of the jugular vein in the same animals. Professor Dalton (Physiology, 1871, p. 192), by means of a comminuting instrument which enabled him to treat large quantities of liver substance in a very short time, found 1.8 part of glucose per 1,000 of liver at the end of 5 seconds after death, 6.8 parts in 15 minutes, and 10.2 parts in 1 hour. Harley (Proceedings of the Royal Soc., Vol. IX., p. 300) found sugar in the liver within 20 seconds after the death of the animal. The conclusion of all these last-named experimenters is that glucose *is* constantly produced from glycogen in the liver during life, but it is so rapidly removed by the circulation that only very small amounts accumulate in the organ. Hence, after death, the quantity of sugar in the liver constantly increases.

[1] Pavy, Some Points connected with Diabetes, London, 1878, p. 3 and p. 110.

[2] Pavy, op. citat., p. 110.

upon nitrogenous foods since if lean meat be consumed, sugar may still appear in the urine, although in greatly diminished quantity.

Bernard, on the other hand, held that in diabetes the amyloid substance or glycogen is too rapidly converted into glucose to be consumed in the ordinary process of oxidation, and therefore appears in the urine, so that in all instances of diabetes the excess of sugar in the blood is derived from glycogen, and it is an exaggeration of sugar formation rather than a lessening of its destruction.

These were for many years the two prevailing theories, first, that of Bernard, according to which the excess of grape-sugar in the blood, which is the necessary antecedent to its presence in urine is due to an excessive conversion of glycogen into glucose; second, that of Pavy according to which it is in the main the result of defective assimilation of grape-sugar partly into fat and proteid in the villi, and partly into glycogen in the liver, the glucose passing directly through the liver from the branches of the portal vein to those of the hepatic.

At the present day Chauveau and Kauffman are conspicuous among those who claim that diabetes depends upon increased sugar production in the liver, regarding the liver and pancreas as closely related and mutually dependent organs, the pancreas regulating through the nervous system the production of sugar by the liver.

Of late, however, the tendency has been to seek for the solution of the problem of diabetes mellitus in a deficient combustion or oxidation of glucose rather than an over-production. This belief has increased especially since lesions of the pancreas have been so often found associated with diabetes. These will be considered when treating of the morbid anatomy, but it may be said now that this association is so frequent that it is impossible to avoid the conclusion that some as yet undetermined causal relation exists. On the other hand, cases of the severest form of diabetes occur in which no lesion of the pancreas is present, or at least discoverable. Since the internal secretions have been acknowledged to play so important a part in physiology and pathology, it has been suggested that there may be formed in the pancreas such a secretion analogous to that of the thyroid gland, which in health maintains the normal metabolism of glucose. Lepine was the first to suggest such a

glycolytic ferment in the pancreas, finding its way into the lymph and blood, where it is contained in the white corpuscles. Lepine's conclusion was based on experimental investigation and was announced as early as 1890. It is commonly held that this secretion is something distinct from the pancreatic juice, but Alfred C. Croftan,[1] who alone of those who repeated Lepine's experiments confirmed his results, holds that trypsin, the proteolytic ferment of the pancreatic fluid, is the glycolytic ferment in question, requiring, however, the presence of hemoglobin to effect its glycolytic function.

Recent observations go to show an important relation between the suprarenal capsule and the glycolytic function of the pancreas. In the latter part of 1901 Blum[2] announced that the urine of animals subcutaneously injected with an extract of fresh suprarenal gland regularly contains sugar, even when the diet of the animal is free from carbohydrates. In Europe this discovery was confirmed by G. Suelzer[3] the same year and in America by Croftan[4] early in 1902 The most important point in Croftan's paper was the announcement that the suprarenal capsule contains a substance which either causes the formation of sugar or inhibits the normal destruction of sugar. C. A. Herter[5] was the first to use adrenalin chlorid, a substance extracted from the suprarenals, in experimental research and discovered the remarkable fact that if the pancreas be painted with a solution of adrenalin chlorid there *results a transient glycosuria with corresponding glycemia, while no glycemia or glycosuria follows a similar application to the liver and spleen.* On the other hand, after adrenalin chlorid undergoes oxidation it loses its power to cause glycosuria and to raise blood pressure. This power is not confined

[1] An Experimental Investigation into the Causes and Treatment of Diabetes Mellitus, Amer. J. Med. Sciences, April, 1902.

[2] Deutsch. Archiv f. klin. Med., Bd. 71, 1901, Heft 2 und 3, s. 146.

[3] Zur Frage der Nebennieren Diabetes. Berliner klin. Wochenschrift, no. 48, 1901, s. 1209.

[4] Concerning a Sugar-forming Ferment in Suprarenal Extract, A Preliminary Report on Suprarenal Glycosuria, American Medicine, January 18, 1902.

[5] Experimental Glycosuria from Adrenalin Chlorid and its Relations to Other Forms of Glycosuria Dependent on the Action of Reducing Substances on the Cells of the Pancreas, a paper read before the Association of American Physicians, Washington, May 29, 30, 1902; Preliminary Notice, Medical News, February 1, 1902, p. 201.

to adrenalin chlorid but is possessed by other reducing substances, such as sulphurous acid, ammonium sulphid, carbon monoxid, and many others. Whence Herter concludes that many, and probably most, forms of glycosuria and diabetes are due to the action of conditions or substances which interfere with normal oxidation in the cells of the pancreas. Herter says his observations are strongly opposed to the proposition announced by Croftan that suprarenal glycosuria is connected with diastasic ferment formed or stored in the suprarenal gland. Herter also announces that adrenalin injections are sometimes followed by extensive lesions of the gastro-intestinal tract and pancreas; also that after a fatal dose of adrenalin the cells composing the islands of Langerhans were the seat of granular degeneration, very pronounced in some places.

Other facts which point to some relation between the suprarenal capsule and diabetes are: (1) That in a certain number of cases of suprarenal disease glycosuria has been present; (2) that bronzing of the skin analogous to that which occurs in Addison's disease is occasionally found in diabetes (bronzed diabetes); (3)[1] that an intimate relation exists between the normal destruction of sugars and the formation of the bile pigments and their congeners, the abnormal pigments; (4) that subcutaneous injections and injections into the peritoneum of animals, of pancreatic extract, is followed by glycosuria, and that in like manner adrenalin chlorid, a substance derived from the adrenals, has the ability to cause glycosuria when injected into the peritoneum or painted in weak solution over the pancreas.

Phloridzin Glycosuria.—Mention should be made of a form of glycosuria which though very interesting has not as yet helped us to explain diabetes mellitus in man. It is a glycosuria induced in animals by the ingestion of phloridzin, a glucosid obtained from the bark of the root of apple and cherry trees. The discovery was announced by v. Mehring in 1886 that a few hours after the administration to dogs of about one gram of phloridzin to every kilogram of the animal's weight the urine contained 10 per cent. or more of grape sugar. The glycosuria continues as long as the phloridzin is administered. The same is true of human beings to whom the substance

[1] Croftan, A. C. Some Experiments on the Formation of Bile Pigment and Bile Acids, Phila. Med. Jour., Jan. 11, 1902.

is also harmless. The glycosuria is independent of food ingestion and occurs even if the animal is fasting, the albumin of the tissues being drawn upon for the glucose after the carbohydrates and albumin of the food are used up. It is commonly conceded that this glycosuria is nephritic in origin, the epithelium of the kidneys under the influence of this poison being unable to prevent the sugar from passing out of the blood. In phloridzin glycosuria there is no excess of sugar in the blood as in diabetes mellitus. So that as already stated the phenomena of phloridzin glycosuria do not aid us in the solution of the problem.

Influence of the Nervous System.

Bernard discovered as early as 1849 that by puncturing the medulla oblongata in the floor of the fourth ventricle, anywhere between a point 4 or 5 mm. above the nib of the *calamus scriptorius* and another about 4 mm. higher up,[1] the urine in a day or two acquired a considerable amount of sugar, and was increased in quantity. This is the celebrated *picqûre* experiment. The amount of sugar is larger the better fed the animal, while if all food is removed the sugar is trifling in amount, or disappears altogether from the urine. The point thus punctured corresponds with the roots of the pneumogastric nerves. Hence it was supposed that the diabetes was the *direct* result of irritation of these nerves. But it was found on section of the vagus, that galvanization of the *distal* end of the cut nerve produced no effect, while the same irritation applied to the *central* end resulted in glycosuria. Stimulation of the depressor nerve by Lafont and Filehne also produced glycosuria. Whence it was learned that the pneumogastric is not an excitor but a sensory nerve of diabetes, and that the glycosuria produced by irritation of the roots of the vagi or their central cut ends, is the result of a *reflex* action called into play through the pneumogastric as a sensory, and some other nerve probably the sympathetic as a motor nerve.

Schiff[2] in 1859 produced slight glycosuria by vertical section of the

[1] The area thus bounded, which was marked out by Eckhard as the "diabetic area," corresponds very closely with the "vasomotor" area as defined by Owsjannikow. Ludwig's Arbeiten, 1871, p. 21.

[2] Schiff, Untersuchung über Zuckerbildung in der Leber, 1859.

optic thalami and the great crura cerebri. Pavy on the other hand cut through the crura cerebri, completely separating the cerebrum from the parts below without exciting glycosuria.[1] This difference in the results of Schiff and Pavy may be explained by supposing Pavy's section was without irritation while Schiff's involved some irritation. Schiff produced more marked glycosuria by destructive (irritative) lesions of the pons and the middle and posterior crura of the cerebellum; by complete division of the cord between the medulla and the fourth cervical vertebra, and sometimes, but not invariably, by division of the separate columns of the cord, sometimes the anterior and sometimes the posterior. This effect lasts for days or until the animal dies. Finally, Schiff produced glycosuria by irritation of the sciatic nerve. From the clinical standpoint Rosenstein in 1877[2] called attention to the combination of glycosuria with sciatica limited to the peroneal and tibial nerves and ascribes both diseases to a hyperemic condition of the abdominal organs. He also says that treatment directed to the latter relieved the former.

Transverse section of the medulla oblongata always causes glycosuria, and as constantly section of the cord above the second dorsal vertebra, that is above the lower end of its cervical enlargement. But below this point, glycosuria is not produced, at least with any degree of constancy, while section of the filaments of the sympathetic accompanying the vertebral artery is again attended by it (Pavy, Cyon and Aladoff). Now these nerves are vasomotor nerves, and section of their trunks paralyzes their action and results in a dilatation chiefly of the hepatic artery and branches and a more rapid movement of the blood through them. Such dilatation and rapid movement of the blood is always attended by glycosuria. Similar results follow compressing any large artery, the effect being to increase pressure in the hepatic artery, as shown by Schiff, and by causing an animal to struggle as found by Pavy. A like effect follows a convulsive seizure, as announced by Michea and Reynoso.

Cyon and Aladoff[3] also noted diabetes succeeding section of the

[1] Pavy on Diabetes, 2d Ed., 1869, p. 164 et seq. 2.

[2] New York Medical Journal, July, 1877.

[3] Cyon and Aladoff, reprint from Mélanges Biologiques, and Bulletin de l'Académie Impériale de Petersbourg, Vol. III., p. 91; cited by Dr. Brunton in Lectures on the Pathology and Treatment of Diabetes Mellitus, reprinted

inferior cervical and upper dorsal ganglia and of the fibers forming the annulus of Vieussens around the subclavian, as well as of the fibers accompanying the vertebral artery above noted. Whence they inferred that the vasomotor nerves of the liver leave the spinal cord to join the sympathetic by the fibers (*c*) accompanying the vertebral artery, thence through the lower cervical ganglion and along the fibers (*d*) in the annulus Vieussens to the first dorsal ganglion (*e*) and thence through the ganglionated cord of the sympathetic (*f*), the splanchnics (*h*) to the celiac ganglion (*i*) and along the hepatic vessels to the liver (fig. 42).

It has been mentioned that Schiff[1] found that diabetes sometimes results from section of the *anterior* column of the spinal cord between the medulla and fourth cervical vertebra, and as the experiments of Eckhard[2] show that diabetes is not the invariable result of section of the fibers which accompany the vertebral artery, of section of the last cervical or first dorsal ganglion, or of the fibers of the annulus of Vieussens, Sir Lauder Brunton suggests that the glycosuric influence does not always pass from the spinal cord by the filaments above mentioned, but may *sometimes* pass further down the spinal cord and leave it by the communicating branches going to some of the dorsal ganglia, as indicated by the dotted line in figs. 42 and 43. Similar variations occur in the case of the cardiac nerve filaments.

An important phenomenon bearing on these facts has received an explanation from Cyon. We have seen that the vasomotor nerves of the liver pass along the dorsal ganglionated sympathetic, and one would suppose that its section would be followed by glycosuria. On the other hand, one may cut the sympathetic between the tenth and twelfth ribs or the splanchnics and no sugar appears in the urine. Nay more. After these nerves have been cut, even the floor of the fourth ventricle may be punctured and no sugar appear in the urine. The explanation offered by Cyon is that the blood is drawn away from the liver by the simultaneous dilatation of the intestinal blood-

from the British Medical Journal, London, 1874. See also British Med. Jour., December 23, 1871, and Brunton on Disorders of Assimilation and Digestion, London, 1901, p. 22.

[1]Schiff, Untersuchung über Zuckerbildung in der Leber, 1859, p. 108.

[2]Eckhard, Beiträge zur Anatomie und Physiologie, Vol. VII., 1, 1873, s. 19.

FIG. 42.

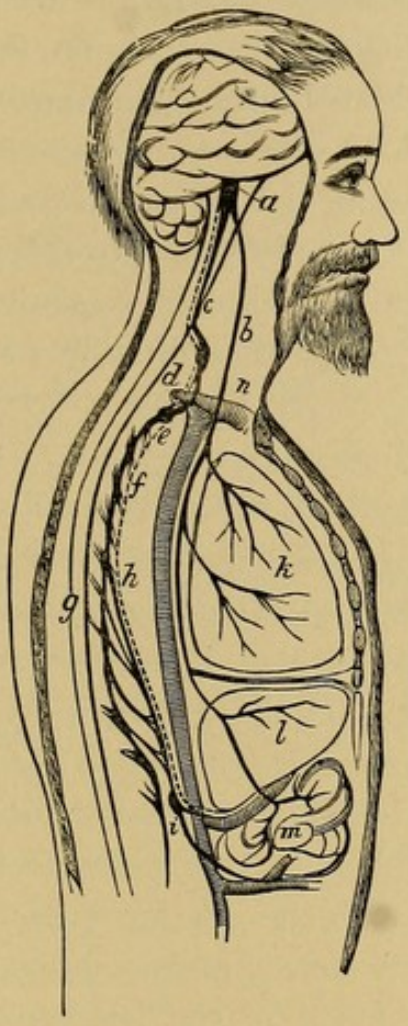


FIG. 43.

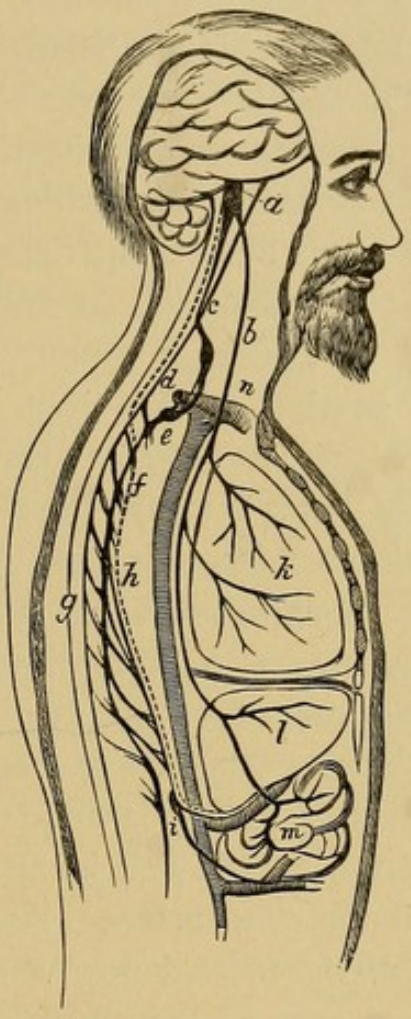


FIG. 42.—Diagram showing the course of the vasomotor nerves of the liver according to Cyon and Aladoff. These nerves are indicated by the dotted line which accompanies them; *a*, vasomotor center; *b*, trunk of the vagus; *c*, passage of the hepatic vasomotor nerves from the cord along the vertebral artery; *d*, fibers going on each side of the subclavian artery, and forming the annulus of Vieussens; *e*, first dorsal ganglion; *f*, ganglionated cord of the sympathetic; *g*, the spinal cord; *h*, splanchnic nerves; *i*, celiac ganglion, from which vasomotor fibers pass to the hepatic and intestinal vessels; *k*, the lungs, to which the fibers of the vagus are seen to be distributed; *l*, the liver; *m*, the intestines; *n*, the arch of the aorta.

FIG. 43.—Diagram showing another course which the vasomotor nerves of the liver may possibly take. The letters indicate the same parts as in Fig. 42. The hepatic vasomotor nerves are here represented as passing lower down the cord than in Fig. 42, and leaving it by the communicating branches to the second dorsal ganglion; or they may leave it, at other times, by branches to the first, or even a lower dorsal ganglion. In the latter event irritation of the third or other of the cervical ganglia may cause diabetes by being conveyed along the vertebral artery and up the cord, as indicated by the dark line, to the vasomotor center, where it may cause reflex inhibition, in the same way as any irritation to the vagus.—After BRUNTON.

vessels whose vasomotor nerves are also contained in the dorsal sympathetic and the splanchnics, and whose capacity equals that of the whole remaining vascular system together. If, on the other hand, the vessels of the liver be first dilated by the piqûre experiment so as to start the movement of the blood into them we may then cut the cord or splanchnics without arresting the formation of sugar.

A result of Pavy's experiments announced to the Royal Society as far back as 1859, also at first difficult of solution is similarly explained by Lauder Brunton. Pavy found that division of all the nerves passing to the liver leaving intact the blood-vessels and hepatic duct failed in every instance to produce glycosuria. Brunton suggests that it is impossible to divide all the nerves of the liver without irritating the intestines, diverting the blood to them and not leaving enough circulating in the liver to produce glycosuria.

Whatever may be the precise course pursued, it is evidently by the vasomotor fibers of the sympathetic that the glycogenic influence is regulated, whence the oneness of the center for the two regulations. The effect of section of these nerves is easily explained, since dilatation of the vessels and increased rapidity of the movement of the blood is the consequence. And although the dilating influence may be peculiarly exerted upon the *hepatic artery* and its branches, yet increased rate of movement of the blood in the latter must also accelerate the movement of the blood in the *portal vein* and its branches.

The effect of irritation upon the glycogenic function, whether propagated through the pneumogastric or some other sensory nerve, is nearly as simple. The effect of the irritation conveyed to the glycogenic center is to withdraw the usual tonic influence of the vasomotor nerves on the vessel-walls. Such inhibition results in a dilatation of the vessels of the liver and a speeding of their contents. Thus the same result is brought about in two different ways,—the one being direct, the other reflex.[1]

[1] It should be stated that the effect of irritation of the vasomotor center is not ascribed by all experimenters to the withdrawal of an accustomed nervous influence, that is, to a paralysis, but rather to an excitation. Eckhard (Beiträge, IV., 1, 1869; VII., 1, 1873) is one of these, and he bases his objection to the usual view on the ground that, while mechanical injury to the first thoracic ganglion will produce glycosuria, no such effect follows

Among the experimental irritations already mentioned, besides puncture of the fourth ventricle, which produce glycosuria by a reflex action, are injuries of the cerebral lobes and cerebellum, superior cervical ganglion, optic thalami, cerebral peduncles, pons varolii, middle cerebellar peduncles, cervical, sympathetic, and even sciatic nerve, and brachial plexus. It may be reasonably inferred, therefore, that pathological irritations of these same situations will result in

careful removal of the ganglion, or the severing of its connections with the remainder of the thoracic chain. Bernard also, in his lectures at the College of France, in 1873, reversing his original view, concluded that the glycosuric nerve-filaments, which, starting from the floor of the fourth ventricle, pass through the substance of the cord to the fourth dorsal vertebra, and thence through the sympathetic to the liver, are *excitor* in their character and analogous to the *chorda tympani* nerve. Their irritation, according to him, produced active hyperemia and increased sugar-formation, as irritation of the chorda tympani causes hyperemia of the submaxillary gland and increased secretion of saliva.

Later in further confirmation of this view M. Lafont (Medical News and Abstract, December, 1880, p. 730, from Lancet of October 23, 1880), isolated in dogs a segment of the spinal cord containing the first and second dorsal pairs of nerves. He next exposed the liver and irritated by faradization the isolated segment of the cord, whereupon the liver was observed to present a disseminated congestion, accompanied by a corresponding injection of the intestine and turgidity of the spleen. He also ascertained that the stimulation of these nerve-roots by a weak faradic current always caused a fall in the arterial pressure in the abdominal organs, if the root is carefully isolated. The least extension of the current to the spinal cord itself caused an increase in pressure. He found, too, that intermittent stimulation by a weak faradic current of the central extremities of the depressor branch of the vagus in the rabbit produced glycosuria; that stimulation of the central extremities of the pneumogastrics themselves produced the same result; and that division of the first two pairs of dorsal nerves caused a decided diminution of the glycosuria excited by the diabetic puncture. He found also that feeble stimulation of the central ends of the pneumogastric and any degree of stimulation of the depressor nerve always produced a fall of blood-pressure, while after division of the first three or four dorsal nerves, such stimulation produced a rise in blood-pressure.

Finally he found that painful stimulation of any mixed nerve, frequently repeated, caused glycosuria.

M. Lafont concludes from these experiments that he has confirmed the view of Bernard, that the glycosuria which results from stimulation of the central extremities of the pneumogastric in the dog, the depressor nerves in the rabbit, and the sensory nerves generally, is the result of an impression conveyed to the bulbar vaso-dilator center, the path from which is by the cervical cord, the first dorsal nerve-roots, and the sympathetic and splanchnic nerves; and that it is irritative rather than paralytic.

diabetes; that if permanent the diabetes resulting will be permanent, and if temporary the diabetes will be temporary. And in point of fact, observation has in numerous instances confirmed this supposition, as will be seen later, when the pathological anatomy of diabetes is discussed.

But it is not to irritation applied to nerve-centers or to trunks in their continuity alone that glycosuria is due. Irritation of the peripheral distribution of nerves has a similar effect. Thus, embarrassed respiration, whether due to disease of the respiratory passages, strangulation, or inhalation of irrespirable gases, as carbonic acid, carbonic oxid, etc., and anesthetics, as ether, chloroform, nitrite of amyl, is capable of producing glycosuria in dogs and rabbits, although the symptom has rarely been shown to attend these conditions in the human subject. In all these instances it is probably irritation of the terminal filaments of the pneumogastric—the sensory nerve of glycosuria—which causes the diabetes, by inhibiting the usual tonic action of the vasomotor nerves and producing hyperemia of the liver. So, also, substances introduced into the blood, as woorara, and even strychnia, morphia, and phosphoric acid, produce glycosuria probably in the same way, by irritating the terminal filaments of the vagi, though Schiff asserts that woorara and strychnia act, not by directly irritating the filaments of the pneumogastric, but through the resulting embarrassed respiration, in the course of which the terminal filaments of the pneumogastric are irritated; and this may be true in part. Bernard found that woorara produced, first, increased saccharinity of the blood, and, second, glycosuria when given in quantities insufficient to paralyze the muscles of respiration, and, therefore, independently of embarrassed respiration; in other words, that it acts like puncture of the floor of the fourth ventricle, paralyzing the vasomotor nerves of the liver by inhibition. He considered that morphia introduced into the blood acted in the same way. While admitting that this is true as to woorara, Sir Lauder Brunton believes that the glycosuria which appears after injecting woorara into the blood is also in part due to the deficient combustion of sugar in the muscles which it paralyzes, and in part also to the artificial respiration employed to keep the animal alive.

Finally, Schiff[1] has shown that irritation of the liver by needles and by galvanic currents[2] passed through them produces glycosuria. This is also due to resulting hyperemia, whether direct or indirect; whence it may be inferred that congestion of the liver from any cause may produce glycosuria, although it is not unreasonable to suppose that the results of active and passive hyperemia may be somewhat different in this respect. The hyperemia of the liver from embarrassed respiration is passive so far as results from the backing of blood, but active so far as it is a reflex phenomenon.[3] That an active rather than a passive hyperemia is essential for the production of glycosuria would appear from the fact that valvular disease of the heart is almost never attended by glycosuria, while it is always accompanied by passive congestion of the liver.

Irritation of other peripheral branches of the pneumogastric, as of the stomach and intestines, are less frequently attended by glycosuria; but that their irritation may be thus attended is shown by cases of intestinal irritation like that caused by tapeworm being attended by glycosuria. Brunton[4] mentions such a case immediately cured by the removal of the worm. Teething is a like cause.

Dr. Pavy discovered that the injection of oxygenated blood into the portal system produced glycosuria; also, that surcharging the blood with oxygen through the medium of respiration produced the same results. The introduction of venous blood produced no such effect; whence he concluded that oxygenated blood promotes the transformation of amyloid substance into glucose. Now this, he believes, is just the state into which the portal blood is thrown by the vasomotor paralysis affecting the vessels of the chylopoëtic viscera, including the liver, the resulting hyperemia causing the blood to flow through the organ too rapidly to admit its dearterialization.[5]

[1] Schiff, Untersuchungen über Zuckerbildung in der Leber, 1859, p. 106.

[2] Pavy, On Diabetes, 1869, p. 137.

[3] Dr. Pavy suggests (Certain Points connected with Diabetes, p. 111) another explanation of the production of sugar under these circumstances of hepatic congestion. In this state he says the *hepatic cells are subjected to undue pressure,* which may lead to more or less transudation and direct admixture of their contents with the blood.

[4] Brunton, op. citat., p. 14.

[5] Pavy, Certain Points connected with Diabetes, p. 96 et seq. Dr. Pavy considers that carbonic oxid acts in the same manner as oxygen in pro-

Summary.

It must be admitted that the foregoing is a somewhat chaotic collection of facts bearing upon the subject of diabetes. At the same time it is necessary, where we are still ignorant of the precise pathology of a disease, to bring together all matters bearing on it, to sift therefrom such as seem to be of major importance, and from them deduce the most reasonable conclusions. From the foregoing the following inferences may be made:

First, the liver is constantly storing up in its cells a substance identical in its composition with vegetable starch, and readily convertible by a diastatic ferment into grape-sugar.

Second, this substance, called by Bernard *glycogen,* and by Pavy *amyloid substance,* is derived chiefly from the amylaceous and saccharine articles of food, but partly, also, from albuminous food; possibly only one of its sources is fat.

Third, the blood contains at all times a small quantity of glucose, which in health is mainly derived from the glycogen in the liver-cells. A very minute and probably unrecognizable trace may be absorbed directly from the intestine by the lacteals. So long as the quantity of sugar present in the blood is restricted within certain limits, which are not precise, but which may be put down as from .25 to .6 per cent. in dogs, sugar does not appear in the urine, but if these amounts are exceeded glycosuria occurs.

Fourth, various injuries to the nervous system, among which puncture of the fourth ventricle, transverse section of the medulla oblongata, and section of the cervical sympathetic nerve and certain of its branches are conspicuous, produce pathological glycemia and glycosuria, which are the result of increased sugar-formation and not diminished consumption.

Fifth, it is probable that the immediate result of these nervous lesions, and therefore the immediate cause of the glycosuria thus induced, is an active hyperemia of the liver. The sources of the

ducing glycosuria, either through the direct action of the gas itself, or a compound between it and hemoglobin; the more temporary effect of the oxygen being due to the very feeble combination between oxygen and hemoglobin, the gas being readily displaced from the corpuscle by carbonic acid, while carbonic oxid, on the other hand, is displaced with extreme difficulty.

sugar in the blood and urine under these circumstances, *i. e.*, rapid movement of the blood through the liver, are probably two: 1st, the *grape-sugar absorbed from the intestine,* which is carried through the liver too rapidly to permit its conversion into glycogen; and, 2d, the *glycogen itself,* which is more rapidly converted into grape-sugar by the ferment in the blood than in health. This seems reasonable, because it is acknowledged that glycogen is very readily and rapidly convertible into grape-sugar, while the grape-sugar requires a longer time to convert it into glycogen. Hence an acceleration of the blood-current would operate differently on the two substances.

Sixth, two other sources of an excess of sugar in the blood and urine, quite independent of the nervous system have been suggested by Senator[1] and Pavy. The former suggested that an abnormal amount of glucose may be taken up with the chyle by the lacteals because of some impediment to portal absorption, and carried directly into the general circulation causing a glycemia on which would ensue a glycosuria; Pavy suggested that the same result may follow an ingestion of carbohydrates over and above the ability of the economy to assimilate after its absorption into the portal circulation (*normal alimentary glycosuria*). These sources are not essentially different.

It is conceivable, too, that there may be an over-conversion of glycogen into glucose in the liver, through over-activity of the diastasic ferment in the blood. If it be true as held by Plasz and Tiegel[2] thirty years ago that the ferment is contained in the blood corpuscles it is only necessary to suppose a rapid disintegration of blood corpuscles to have the necessary condition of such energetic action. It is not likely that any one of these three possible causes enter into the causation of permanent pathological conditions.

Seventh, it was early suggested that diabetes may result from diminished combustion of the sugar normally supplied to the tissues by the blood. Its possibility is further substantiated by the occasional results of treatment by muscular exercise, to which especial attention was called in 1871 by Dr. William Richardson, of London, in his little work on *Diabetes and Its Treatment,*[3] and which he so

[1] Senator, article on Diabetes in Ziemssen's Cyclopedia of Practical Medicine, Vol. XVI., p. 952, New York, 1877.

[2] Pflüger's Archiv, 1873, Bd. VI., s. 249, and Bd. VII., s. 391.

[3] London, 1871.

successfully applied to the treatment of his own and other cases. Other facts have a bearing upon the subject. In the first place, Ludwig and Genersich,[1] and Bernard[2] have shown that the blood which issues from a contracting muscle by the vein, contains much less sugar than that which enters it by the artery. Ludwig and Scheremetjewski[3] have shown that grape-sugar, as such, is not burnt off in the body, while lactic acid and glycerin are; and Bernard that as sugar disappears from the blood it is replaced by lactic acid, while Schultzen[4] concluded from his experiments that the sugar, which is normally present in the blood, is split up by a ferment into lactic acid and glycerin, which undergo combustion, and thus sustain the temperature of the body. If the ferment which Schultzen considers necessary for the conversion of the sugar into lactic acid and glycerin should be absent or deficient, the sugar is not split up, is not burnt up, and, therefore, appears in the urine. This Schultzen early suggested might be the case with certain diabetics.

We have seen what a new impetus the modern studies of Blum, Suelzer, Herter and Croftan have given to this view of the pathogeny of diabetes, and we await with interest further additions to our knowledge in this direction.

From the above it would seem possible to make three categories of all cases of glycosuria: *First,* cases of alimentary glycosuria whereof diminished carbohydrate ingestion is the cure; *Second,* cases of nervous lesion or diseases in which directly or indirectly through the nervous system the inhibitory center in the medulla oblongata lets go its hold and an active hyperemia of the liver and consequent diabetes results. These cases get well if the nervous lesion is curable; *Third,* cases in which there is no lesion or disease of the nervous system, in which, however, the symptoms of diabetes are very pronounced. These, for convenience, may be called essential diabetes. In a certain proportion of these the pancreas is diseased; in others no such disease is discoverable, while modern studies go to show that there is, nevertheless, some functional derangement of the pancreas over which in health the internal secretion of the suprarenal capsule has some regulating effect.

[1] Ludwig's Arbeiten, 1871, s. 75.
[2] Bernard, Revue Scientifique, 2d series, Tome IV., p. 1022.
[3] Ludwig's Arbeiten, 1869, s. 141, 144.
[4] Schultzen, Berliner klinische Wochenschrift, No. 35, 1872, s. 417.

Causes of Diabetes Mellitus.

Excepting the *injuries to the nervous system* and the *lesions of the pancreas* which are known to cause diabetes, our knowledge of its causes is not precise. Among the former are included *blows upon the skull,* with or without fracture; also *concussions* communicated to the brain, spinal cord, and vasomotor centers in other ways, as by falls, in which the patient lights elsewhere than upon the head. Nor does it seem necessary that such injuries need be applied to parts adjacent to the nerve-centers; since blows upon the abdomen, back, legs, thorax, kidneys, and liver have all been followed by symptoms of diabetes. Succeeding such injuries to the nerve-centers, the diabetes is not always immediate but may appear weeks after the injury. The number of cases succeeding injury are however few as compared with those resulting from other causes. Thus Griesinger collected 225 cases, of which but 13 were traumatic, being 5.7 per cent., including cases in which the injury was not adjacent to nerve centers.

Next, *disease* of the nervous system, either acute or chronic, may be attended by glycosuria. Among these meningitis, tubercular as well as traumatic, epilepsy, apoplexy, and tumors of the brain, especially those in the neighborhood of the medulla oblongata, are conspicuous. A large number of cases thus caused were collected by Fritz,[1] Goolden,[2] and Fischer[3] years ago. In some of the cases thus induced there was simply transient glycosuria. At times *mental emotion* and *anxiety* and *mental strain* have been sufficiently associated with diabetes to make it reasonable to consider them causes of the disease. The same is true of *hard work* especially when combined with *bodily fatigue* and *exposure*. *Fright* and *anger* may be placed in the same category. The latter two causes alone have been assigned a position among the causes of the disease. The influence of mental and bodily fatigue in diabetes is seen also in the marked aggravation which these agencies exert on existing cases.

Heredity seems to be an acknowledged influence, though it has not

[1] Fritz, Gazette Hebdomidaire, Vol. VI., 1859.

[2] Goolden, London Lancet, June and July, 1854, March and May, 1862.

[3] Fischer, P., Du Diabète Consécutif aux Traumatismes, Archives Générales de Médecine, 5 serie, T. XX., 1862, pp. 257 et seq.

been as noticeable in my experience as in that of some others. J. Hall Pleasants in a paper published in the John Hopkins Bulletin for December, 1900, has collected the experience of a number of physicians and found the percentage of hereditary cases as follows:

Wegeli (in children)	29.	Seegen	14.
Flint	27.7%	Naunyn	11.7
Bouchard	25.	Zimme	10.6
Fitz & Joslin	23.8	Williamson	10.3
von Noordon	21.8	Frerichs	9.75
Schmitz	21.1	Grube	7.9
Johns Hopkins Hospital Series			5.3

My own experience finds hereditation in 5.75 per cent. coinciding nearly with the Johns Hopkins experience.

On the other hand it is especially a family disease, that is, it recurs in a number of brothers and sisters in the same generation of one family. It is not unusual to have two, three or even more brothers and sisters in one family, with diabetes. Hereditary tendency is observed more frequently in private than in hospital practice.

We have only to recall the acknowledged effects of diet on diabetes to make it reasonable to suppose that the constant use of *certain foods* may cause diabetes. Such foods would of course be the farinaceous and saccharine, and it may be this circumstance that makes diabetes more common in the agricultural counties of England and in Thuringia. It is well known that in some countries the people live almost exclusively upon bread and potatoes. Among these we should expect diabetes to be more prevalent. But cases directly traceable to dietetic causes are not numerous.

Dr. George Harley[1] insists that *alcoholic stimulants* are a common cause of diabetes. His belief is based chiefly upon experimental results of his own, of Bernard,[2] and of Rosenstein. Harley himself showed that if alcohol is injected into the portal vein of dogs, glycosuria promptly appears; Bernard, that if alcohol is introduced into the small intestine of dogs the same result follows; while Rosenstein[3] showed by experiments upon human subjects, that Bavarian

[1] Harley, The Urine and its Derangements, Philadelphia, 1872, p. 229; also, Harley, On Diabetes, London, 1866, p. 44.

[2] Bernard, Gazette Médicale de Paris, May 10, 1856.

[3] Rosenstein, Virchow's Archiv, 1858, s. 461.

beer and wine diminish the elimination of urea and increase that of chlorid of sodium and sugar. To these results of experiment he adduces the fact that diabetes is a much more common disease in Great Britain than on the Continent, where the quantity of alcoholic drinks consumed is much less than in the former country.

Of the older authors, Willis[1] and Prout (Prout more particularly as to cider) held the same view, but of modern observers I know no one who agrees with Harley. Dickinson, Pavy, and Senator all say that alcoholic drinks cannot reasonably be charged with being causes of diabetes, and most cases of diabetes I have seen have been among temperate people. On the other hand there can be no doubt that diabetics have often been free eaters and drinkers prior to acquiring the disease and some would ascribe the frequency of diabetes among Hebrews to this cause because it is among the prosperous that we find it more frequently. Yet I have met it among the poorer class of this race. I am disposed to ascribe it to heredity and the close intermarriage in the race, already mentioned.

Gout, rheumatism, malaria, the continued fevers, the effect of cold both externally and in the shape of cold drinks have all been charged with producing diabetes. One or two instances in my experience would lend support to the view that malaria might cause diabetes and there is an undetermined relation between gout, probably between rheumatism and diabetes, but with these exceptions the last named causes are inoperative. Extravagant sexual indulgence has been known to cause glycosuria as well as restrained sexual desire, doubtless through the nervous system.

The numerous cases arising in little children where there has been absolutely no hereditary tendency are inexplicable. So that taken all in all the question of the etiology of diabetes is at least as unsatisfactory as its pathogenesis.

Pathological Anatomy.

Except the lesions of the nervous system and of the pancreas referred to, the morbid conditions found at necropsy in diabetes are in the main such as are the consequence of the continued glycemia and

[1] Willis, On the Operations of Medicines in Man's Body, p. 74.

glycosuria rather than their cause. Often there are absolutely no alterations discoverable either by the naked eye or the microscope.

To begin with the organ which has so much to do with normal glycogenesis, the *liver,* it frequently presents the appearance of a hyperemic organ; that is it is darker and harder than the normal organ, while it is also enlarged, sometimes decidedly, at others only slightly. The maximum enlargement reported is thrice the normal size, say 9 pounds as compared with $2\frac{3}{4}$ to $3\frac{1}{2}$. Corresponding to this the microscope with moderate powers shows large and distinct acini with capillaries more or less dilated and distended with blood. Higher magnifying powers,—300 to 400 diameters—show the liver cells to be enlarged, distinctly nucleated, rounded, and disposed to fuse into each other. If a weak solution of iodin is added they strike a wine-red color, which, according to Rindfleisch, is confined to the nucleus; but according to Senator, may extend to the whole of the cell. Klebs ascribes this reaction to post-mortem changes in the glycogenic substance. The minute changes described are said by Rindfleisch to be more striking in the peripheral zone of the lobule, that of the *portal vein;* while the intermediate zone, or that of the hepatic *artery,* is fatty, and the central part, including the rootlets of the hepatic *vein,* is nearly normal. Stockvis and Frerichs assert that the enlargement of the liver is partly contributed to also by a formation of new liver-cells. In one instance Dickinson[1] found, in addition to general venous thrombosis and apparently in connection with it, patches of a remarkable spongy transformation, which he ascribed to "extravagant dilatation of the capillaries belonging to the hepatic vein." Under the microscope sections had a worm-eaten or honey-combed look. The threads of the network were chiefly composed of glandular epithelium compressed and elongated; the cavities were empty, and proved to be contorted tubes, which opened into branches of the hepatic *vein;* whence he concluded them to be dilatations of the capillaries in connection with this venous trunk. The description suggests that of an angioma of the liver.

Dickinson describes an overgrowth of connective tissue as well as of epithelium resulting in a "hypertrophic cirrhosis," to which Trousseau also alludes in connection with diabetes, and of which

[1] Dickinson, op. citat., p. 50.

Budd[1] reports a single case. Klebs says that as the disease continues, the liver again becomes reduced, and a diminished size has occasionally been observed. Further allusion will be made to this hypertrophic process in the liver on page 292.

A diminution in the normal proportion of fat in the liver-cells is quite a frequent occurrence, according to Beale, and quantitative analysis by Folwarczny[2] sustained this statement, while Frerichs also found fat absent from the hepatic cells in four cases and greatly diminished in another. This observation is very interesting in connection with the statement of Pavy that glycogen is normally converted into fat, which is stored up for further use in the economy, but that in diabetes this conversion fails to be made.[3]

As to the *pancreas,* its frequent involvement has already been alluded to. As far back as 1788, Thomas Cowley reported a case of diabetes in which there was atrophy of the pancreas which was also stuffed with calculi. Similar cases were reported in 1833 by Lloyd and Elliotson, and in the same year by Bright in which the lesion was cancer. Bouchardat was apparently the first to call attention, in 1851, to the probability of some causal relation between the two conditions. Hyde-Salter, also prior to 1871, found the pancreas degenerated in four successive cases of diabetes so that he thought he had discovered its true pathology.[4]

In 1877, Lancereaux[5] presented to the French Academy of Medicine specimens of profound lesions of the pancreas from persons who had died of diabetes mellitus and argued for a causal relation of the lesions to the symptoms of the disease. This he alleged constituted a special and distinct variety of diabetes, characterized by sudden onset, considerable emaciation (*Diabéte maigre*), polydipsia, polyphagia and peculiar alvine dejections. He adduced in support of his views the effect of extirpation of the pancreas in the lower animals

[1] Budd, Diseases of the Liver, London, 1845.

[2] Leberanalysen bei Diabetes mellitus, Wiener Zeitschr., N. F., 1859, II., 6.

[3] See Pavy's most recent paper on this subject, entitled Experimental Glycosuria, British Med. Journal, October 12, 1901.

[4] Referred to without date by Dr. William Richardson in his little book on Diabetes, published in London, 1871.

[5] La France Medicale, November, 1877.

long prior to the experiments of von Mering and Minkowski announced in 1889.[1]

In 1879 A. La Pierre[2] again called attention to this variety, characterized by its very rapid course (six months to three years) the habitual presence of diarrhea with greasy or creamy stools, containing also undigested nitrogenous substances, which may aid in the differential diagnosis.

As to the proportion of cases in which lesions of the pancreas have been found, observers differ widely. Hansemann found them in the pancreas in 40 out of 59 cases, or in about 69 per cent. of the cases of diabetes which came to autopsy. Windle found the organ diseased in 74 out of 139 cases, or 53 per cent.; Frerichs, in 12 out of 40 cases, or 30 per cent.; Seegen, in 17 out of 92, or 19 per cent. Naunyn, on the other hand, found the pancreas diseased in only one out of 40 cases, and, moreover, suggests that some of the atrophied pancreases found associated with diabetes may be a result rather than a cause. This relation will be referred to again. Taking up the question from the other side, Dieckhoff found that out of 19 cases of pancreatic disease, 7 had diabetes. In a study of the records of the Berlin Pathological Institute, tabulated for ten years, Hansemann found 40 cases in which diabetic and pancreatic disease were associated; 8 cases of diabetes without pancreatic disease; 6 cases in which there was no reference to the pancreas; and 19 cases of pancreatic disease without diabetes. In 99 cases of disease of the pancreas studied by Hale White there was diabetes in 13.

Out of 23 cases of diabetes collected by Dr. R. T. Williamson[3] the pancreas was either normal or only atrophied in proportion to the general wasting in 12, *i. e.*, was diseased in slightly less than 50 per cent. *Roughly estimated the pancreas may be said to be diseased in about half the cases.* Senator makes the same estimate.

[1] Halle had stated that extirpation of the pancreas in the dog was followed by increased hunger and thirst. Bernard had shown that tying of the duct of Wirsung produced no effect and Schiff had produced atrophy by injecting fat into the ducts apparently without causing diabetes.

[2] The Medical News, and Abstract, Philadelphia, June, 1881, from London Med. Record, April 15, 1881, from Jour. de Méd. et de Chir. Pratique December, 1880. Sur la Diabète maigne dan ses rapports avec les altérations du pancreas, 94 pp., 4to, Paris, 1879, 388.

[3] Williamson, Diabetes Mellitus, London, 1898. Senator, loc. citat., p. 887.

As to the form of lesion, calculous obstruction is generally considered most common and atrophy next, although this order seems hardly sustained by the facts. Out of the 72 cases of diabetes associated with pancreatic disease collected from the bibliography by Hansemann only 14 were cases of pancreatic calculus, while of 40 cases of associated disease collected by Hansemann from the protocols of the Berlin Pathological Institute 36 were cases of simple atrophy, 3 of fibrous induration and one of a complex nature, a very much larger proportion of atrophy than of calculus. Out of 16 cases of pancreatic atrophy collected by Hale White from the autopsy records of Guy's Hospital diabetes was present in 13.

Seegen found the pancreas strikingly small and anemic in 13 out of 30 diabetics examined in the Vienna dead house.[1] The second William Pepper[2] reported a case of diabetes with jaundice and widespread syphilitic disease in which there was cystic degeneration of the pancreas with pancreatic calculus. I have myself met but one case of diabetes associated with pancreatic calculus confirmed by necropsy, but as but few of my cases came to necropsy, there may have been more instances of calculus. In this case there was diarrhea and it was quite like the cases reported by Lancereaux and Depierre. Pancreatic obstruction leads to atrophy, but primary atrophy is referred to.

A second variety of atrophy of the pancreas found associated with diabetes, which Naunyn especially insists may be the result and not the cause of diabetes, has been called the cachectic form. Friederich also refers to such cases and Hansemann sought to differentiate the two forms. In the cachectic variety he says the organ is cylindrical and sharply demarked from surrounding structures. The stroma and cells are uniformly atrophied. In diabetic atrophy, on the other hand, there is interstitial pancreatitis which causes the organ to be adherent. It is brownish in color but not pigmented, smoother, and there is hypertrophy of the stroma with atrophy of the parenchymal cells. It should be mentioned, however, that this form has been found without diabetes.

[1] Senator, loc. citat., p. 887.

[2] Medical and Surgical Reporter, Philada., 1881, XLIV., 401–3.

The discovery of Opie[1] that the islands of Langerhans in the pancreas are the seat of a hyaline degeneration in diabetes, marked an era in the history of our knowledge of the disease, but has not been sufficiently confirmed to justify us in assigning much weight to it. With another variety of pancreatic disease is found hypertrophic cirrhosis of the liver and to this combination Hanot ascribes the so-called *bronzed diabetes.*

Williamson collected 100 cases of diabetes in which there was pancreatic disease, and found the following varieties of lesion:

	No. of Cases.
Atrophy of the pancreas (more or less marked)	39
Very marked atrophy, gland almost absent	3
Very marked atrophy, gland not recognized by naked eye	2
Very marked atrophy, with cystic dilatation of duct	2
Very marked atrophy and induration	1
Calculi present, other conditions not stated	1
Marked fatty degeneration	10
Marked fatty degeneration with calculi	3
Fatty degeneration, with increase of connective tissue	1
Complete fatty degeneration and marked atrophy	1
Complete transformation of pancreas into a fatty mass	2
Cystic disease	3
Large pancreatic cysts	3
Cyst of pancreas, with necrosis	1
Transformation into a firm mass of fibrous tissue, pancreatic tissue being almost absent	10
Marked cirrhosis	3
Cirrhotic and cystic pancreas	1
Calcified pancreas	1
Peripancreatitis and pancreatitis hemorrhagica	2
Abscess	3
Cancer	8
	61
	100

The relation of pancreatic disease to diabetes has been discussed on p. 271. It must be admitted that nothing is settled. On the other hand both Senator and Klebs believe there is ground for believing that the coexistence of diabetes mellitus and pancreatic disease depends upon lesion of the *celiac axis.* Senator says: Either the dis-

[1] Relation of Chronic Interstitial Pancreatitis to the Islands of Langerhans and to Diabetes Mellitus, Journal of Experimental Medicine, Vol. V., pp. 397 and 527.

ease (cancer, formation of calculus, and inflammation of the surrounding tissue) starts from the pancreas, encroaches upon the plexus, and gives rise to diabetes by destroying its ganglion, or else the celiac axis is first affected, and in consequence thereof circulatory disturbances arise in the territory supplied by the celiac artery, which lead to degeneration and atrophy of the pancreas."

The *kidneys,* primarily unaffected, are undoubtedly sooner or later influenced by the constant irritation to which they are subject in eliminating the sugar, although as there is a free movement of the blood through the organ, it is not to be expected that any changes should appear early or be invariably present. The appearances commonly met are those of hyperemia and hyperplasia of epithelium, in a word those of epithelial nephritis. Occasionally the changes are more advanced and the epithelium is fatty. These changes need not necessarily be attended with albuminuria, although they not infrequently are. In long-continued cases of diabetes and in some of comparatively short duration arterio-sclerosis of the blood-vessels of the kidney as well as those of the system at large is found. Such sclerosis is the direct result of the irritating qualities of the diabetic blood on the intima.

In addition to the changes characteristic of chronic nephritis in different stages, there are found in severe toxic forms of diabetes two sets of minute changes, one described by Ebstein, known as the cellular necrosis or hyaline change of the tubular epithelium, the other Ehrlich's lesion, a glycogenic degeneration of Henle's loop and the straight tubes. These are supposed to be the direct result of the presence in the blood of the toxic substances so characteristic of the later stages of diabetes, viz., aceton, diacetic acid and oxybutyric acid. They are invariably associated with albuminuria.

In a certain number of cases where nephritis and diabetes are associated I believe the coincidence accidental, the usual causes of nephritis operating in association with diabetes as well as apart from it. As to the proportion of cases in which the kidneys reveal morbid changes it is a decided majority. I know of no observations more recent than those published in my first edition, where Griesinger is quoted as finding them in 32 out of 64 autopsies, Seegen in 20 out of 30 cases examined in the Vienna dead house, and Dickinson in 25 out of 27 autopsies at St. George's Hospital, London.

Catarrh of the pelvis of the kidney and of the ureters is mentioned by Senator as found rather frequently, and as due partly to the final complications which prove fatal, and partly to the irritating effects of the sugar and other abnormal constituents of the urine.

Atrophy of the testes is named by the same author on the testimony of Romberg and Seegen as occasionally present in young persons. Thus may be accounted for some of the instances of sexual impotence found so often in diabetes.

The *lungs* are frequently the seat of *tubercular deposits* and cavities resulting from their softening associated with the symptoms of phthisis so common in the later stages of diabetes. The changes in the lung are tubercular, though bacilli seem to be less easily found than in tuberculosis not thus associated.

Gangrene of the lung is sometimes met. Still another rare lesion of the lung is fat embolism described by Sanders and Hamilton and by J. H. C. Simes. (See also p. 303.)

Many other isolated lesions are described as occurring in diabetes mellitus, but as they bear no evident or necessary relation to the disease, they need not be especially mentioned. Among these are gastric and intestinal catarrhs, hemorrhagic erosions of the gastric mucous membrane, pleuritic exudations, etc. Recently increased emphasis has been placed by Hédon[1] on a *hyperplasia of the intestinal mucous membrane* as a constant lesion, probably *secondary* to the pancreatic lesion.

Nervous System.—In addition to the more palpable lesions of the nervous system so often alluded to, attended by glycosuria as an isolated and more or less harmless symptom, Dr. Dickinson claims he has found, upon close examination even by the unaided eye, a set of changes which are essentially associated with diabetes, and which may be said indeed to constitute its pathology, insomuch that he defines diabetes as a disease of the nervous system characterized by saccharine urine. These changes were described in detail in my first edition but as they have not been confirmed they are here omitted.

Symptoms, Course, Duration.

Almost invariably the earliest symptoms noted by the diabetic are *thirst* and *frequent micturition*. One or the other of the two may

[1] Physiologie Normale et Pathologique du Pancreas, p. 151.

be noticed first, or the patient's attention may be called to both simultaneously. It occasionally happens that a *dryness of the fauces* and a glutinous *viscid saliva* attract attention before any other symptom. It is surprising how long even these symptoms will escape notice, and even when attention is called to them the patient will often say: "I have always drunk a good deal of water," and thus parry the question. On the other hand the quantity of water consumed is often enormous, and the patient will take water to bed with him. Sometimes a drop of urine falling upon the boots or clothing, and there evaporating, leaves a persistent white spot, which is sugar, And this may attract the attention of the patient. A *dryness* and *harshness of the skin,* due to absence of perspiration, soon make their appearance and may early excite his attention, especially if in health he perspire easily. *Itching of the skin* is also sometimes present. Notwithstanding the dryness of the skin, the *temperature* of the body is *not increased,* at this stage scarcely altered, although later in the disease it may be subnormal. A *voracious appetite* is characteristic, notwithstanding which, the patient observes that he slowly loses in weight and grows daily weaker. The rapidity with which these symptoms succeed each other is not uniform. Sometimes they follow in rapid succession, at others the successive stages are exceedingly slow in developing. A feeling of languor and debility may be early noted.

The above category includes all the symptoms of the milder form of the disease, as seen in adults past middle life, and ordinarily quite amenable to treatment. One or more of these even may be wanting; but all of them sooner or later appear and become intensified. The patient complains of constant burning thirst, urinates frequently and as constantly drinking water to quench his thirst. While eating enormously, he grows emaciated, although at the onset of the disease he may have been a robust and even portly man. He becomes very weak and all exertion requires great effort.

Dyspeptic symptoms appear at various stages, seldom very early, because they are generally the result of the large amount of food consumed. Acid eructations, flatulence, and epigastric pain, alternating with diarrhea are among these symptoms. Dilatation of the stomach is one of the more unusual ones. *Constipation,* probably

in consequence of free eating and abundant residual waste, is not, usually, a very early symptom; but, sooner or later, the general "dryness" makes itself felt in the bowels as elsewhere, and more or less constipation results. This is often very obstinate and in my experience such constipation is an unfavorable symptom. In other cases where there is neither constipation nor diarrhea the stools are *very large,* due also probably to the large ingesta.

Sometimes among the later symptoms is a peculiar *vinous* or *acetous* odor of the breath, which has been compared to that of stale beer, and by Sir Thomas Watson to the odor of a place in which apples are kept. This has been ascribed to *acetone,* or *diacetic acid* or both, both being found in the blood of profound diabetics during life.

Cough is often one of the later symptoms as the result of tuberculosis and bronchitis, and, with the copious expectoration incident to them, adds to the debilitating agencies already at work. Roberts thinks phthisis occurs in one half the cases. In my experience the proportion is not nearly so large. The consumption thus induced sometimes rapidly hastens the fatal termination, while at others it appears to have but a trifling influence in this respect. The other symptoms characteristic of pulmonary consumption are also present, not even excepting hectic sweats. The perspiration thus arising may contain sugar.

The early *loss of sexual desire* is said to be characteristic, but is probably not more so than in exhausting diseases generally.

In advanced stages the *temperature* of the body, unless influenced by intermittent febrile disease, is almost invariably lowered from 1° to 2½° F. Dr. Dickinson refers to the case of a boy of six, in whom the temperature ranged from 93.6° to 94.8° F., and who died of pneumonia, during which the temperature rose only to 97.8° F. During diabetic coma the temperature may also be subnormal.

Boils and *carbuncles* are frequent symptoms and are sometimes the first symptoms noticed. In all cases of boil and carbuncle the urine should be promptly examined. Such examination has often disclosed glycosuria when none was suspected. A carbuncle thus developed is frequently the immediate cause of death. The same is true of gangrene of the extremities, especially of the toes. This often

succeeds upon slight operations, such as paring corns and many a diabetic previously in seeming good condition dates his beginning decline from the date of such operation. Such gangrene may succeed upon a blister or even a painting with iodin. In explanation there can be no doubt but that the sugar-infiltrated tissue is a favorable nucleus for the development of pathogenic fungi. Gangrene may be caused by arterial sclerosis, so often present in diabetes.

Eczema and other forms of skin disease are sometimes obstinate symptoms. The palms of the hands are among the seats of a dry eczema. Such eczema may be the cause of an intense *pruritus* sometimes of the skin generally, but often of the vulva in women and less frequently of the glans penis and prepuce in men, which is one of the most annoying symptoms of the disease. The itching is sometimes maddening in its intensity and most difficult to relieve. A purulent-looking discharge has been found issuing from the urethra in which the spores of penicillium glaucum have been found by the microscope.

Nervous System.—Insomnia is an occasional symptom. Intense neuritic or neuralgic pain is one of the more unusual symptoms and sometimes stubborn. Most frequent in the sciatic nerve it may involve any of the deep or superficial nerves, including the trigeminus and intercostals. I have known it to be especially severe in the musculo-spinal distribution in the shoulder. The cramp-like pain in the legs and arms sometimes noted may be thus caused. Even nephritic neuralgia has been ascribed to it by Berger.[1] Another consequence of neuritis is paresis and even paralysis of the distribution of a nerve, such as the facial and the sciatic. Numbness and tingling, the "pins and needles" sensation sometimes noted may be due to mild degrees of neuritis or to alteration of vaso-motor control over the circulation in the extremities. Neuritis may not unreasonably be ascribed to the presence of sugar and its decomposition products.

[1] Diabetic and Nephritic Neuralgia, Med. News, March 3, 1883, p. 246.

As the disease advances the normal reflexes diminish and the total *absence of knee-jerks* is an ultimate symptom. This may be the result of a polyneuritis or of central nervous influence. It is not necessarily an unfavorable symptom. Exaggerated tendon reflexes, on the other hand, may rarely be present.

The latest data on this subject are furnished by Dr. R. T. Wil-

liamson,[1] who has ascertained that in diabetes mellitus, as in locomotor ataxia, the tendo-Achilles jerk may disappear before the knee-jerks are lost. Thus in eight cases of diabetes in which the tendo-Achilles jerks were lost, the knee-jerks were present.

In tabular form:

	Cases.
B. One Tendo Achilles jerk absent, one present in	2
In these cases knee-jerks both present in	8
One knee-jerk absent, one present in	3
Both knee-jerks absent in	8
B. One Tendo Achilles jerk absent, one present in	2
In these cases both knee-jerks present.	
C. Tendo Achilles jerks present in	29
In these cases both knee-jerks present in	28
One knee-jerk present, one absent in	1

He also finds that knee-jerks are often lost in severe forms of diabetes in hospital practice while among private patients in better social conditions they are lost less frequently.

In 100 cases of diabetes, nearly all of whom were hospital cases, he found the condition of knee-jerks as follows:

	Cases.
Both jerks lost in	49
One present, one absent in	6
Both present in	45
	100

Among 50 cases of diabetes recently examined in private practice he found:

	Cases.
Both knee-jerks lost in	6
One present, one absent in	1
Both present	43
	50

In severe cases of diabetes the wrist-jerks are often absent; usually they are lost when the knee-jerks are absent. In 50 cases (mostly of the severe form) the condition of wrist-jerks was as follows:

[1] Note on the Tendo Achilles Jerk and other Reflexes in Diabetes Mellitus. Reprinted from the Review of Neurology and Psychiatry, October, 1903.

	Cases.
Both absent in	30
Both present in	19
One absent, one present in	1

Referring to the fact that the wrist-jerk is sometimes absent in healthy individuals, Williamson examined over 100 individuals, who were either in good health or suffering from some local surgical affection not likely to have any influence on the reflexes and found the wrist-jerks present in 75 per cent. and absent in 25 per cent.

In 19 cases of diabetes in which the wrist-jerks were present, the knee-jerks were also present in 18. In the 30 cases in which the wrist-jerks were lost, the knee-jerks were absent in 25. Williamson observes also that the superficial reflexes—plantar, abdominal and epigastric—are seemingly not influenced in diabetes.

Heart and Blood-vessels.—Arterial sclerosis sooner or later presents itself in almost every case of diabetes mellitus. That it is in some instances at least the direct result of the irritating qualities of the blood seems substantiated by the fact that it is so often found in young subjects, not in the very young, but in those under thirty, as well as in older persons in whom, of course, it may be due to other causes, operating in the old. Such sclerosis is doubtless responsible for many cases of nephritis and albuminuria often associated with diabetes. Sclerosis may also be one of the causes of gangrene so often the terminal event in diabetes, and of the rarer termination by apoplexy. The involvement of the coronary arteries may account for the cardiac asthma and angina pectoris which are occasionally found in diabetes. Doubtless these conditions may also be quite independent of the disease.

Prominent *cardiac* symptoms are not usual in diabetes, nor is there any form of cardiac disease to which diabetes itself directly predisposes. Yet a good deal has been written on this subject by J. Mayer, Ord, Huchard, Vergely, Israel, Ebstein, Leyden and Naunyn. J. Mayer,[1] of Carlsbad, found enlargement including dilatation as well as hypertrophy of the heart in 82 out of 380 cases. Mayer also found cardiac hypertrophy recorded in 13 per cent. of the cases of

[1] J. Mayer, Zeitsch. f. klin. Med., Bd. XIV., 212; Berliner klin. Wochenschr., 1890, 457.

diabetes examined in the Pathological Institute of Berlin, and Israel[1] found hypertrophy in 10 per cent. of cases of diabetes examined *post-mortem*. Hypertrophy may be the direct result of arterial sclerosis or of the renal complications of diabetes. This is sustained by the fact that in all of the 13 per cent. of cases of cardiac hypertrophy Mayer also found recorded hypertrophy of the kidney, probably the parenchymatous enlargement referred to when treating of morbid anatomy. Prolonged arterial sclerosis always leads to hypertrophy and its symptoms may be expected at times. On the other hand, cardiac weakness attested by feebleness of pulse and frequent rate are often seen in the terminal stages when the heart, too, may share in the atrophic process. Cardiac asthma and angina pectoris may be the result of such weakness as well as of arterial sclerosis, to which last Leyden[2] especially ascribed "diabetic asthma." I have met profuse, blood-stained bronchorrhea, associated with diabetic asthma, recurring at intervals in one of my cases.

The late Dr. Charles W. Purdy called attention to *increased arterial tension* as a frequent symptom of diabetes mellitus. This is a symptom which might be reasonably expected as the glucose is an irritant which may readily excite vasomotor tension, which in turn is a natural forerunner to endarteritis and arterio-sclerosis referred to. Dr. Purdy however also found increased arterial tension in the only two cases of diabetes insipidus in which he made the sphygmographic examination. These cases do not admit of a similar explanation.

Among *vasomotor* and *trophic* derangements of the skin which may be ascribed to neuritis are herpes zoster, glossy skin, perforating ulcer and various forms of local asphyxia, including dropping of the nails and even fingers and toes—the various manifestations of Raynaud's disease. Herpes zoster is accompanied by the usual neuritic pain. Perforating ulcer differs from that occurring in other circumstances in being found in unusual situations (soles and between the toes). It invades the deeper parts and lays open especially the metatarso-phalangeal joint. I have met two cases of perforating ulcer of the foot in diabetes mellitus.

[1] O. Israel, Verhand. d. Congr. f. innere Med., Wiesbaden, 1892, I., 353; Virchow's Archiv, Band LXXXVI., 299.

[2] Leyden, Asthma und Diabetes Mellitus, Zeitschr. f. klin. Med., Bd. III.

Eye Symptoms.—See also Section on Ocular Manifestations in Diabetes Mellitus by Dr. de Schweinitz.

Cataract was long ago noted by Prout in association with diabetes. Griesinger found it present twenty times in 225 cases collected, Bouchardat once in 38, Roberts once in 45, and Dickinson once in 28 cases dying of diabetes in St. George's Hospital, London. v. Graefe, from the standpoint of the ophthalmologist drawing material from Berlin hospitals, thought cataract occurred in 25 per cent. of all cases. Frerichs in a mixed practice found it 19 times out of 400 and Seegen in pure private practice found it in about 4 per cent. of cases. Cataract is the more sure to be the direct result of diabetes the younger the subject. It usually occurs in advanced stages, but has even been the first symptom of the disease noticed. It develops rapidly, and is nearly always symmetrical, involving both eyes simultaneously, but not to the same degree. Litten says this is true only of children or persons under 20, and that in old people it is often unilateral.

The experiments of Kunde,[1] Dr. S. Weir Mitchell[2] and Dr. B. W. Richardson[3] led them to conclude that the cataract is due to an exosmotic loss of fluid from the lens, but Von Graefe, from the vantage-ground of a large experience, concluded it was the result of an impaired nutrition, itself caused by the vitiated sugar-laden blood.

In 1880 the late Dr. Albert G. Heyl,[4] from a case in the practice of Dr. Louis Starr, in which there was also cataract, discovered and pictured an unusual condition of the ocular fundus not heretofore described, to which he gave the name *intraocular lipemia.* This condition is characterized by the light-salmon color of the blood contained in the branches of both retinal vein and artery, as contrasted with the yellow-red color of the arteries and the dark cinnabar-red of the veins in health, by the apparently large diameter of these vessels, and by the very light color of the fundus, these appearances being due to the presence of molecular fat in abnormal amount in the blood.

[1] Kunde, Wurzburger Verhandlung., VII., 1856; Archiv für Ophthalm., Bd. III., p. 275.

[2] Mitchell, On the Production of Cataract in Frogs by the administration of Sugar, Amer. Jour. Med. Sci., N. S., Vol. XXXIX., 1860, p. 106.

[3] Journal de la Physiologie, par Brown-Séquard, 1860.

[4] Lipæmia and Fat Embolism in Diabetes Mellitus, New York Medical Record, Vol. XVII., 1880, p. 477.

Amblyopia is occasionally present. Nine cases were reported by Edmunds and Nettleship at a meeting of the Ophthalmological Society of the United Kingdom of Great Britain and Ireland in 1883,[1] in none of which were ophthalmoscopic changes visible, though in one, after death, on section of the nerve, changes were found extending through its length limited to a central group of fibers in which were observed thickening of connective tissue and degeneration of nerve filaments. Most of the patients were smokers.

Other affections of the organs of vision include retinitis which, though much less common than in Bright's disease, nevertheless sometimes leads to a recognition of diabetes. It is most usual in advanced cases, although it has been found in the milder grades. Ophthalmologists do not generally attempt to differentiate it from the retinitis of Bright's disease by its anatomical characters. As in Bright's disease retinal hemorrhages are a part of it, and it may be associated also with cataract. It may terminate in hemorrhagic glaucoma. Optic nerve atrophy may also be found in diabetes, but other causes must be carefully eliminated.

Among other rare eye conditions may be mentioned iritis, keratitis and simple amblyopia without lesion of the eye ground.

Conjunctivitis and hordeolum are sometimes troublesome symptoms.

Loss of accommodating power due to weakness of the nervo-muscular apparatus should also be mentioned. It may occur in any stage and improves with improvement in the general condition of the patient.

Affections of the ear include furuncle and *otitis media* with all the possible terminations of the latter. Tinnitus aurium was a striking symptom in one of my cases. Derangements of smell and taste also occur.

A *spongy state of the gums* with recession, and a flow of pus around the necks of the teeth is sometimes present, resulting in extreme cases, in absorption of the alveolar processes and falling out of the teeth.

Albuminuria is a symptom frequently found in advanced stages of diabetes. See Changes in the Urine.

[1] Philadelphia Medical Times, April 10, 1883, p. 350.

Unilateral sweating has been observed. Senator refers to three cases, one by Koch and Nitzenadel in a man of 30, where the left half of the face was involved; one by Kuelz in a man of 51, in which the left half of the face was affected, and a third by the same observer in a man of 46, in which the right half was involved. Some lesion of the sympathetic is believed to be responsible for this symptom.

Edema, a rare symptom, which sometimes appears late in the disease, may or may not be the result of the renal involvement. This symptom, when coincident with the enormous diuresis, is a truly remarkable one. It is probably due to the profound watery anemia established before the dropsy appears.

The term *diabetic coma* has been applied to a form of coma which sometimes is the immediate cause of death or at least immediately precedes death. The condition is one of sudden or gradually supervening unconsciousness, with or without previous irritability or uneasiness. Convulsions do not usually occur. In addition to coma there is frequent and feeble pulse, rapid and deep breathing. The strong respiratory movements contrast with the muscular weakness. The comatose symptoms are sometimes preceded for a day or two by intense muscular pain throughout the body and by abdominal cramp. It has been variously ascribed to poisoning by sugar, acetone, alcohol, diacetic acid, oxybutyric and other unknown substances, and by Professor Sanders and D. J. Hamilton[1] to slow carbonic acid poisoning due to fat embolism of the pulmonary vessels, the result of lipemia. In Dr. Starr's case of diabetes, alluded to on p. 303, a careful study by Dr. J. H. C. Simes of sections of the lung, treated by perosmic acid, "demonstrated the fact that the pulmonary blood-vessels were occluded by fat emboli." But as Dr. Starr says, the share of the embolism in producing the coma in this case is very uncertain, since the patient had a pneumonia which though limited in extent was quite sufficient to cause the fatal issue.

[1] Edinburgh Med. Journ., July, 1879. The conclusions of these gentlemen were based upon the clinical histories and the results of the post-mortem examination of several cases. For these I must refer the reader to their original paper in the Edinburgh Medical Journal. A summary of the data leading to their hypothesis will be found in Dr. Starr's paper on Lipemia and Fat Embolism in Diabetes Mellitus, published in the New York Med. Record, Vol. XVII., 1880, p. 476.

At the present day it is held by most authorities, including Stadelmann, Minkowski, von Jaksch, and Naunyn, that diabetic coma is caused by an acid intoxication of the blood with organic acids among which diacetic, oxybutyric and lactic acids and acetone are conspicuous. These substances will be considered later in treating of changes in the urine. Any one or all of them may be wanting and it is thought there may be other fatty acids as yet undiscovered which may be responsible.

Von Noorden, on the other hand, is not inclined to accept the view of the acid nature of the poison and cites in opposition the almost total failure of the alkaline treatment to arrest diabetic coma. He is inclined to accept the theory of Klemperer, who holds that at certain stages of diabetes there are present poisons of unknown nature. These poisons exert: (1) An injurious effect on the brain (coma), (2) a destructive effect on protoplasm, as the result of which are produced large amounts of diacetic acid and oxybutyric acid, so that coma, the formation of diacetic and oxybutyric acid and diminished alkalescence of the blood are not subordinate but coördinate events. "Apart from theory," adds v. Noorden, "we may say: mild degrees of acetonuria and diaceturia, such as sometimes occur on the withdrawal of carbohydrate food and disappear in a short time are without serious significance. Higher degrees, especially when associated with oxybutyric acid, are always a serious symptom and demand measures for improving the nutrition of the patient. *They are not, however, to be regarded as contraindicating the rigid withdrawal of carbohydrate food.*"

It would seem, however, that the mystery of diabetic coma is on the eve of solution. At least we are now able to furnish a reasonable explanation of its phenomena, especially well stated by F. W. Pavy in a recent paper, "On the Aceton Series of Products in Connection with Diabetic Coma."[1] It is well known that in health the blood conveys to the tissues the oxygen absorbed by the lungs, and from the tissues back to the lungs the carbonic acid produced in the so-called "internal respiration." The oxygen thus conveyed is in loose combination with the hemoglobin whence it is appropriated by the living protoplasm and in the course of a succession of retrograde changes

[1] The Lancet, February 12, 19, 26 and August 9, 1902.

unites with its carbon and hydrogen to form carbonic acid and water. The carbonic acid thus formed combines with sodium carbonate, forming bicarbonate, which returning to the lungs, yields its looser carbonic acid and again becomes sodium carbonate.

In the conditions favoring diabetic coma the acetone series and especially the oxybutyric acid not only seizes on the sodium of the blood but on the ammonium of normal catabolism and thus this transport-service of the blood is interfered with. Hence the carbonic acid accumulates, the tissues become choked with the product of their activity and coma results with an ultimately fatal termination. Pavy continues: "A corresponding defect in the carrying power of the blood for oxygen is occasioned by carbonic oxid. This gas reaching the corpuscles, combines so tenaciously with their hemoglobin as to prevent the subsequent ingress of oxygen. The tissues are in this way prevented from obtaining their supply of oxygen just as they are prevented from getting rid of their carbonic acid under the existence of acidosis.

Such an explanation is sustained by the forced effort at respiration which characterizes the patient with diabetic coma. The respirations are deep and prolonged but ineffectual, although there is no obstruction to the entrance of air into the chest. The difficulty is not in the mechanism of the lungs but in carrying out the conditions of a successful internal respiration as already explained in response to "air hunger," *the besoin de respirer* of the French physiologists.

The theory of a direct toxic action of the acetone series has also received support from recent studies, especially of Sternberg,[1] who refers the coma to the toxic action of an assumed antecedent of oxybutyric acid, viz., amidobutyric acid. His conclusions are based on experiment as to the effect of the amidobutyric acids upon the system, which went to show that β-amido-acid acted toxically, producing symptoms resembling those of diabetic coma. Grube[2] has repeated Sternberg's experiments with confirmatory results.

[1] Zeitschrift für klinische Med., 1899, Bd. XXXVIII., pp. 1, 5.

[2] Archiv. für Experimentelle Pathologie und Pharmakologie, 1900, Bd. XLIV., p. 349.

Alterations in the Blood, Urine and Other Secretions.

The Blood.—It has already been mentioned that in diabetes the blood becomes highly charged with sugar, and that acetone, diacetic and oxybutyric acids are also found in it. From a proportion of .5 to 1.5 per 1000, glucose may reach 1.54 and even, according to Seegen, 5.76. From the presence of glucose, we should naturally expect a viscidity and higher specific gravity of the blood serum, which has been found as high as 1033, that of the normal serum being 1028. On the other hand, the serum has been found thinner than normal, containing, according to different analyses, from 80.2 to 84.8 of water instead of the normal 78–79 per cent. The specific gravity of the whole blood has been found by Davy to be 1061 as compared with a normal of over 1050. Nasse found it slightly below normal 1048–50. From the fact that no sugar at all has been found in the blood in certain cases after death, it does not follow that sugar was not present, since it very rapidly undergoes decomposition in cadaveric blood.

The presence of fat in the blood of diabetics was shown as far back as 1799 by Mariet of Edinburgh. It is found only in the severest cases. The quantity found ranges from 3 to 123 per 1000. The fat is in a state of molecular subdivisions. It must not be forgotten that fat occurs also in the blood of healthy individuals, especially after a full meal, but it does not exceed 1.6–1.9 per cent. Lipemia occurs also in other diseases.

As to other blood changes there is a tendency to reduction in red blood cells and an increase in the relative proportion of colorless cells. The former is not marked at first, but may become decided. The leucocytosis may reach 50,000 cells per cubic millimeter, as contrasted with a normal of 6 to 8,000. The reduction in red cells is probably the direct result of their disintegration, though its cause is unknown. Extensive destruction of this kind is associated with a hemosiderosis or pigmentation by iron particles, especially of the liver, spleen, pancreas and heart muscle. Quincke[1] first demonstrated this peculiar pigmentation in 1877. Allusion has been made to the occasional association of such sideroses with hypertrophic cirrhosis of the liver in the so-called "bronzed diabetes." The pigmentary deposit

[1] Festschrift für Albrecht v. Haller, 1877.

in these cases is less difficult of explanation, for in such the blood contains biliary salts which readily dissolve red corpuscles.

Bremer[1] made an interesting discovery as to the behavior of the blood of diabetics towards staining fluids, by which the former may be distinguished from non-diabetic blood. A cover-glass preparation of blood is made in the usual manner, and a thin, even film obtained. For comparison a similar preparation of normal blood is made. Both are placed in a wide-mouthed bottle or small beaker containing 10 grams each of alcohol and ether. This vessel is then placed in hot water, and the ether-alcohol allowed to boil for four minutes. The cover-glasses are then stained in a solution prepared as follows: Saturated watery solutions of eosin and methylen blue are mixed in equal parts. A precipitate forms; this is filtered off, washed and dried. It is then reduced to a powder, and one twenty-fourth part of eosin and one sixth of methylen blue are added. From 0.025 gm. to 0.05 gm. of this mixture is dissolved in 10 gms. of a 33 per cent. solution of alcohol. This staining fluid does not keep well and must be freshly prepared shortly before the cover-glasses are stained. After remaining in the above fluid for four minutes the cover-glasses are washed in water. The *film* of diabetic or glycosuric blood is stained *bluish-green,* non-diabetic blood *reddish-violet.* Under the microscope the red corpuscles of diabetic or glycosuric blood are stained green, whilst those of non-diabetic blood are stained of purple or madder color. Bremer found this reaction in fifty cases of diabetes mellitus or glycosuria, and believes that in these diseases a diagnosis can be made by examination of a drop of blood. In a postscript he adds that in one case recently examined he has obtained negative results. Le Goff has confirmed the results of Bremer.

More recently Bremer[2] has suggested the following method of distinguishing the blood of diabetes from normal blood by aniline stains:

A drop of blood is smeared by means of a slide over a second slide, so as to cover about one half or one third of the surface. A number of slides are prepared from diabetic and non-diabetic blood

[1] Centralblatt f. d. med. Wissenschaft, Berlin, 1894, Med. News, February 19, 1895; New York Med. Jour., March 7, 1896.

[2] Centralbl. f. innere Med., Leipzig, 1897, No. 22.

(the latter for control staining). As the reaction can be seen by the naked eye, tolerably thick layers of blood are employed, and these have, as nearly as possible, the same thickness. The blood preparations are now heated in a hot-air chamber for six to ten minutes, at a temperature of 125° C., avoiding especially heating above 140° C.; and the heat should not be applied for more than ten minutes. The slides are then stained, in a 1 per cent. watery solution of one of the following stains: Congo red, methylen blue, Biebrich scarlet, or Ehrlich-Biondi's staining fluid. Slides of diabetic and non-diabetic blood are treated in exactly the same manner for comparison. The results are as follows: After staining in Congo red for one and a half to two minutes, then washing rapidly in water and drying, the non-diabetic blood is stained, whilst the diabetic preparation is not stained, or only indifferently stained. Methylen blue stains non-diabetic, but not diabetic blood. With Biebrich scarlet diabetic blood is stained deeply, the non-diabetic is unstained. If preparations be placed in Ehrlich-Biondi's fluid two to three minutes the diabetic blood is stained orange, whilst the non-diabetic blood is stained violet. Beautiful contrasts are obtained by double staining as follows: Preparations of diabetic and non-diabetic blood are stained in a 1 per cent. watery solution of methylen green for one and a half to two minutes and then washed. Both preparations are green, the diabetic being more deeply stained. They are next placed in a one eighth per cent. watery solution of eosin for eight to ten seconds. The diabetic preparations remain green; the non-diabetic take the eosin stain. Similar results are obtained with methylen blue and eosin.

Dr. R. T. Williams has called attention to a property possessed by diabetic blood in bulk of decolorizing methylen blue, by which it may be distinguished from non-diabetic blood. The following is his exact method:[1]

A small *narrow* test-tube[2] is well cleaned, and at the bottom of the tube are placed 40 cu. mm. of water, to measure which he uses the capillary tube of a Gower's hemoglobinometer, graduated for

[1] Diabetes Mellitus, London, 1898, p. 189.

[2] It is important to use a narrow test-tube, so that the upper surface of the fluid, with which the air comes in contact, may be as small as possible.

20 c.c. The tip of one of the patient's fingers is cleaned and dried, then pricked, and when a large drop of blood has escaped, 20 cu. mm. are sucked up into the small capillary hemoglobinometer tube. The blood is then blown gently into the water at the bottom of the small test-tube. Any adhering to the side of the tube is carefully shaken to the bottom. Then 1 c.c. of a 1 in 6,000 watery solution of methylen blue is added. (To measure this Dr. Williamson uses the 1 c.c. tube supplied with Southall's ureometer.) To the mixture, finally 40 cu. mm. of liquor potassæ are added. The contents of the tube are then well mixed by shaking. As a control experiment, a second test-tube of similar size is taken, and into this is placed the same quantity of non-diabetic blood with the same proportion of water, methylen blue, and liquor potassæ.

The fluid in each tube has a fairly deep blue color. Both tubes are then placed in a beaker, capsule, or very wide test-tube containing water. Heat is applied until the water boils and is allowed to continue boiling for about two minutes. By the end of this time the fluid in the tube containing the diabetic blood changes its color from fairly deep blue to a dirty pale yellow (almost the color of normal urine). Whilst the fluid in the tube containing the non-diabetic blood remains blue, occasionally it becomes bluish green, sometimes pale violet, but it is never decolorized, that is, it never loses its blue color. The tubes should be kept quite still while in the water-bath, as, by shaking, the decolorized methylen blue is oxidized by the oxygen of the atmosphere, and a blue tint may then return to the fluid. This is the reason why it is necessary to use a water-bath, since, if the test-tubes be heated directly over the spirit-lamp, it is difficult to avoid shaking the fluid. Dr. Williamson ascribes the decolorizing effect to the glucose in the blood.

The Urine.—The most noticeable peculiarity of diabetic urine, to the patient, is its *enormous quantity,* which has been known to exceed 70 lbs. (31.78 kilograms) in 24 hours, while apocryphal accounts of larger amounts are extant. Frank records 52 lbs. (23.6 kilograms). Bardsley[1] 36 pints (20.4 liters) and 32 pints (18.16 liters). Bence Jones found 56 pints (31.78 liters), Sir Thomas

[1] Bardsley, article on Diabetes in the Cyclopædia of Practical Medicine, Philadelphia, 1845, p. 607.

Watson and Dr. Dickinson 26 pints (14.77 liters), and Dr. Pavy 32 pints (18.16 liters). I recall fifteen pints (half as many liters) as the twenty-four hours quantity and doubtless have met larger quantities. From 70 to 100 ounces (2,100 to 3,000 cubic centimeters) are common quantities.

The quantity of urine passed is limited by the amount of fluid ingested. For while it is possible that the amount of urine secreted may exceed for a very short period that taken in, it is evident that this cannot continue for any length of time, and in point of fact it is found to be almost invariably a little less, the remainder being removed by the lungs, skin, and bowels. On the other hand, it was early observed by Cowley[1] (1788), that the quantity of water occasionally is not at all, or but slightly increased. To this condition Frank,[2] another old author, gave the name of *diabetes decipiens.* But all modern observers unite in saying that this phenomenon, though occasionally occurring, is but a temporary one. It may characterize the beginning, or appear for a time in the course of the disease.

It is well known, also, that intercurrent disease, especially febrile affections, sometimes diminish the quantity of urine as well as the amount of sugar excreted; while the same diminution of urine and sugar also occasionally occurs towards the fatal termination of the disease.

The most important change in the urine is the *presence* of sugar in the form of *glucose.* Of this the quantity varies greatly in different cases and at different times in the same case. Every case of trifling and temporary glycosuria should not however be considered a case of diabetes. The sugar should be easily recognizable by the ordinary tests, and should be constant. From what may be indicated as "evident traces" the proportion of sugar may reach as much as 15 per cent. The largest percentage I have ever met was 11 per cent., though another physician estimated 25 per cent. for this same urine. My titration made with Fehling's solution was confirmed by the polarizing saccharimeter. The twenty-four hours' quantity varies similarly. The maximum quantity secreted in this

[1] Cowley, Th., London Medical Journal, 1788.

[2] Frank, J. P., De curandis hom. morbis epitome. Lib. V., De Profluviis, Pars. I., Manheimii, 1794.

time appears to be that reported by Dickinson, wherein a man 25 years of age voided 50 ounces, or 1,500 grams, in 24 hours. But the more usual quantity is from 10 to 80 milligrams to the cubic centimeter, or from 20 to 25 grams in 24 hours; this corresponds nearly to from 5 to 30 grains to the fluid-ounce of the English system, or from 300 to 3,800 grains in the 24 hours.

The effect of intercurrent febrile disease in producing a diminution in the amount of sugar excreted has been alluded to; also a similar decrease and even disappearance towards the fatal termination of a case. The possibility of this occurrence should be remembered, lest an illusory improvement thus produced be mistaken for an actual one.

A diminution and even disappearance of sugar from the urine has been observed by Bouchardat, and more recently by Kuelz and others, as the result of muscular exercise, while it is scarcely necessary to say that accidental as well as intended changes in diet are followed by consequent variations. So, too, urine passed after fasting, as on rising in the morning, contains generally less sugar than that passed after a meal, and in testing urine whence sugar is disappearing, it is well to remember this fact also, as sugar may entirely have disappeared from a urine passed on rising, while it may be present in that passed after a meal.

The sugar found in urine in diabetes is almost invariably glucose. Other varieties of sugar have, however, been met. Thus *levulose* or left-rotating sugar has been found in several cases both alone and associated with grape-sugar. The quantity of levulose is never large, not, it is said, exceeding one per cent. The occasional occurrence of levulose, as Naunyn says, is very interesting, because this variety of sugar is easiest of assimilation by diabetics, sometimes in quite large quantity, so that it may even be used in sweetening. When taken in very large quantities it appears in the urine for the most part as dextrose. Le Noble and Van Ackeren have both found maltose in urine, but neither say whether it occurred alone or in association with glucose.

Inosite is rarely found. Gallois met it in 5 out of 35 diabetics.[1] A remarkable case is that of von Vohl,[2] in which 18 to 20 grains were

[1] Gallois, Comptes Rendus, 1863, p. 533; also De l'inosurie, Paris, 1864.

[2] Vohl, Archiv für physiol. Heilkunde, 1858, N. F., II., s. 410.

excreted daily. This is commonly regarded as a case of glycosuria which passed over into inosituria. Naunyn says it does not appear that Vohl produces any evidence that this is the case and thinks it should be characterized rather as a case of diabetes insipidus with inosite secretion, since "inosit is not a sugar."[1] *Pentose*[2] has been found associated with dextrose in diabetes mellitus.

Consistently with this increased amount of solid matter in solution, the *specific gravity* of diabetic urine is, as a rule, high, 1040 being very common, 1050 not infrequent, while Bouchardat found it as high as 1074 in one instance. The well-known disposition of diabetic urine to become *frothy* on shaking, and to maintain this frothy condition, is a natural physical result of its increased density. Sugar is found, however, in urine with as low a specific gravity as 1005. Pavy records a specific gravity of saccharine urine as low as 1010, and Dickinson as low as 1008. Such low specific gravities may be due to previous destruction of sugar by fermentation, as well as to low proportion of other normal ingredients.

Concurrent with the increase in quantity of urine is a *paleness,* which amounts at times to an almost absolute absence of color, the urine, in moderate bulk, being as colorless as spring-water. This clearness may diminish on exposure, and almost all diabetic urine, sooner or later after exposure at a moderate temperature, becomes a little cloudy from the multiplication of fungi.

The *odor* of the urine is usually normal when first passed, but sooner or later, in consequence of fermentation setting up, it may acquire an acetous odor. The latter change also increases the intensity of the normal acid reaction, and maintains it much longer after exposure to the air than is the case with normal urine. This acetous odor is also due to acetic acid developed in the acetous fermentation. The urine may have a sweetish odor when passed, an odor which has been compared by one of my medical friends who has diabetes, to "sweet brier."

[1] Naunyn, Diabetes Mellitus, Wien, 1898.

[2] Pentoses or pentaglucoses are varieties of sugar whose molecules contain five atoms of carbon or multiples thereof, as distinguished from the hexoses which have six atoms of carbon. They reduce alkaline copper solutions strongly and form with acetate of phenylhydrazin, osazone which is distinguished from hexoses (glucose) by its lower melting point (159° C.).

Along with the absence of color in diabetic urine, the absence of *sediment* is a conspicuous feature. This is not invariable, however, for a copious *uric acid* deposit is sometimes early present, and at others appears sooner or later coincidently with the increased acidity of the urine resulting from fermentation. It is thought by some to be a favorable symptom. In the sediment may also be included the fungus known as *penicillium glaucum,* common to acid urine, as well as the more characteristic yeast or sugar fungus, the *torula cerevisiæ.* This also sometimes appears as a *mould* on the surface of the urine.

Of the normal chemical constituents of the urine *urea* is almost invariably increased. This is contributed by three conditions. The first is the ingestion of large amounts of nitrogenous food, whether to appease the appetite or by the physician's advice. Such ingestion is, of course, followed by an augmented excretion of urea. The second cause is the increased discharge of water by the kidneys, such increase always carrying out with it an increased quantity of urea, washed out of the blood, as it were, by the water passing through them. The third cause is the decomposition of the fixed albumins of the tissues. This cause operates especially in the severest cases or in the last stages, where it contributes to the irresistible wasting which characterizes them, in spite of the enormous food-consumption. In such event, the fixed albumins are split up into urea and sugar.[1] In confirmation of the above are the comparative researches of Reich, Gaethgens, Pettenkofer, and Voit which show that certain diabetics voided with the urine more nitrogen than corresponded with the nitrogen ingested.[2] These early researches are amply sustained by more modern ones of Naunyn, Van Noorden and others.

We have seen how the albumins may be split up into urea and sugar. Dr. Haughton early showed that albumin, by the addition of small quantities of water, carbonic acid, and oxygen, furnishes the elements to produce glucose and urea in the proportion by weight of nearly five grains of glucose and one grain of urea. Dr. Dickinson neatly puts it, "albumin is put into the mill, sugar and urea come out; and, like the flour and the bran, wax and wane together." Such a splitting up takes place in health, but the sugar is not discharged

[1] See section on Etiology.

[2] Senator, loc. citat., p. 899.

in the urine as the urea is, but is oxidized for the production of heat, or converted into fat and stored up as such.

As regards *uric acid,* we have seen it is not unusual as a sediment. The most recent studies also show that there is an absolute increase, which is however moderate and not of much significance. It is probably due to increased meat ingestion.

Kreatinin also was thought by the older observers to be diminished, but the more recent studies of Senator show it to be secreted in increased amount. This increase is probably also due to increased meat ingestion. Kreatin thus introduced is excreted as kreatinin. Of the other constituents of the urine *sulphuric acid, chlorin, phosphoric acid, lime,* and *magnesia* are said to be increased, phosphoric acid and lime especially so. Neubauer, Bœcker, Benecke, Vogel, Gæthgens, Dickinson and Van Noorden are all agreed to this. The phosphoric acid is mainly derived from the animal food especially through the oxidation of the phosphorus contained in the albumin molecule. Lime and phosphoric acid may be possibly increased by the disintegration of tissue containing them. This can only be bone. Van Eckeren and Teubaum in a severe case of diabetes found more lime and phosphoric acid than could be accounted for by the ingested food. While admitting that most of the phosphoric acid, that combined with the alkalies, is derived from the food, Dr. Dickinson is inclined to think that the smaller part, that combined with the earths, is specifically increased by the disease. This phosphoric acid is derived from the disintegration of nervous tissue, while the lime which does not exist in nervous tissue is dissolved out of the other tissues by the acid in its transit.[1]

Ammonia is commonly increased in the urinary secretion of diabetes. Normally present in the proportion of .5 gram to a gram in the 24 hours it is increased by an enlarged meat diet to 1.2 to 1.5 gram. The same cause leads to its increase in diabetic urine. But there is a further stimulus to its increase in severe cases of this disease. It will be seen presently that there occurs in these an accumulation of organic acids which stimulates the organism to produce ammonia for their neutralization and thus to prevent their union with carbonic acid to form urea. Under these circumstances

[1] Dickinson, op. citat., p. 124.

the ammonia in urine has been known to increase to 3.6 and even 12 grams in the 24 hours.

Of abnormal constituents *albumin* is not infrequently present. The proportion of cases with albuminuria varies very greatly, according to different observers. A range of from 10 to 68.7 per cent. by different observers was collected by Von Noorden, while he himself found it in 23.5 of all cases including severe, intermediate and mild. It is interesting to note that the severest cases included those showing the smallest quantity, viz., 13.3 per cent., while the intermediate and mild included nearly equal proportions, 29.3 and 28.9 respectively. Moreover, the number of cases of albuminuria increased with the age of the patient.

The subject of albuminuria in diabetes mellitus has been recently thoroughly gone over by Dr. Arthur R. Elliott, of Chicago.[1] His paper, too, shows quite different proportions by different reporters. Thus Pollatchek found albumin in 37 per cent. of cases. Von Schmitz found albumin in 63.4 per cent. of cases.

Various attempts at classifying the albuminuria of diabetes have been made. A very simple and to me seemingly the best classification is that of *toxic irritative* and *simple irritative* albuminuria.

The *toxic albuminurias* are those associated with the severe forms of diabetes towards their termination and are attended with changes in the renal epithelium of a necrotic character, excited by the acid toxins so often mentioned in connection with the disease. The changes are those already referred to as the "cellular necroses" of Ebstein and the "lesion of Ehrlich." The albuminuria in these cases is seldom large and bears no relation in quantity to the glycosuria. In fact in many cases the glycosuria diminishes as the albuminuria increases, and this circumstance has occasioned much discussion in efforts to explain it. The most satisfactory explanation, and one which is in accord with experimental observation is that, thus altered, the renal tubules lose their permeability for sugar and that the absence of sugar from the urine does not imply its absence from the blood. In confirmation the experiments by Ellinger

[1] Albuminuria in Diabetes Mellitus, a paper read before the Section of Medicine of the American Medical Association at its meeting, New Orleans, May, 1903.

and Seelig[1] demonstrated that while dogs from which the excretion of sugar was constant showed a diminution in the output of sugar after injection of cantharides, the sugar content of the blood was markedly increased. The same results were arrived at by Richter[2] in experiments with phloridzin diabetes. This variety of albuminuria is always accompanied by tube casts, and as stated is found in the terminal stages of severe cases. It is commonly rapid in its development and increases *pari passu* with the toxinuria. Hence his albuminuria is apt to precede and accompany diabetic coma and is of prognostic significance.

The simple irritative Albuminurias constitute by far the larger number. They are due to the irritative effect of sugar circulating in the blood of the kidney, and to the hyperfunctional activity of the organ necessary to the elimination of the sugar. The result is the parenchymatous change and ultimate nephritis already referred to. Such albuminurias are also small and of much less serious import.

According to Naunyn diabetes due to brain injuries and acute affections of the brain is especially apt to be associated with albuminuria.

Non-nitrogenous Organic Substances.—Among the abnormal constituents at times present in diabetic urines are certain non-nitrogenous organic substances already much discussed in connection with diabetic coma and changes in the blood. Among these *aceton, diacetic acid* and *-oxybutyric acid* are conspicuous. Originally supposed to arise from carbohydrate decompositions or fermentations they are now regarded as of proteid origin. In emphasis of this may be mentioned a case in Naunyn's clinic which secreted daily for three years 20 to 40 grams of oxybutyric acid on a diet of pure fat and albumin. So far from carbohydrate food increasing the secretion it seemed to diminish it, indeed at times the oxybutyric acid first makes its appearance when the carbohydrate food is withdrawn. The chief source of these substances is the fixed or tissue albumin, though this cannot be considered the only source as shown by cases in which large amounts of aceton are excreted while the patient still maintains his body weight. Von Noorden, who for-

[1] Verhandlungen des Congresses f. innere Medicin, Berlin, April 16–19, 1901.
[2] Zeitschrift f. klin. Med., Bd. XII., S. 160.

merly held the view that fixed albumin to the exclusion of food albumin is the source of aceton, etc., has explicitly retracted this belief for the reason given. With normal nutrition traces of aceton may be found in the urine, but diacetic acid and oxybutyric acid are totally absent in health.

Aceton and diacetic acid arise by a like splitting off from the albumin molecule, diacetic acid being regarded as the mother substance which passes rapidly over into aceton, so that if a small quantity of diacetic acid is formed in the blood aceton alone is found in the urine, while if a large quantity of diacetic acid is formed both diacetic acid and aceton are found in the urine. The conversion of diacetic acid into aceton may take place in the urine or in the tissues, including the blood, since aceton has been found in the expired air in considerable quantities.

As already mentioned, there is reason to believe that *oxybutyric acid* is the preliminary stage of diacetic acid, and this of aceton. It is found in urine of diabetics much less frequently than are diacetic acid and aceton, and while its abundant secretion is justly regarded of unfavorable prognostic import, threatening diabetic coma, this is not always the case. Van Noorden refers to a case of severe diabetes in which during a period of two and one half years, there was repeatedly a large amount of oxybutyric acid—at least two per cent.—who nevertheless enjoyed comparatively good health. While it is rarely found in diabetics who are in good condition it is often absent in others who are wasted and emaciated.

F. W. Pavy applies the term "composite" diabetes to that form usually severe in which not only sugar, but the aceton series of compounds are found in the urine. He ascribes the presence of sugar alone to a "wrongness of ascending metabolism" and the presence of sugar plus the aceton series to an added "wrongness of descending metabolism." However originating, all of these substances carry with them in their exit from the body "unutilized energy." The aceton series referred to are β-oxybutyric acid, diacetic or aceto-acetic acid and aceton.

The continued presence of the aceton series in the urine of diabetics is nevertheless regarded as an unfavorable symptom. Especially is this true of large quantities of aceton, and although it is commonly

thought that a vivid reaction with the chlorid of iron test, indicating the presence of diacetic acid, is a danger sign of even greater importance than the reaction for aceton, v. Noorden considers it is less to be relied upon than evidence of the presence of large amounts of the latter. Only a strong reaction with the chlorid of iron, such as continues after repeated dilution with water points to a large quantity of diacetic acid plus aceton. A feeble reaction may mean either small or large quantities of aceton.

Of the other secretions the *perspiration* (it is commonly scanty and the skin is more often dry) may contain sugar, sometimes a notable quantity, as much as 6½ grains having been extracted by Fletcher from a piece of flannel three inches square, which had lain upon the skin 48 hours. The *saliva* has rarely been found to contain sugar. Whether the *gastric juice* ever contains it under similar conditions is disputed. This secretion has been studied by von Noorden, Rosenstein, Honigman, Gans and Kirikow, who found no wide deviation from the normal. Sugar has been found in the exudations and effusions of diabetic patients.

Duration.

Acute diabetes may be said to be scarcely known, and although cases are related by Becquerel, Wallach, Senator, Bence Jones, Roberts and Dickinson, in which death followed within a very short time after its detection,—periods ranging from six days to six weeks,—yet in no instance can it be averred that the disease was of as short duration as it seemed, while in several there was reason to believe that it has lasted longer. The shortest case in my own experience was that of a little boy of three who died 17 days after his parents consulted me and declared that he was well a week or at most ten days earlier. This would make the duration of the disease 27 days. But against this is the well-recognized fact that it is difficult to ascertain the exact date of the beginning of any case of diabetes, especially in children. It may be said, then, that diabetes mellitus is a disease almost invariably of long duration. A case of intermittent diabetes, under the successive observation of Dr. Prout and Dr. Bence Jones, lasted 16 years, and one was under similar observation of the last-

named physician and Dr. Dickinson for 15 years. Lebert mentions a case which had lasted 18 years, the patient enjoying good health while on appropriate diet, but lapsing immediately to diabetism on an indiscriminate diet. The younger the age the shorter the duration and the more promptly fatal the result, while after middle age under treatment the duration may be indefinite. A case under my own observation for ten years had well determined diabetes 17 years earlier.

The following table from Dr. Dickinson's work contains the duration of 100 cases collected by Griesinger, and alongside of it that of 25 which ended fatally at St. George's Hospital:

Duration.	St. George's Hospital	Collected by Griesinger.
Less than ¼ year,	1	1
Between ¼ and ½ year,	2[1]	2
" ½ " 1 "	8	13
" 1 " 2 "	6	39
" 2 " 3 "	5	20
" 3 " 4 "	1	7
" 4 " 5 "	0	2
" 5 " 6 "	0	1
" 6 " 7 "	0	2
" 7 " 8 "	0	1
Undetermined,	2	12
	25	100

From which it may be concluded that diabetes rarely proves fatal in less than six months after its accession, while few cases last more than four years. My own experience in private practice in which alone it is possible to watch cases for any length of time, finds the average duration much longer. On the other hand Dickinson's and Griesinger's statistics are drawn from hospital cases, which before admission were necessarily under much more unfavorable conditions than patients in private practice. Hence it is almost certain that the average duration of cases would considerably exceed that deduced from this table.

[1] In both these instances death occurred at six months.

Complications.

The question of complications is a difficult one because the line of demarcation of symptoms and complications is not sharp. Thus some would place pruritus, boils, carbuncles, etc., among complications while I have placed them among symptoms, though not essential symptoms. On the other hand pneumonia is a frequent complication, diabetes favoring its occurrence. So is pulmonary tuberculosis a true complication. Furunculosis should, strictly speaking, be considered a complication because it is a microbic affection directly resulting from the vulnerability of the skin due to saturation with sugar. On the other hand should all but the most essential symptoms be strictly placed the category of symptoms proper would be very small. Jaundice sometimes occurs, and having presented itself twice in the history of a case under my observation, can hardly be considered accidental, although I am at a loss to account for it. Senator says that, when not an accidental complication due to a catarrh of the duodenum, it may result from compression of the biliary capillaries by the overloaded blood-vessels or enlarged gland-cells of the liver.[1] Many other conditions treated by many as complications are considered by myself under morbid anatomy or symptoms. Such are renal and hepatic changes.

Diagnosis.

The diagnosis of diabetes mellitus is usually very easy. Unnatural thirst and copious diuresis should always suggest a chemical examination of the urine, but unfortunately these symptoms sometimes escape attention, and it is only by adopting a careful habit of testing the urine in all cases of disease, the least doubtful in their nature, that some less evident cases are detected. And although there are sources of error in testing for small quantities of sugar in urine, which are only overcome with some trouble, the quantities of sugar thus difficult of detection are not *usually* of clinical significance. Almost any one of the tests, therefore, which are found in the various manuals for the examination of urine, applied with ordinary care, will respond to such quantities of sugar. The power

[1] Senator, loc. citat., p. 912.

of diabetic urine to reduce the protosalts of copper has long been known. The oldest form of copper-test, applicable only for qualitative testing is known as Trommer's.

Trommer's Test.—This test, though spoken of by some as old-fashioned, is the fundamental test on which Fehling's test is based and should therefore be familiar to all. It is done as follows:[1]

1. A portion of urine is thoroughly alkalized by adding say half its volume of liquor sodæ or potassæ in a test tube. To this mixture is added drop by drop a weak solution of copper sulphate say one to thirty. On first adding the copper there is immediately liberated a blue precipitate of hydrated cupric protoxid, *which if sugar is present, is redissolved* on shaking the mixture, producing a clear blue transparent liquid. If, on the other hand, no sugar is present, the fluid will remain turbid. If the copper is redissolved, more should be added until a slight excess remains undissolved. The mixture is then boiled and in the presence of sugar a copious yellow precipitate of *hydrated* cupric suboxid takes place. This subsequently loses its water and becomes the *red suboxid* which falls to the bottom or sides of the test-tube, to which it often closely adheres. Occasionally the precipitate of earthy phosphates is so copious as decidedly to obscure the reaction. In this event they may be removed by filtration after adding the alkali and slightly warming the mixture, before adding the copper and further heating.

2. A second similarly prepared mixture of these ingredients may be made and set aside for from 1 to 24 hours without the addition of heat. If sugar be present a similar precipitate of suboxid of copper will take place. This repetition of the test is not unimportant, since, according to Neubauer, the other organic substances which reduce the salts of copper do so only after long boiling. Hence also *prolonged boiling* should always be avoided.

[1] A reviewer of the second edition of my little book on the Examination of Urine, in the Medical Times and Gazette (London), was pleased to characterize my fondness for this test as old-fashioned. I do not think this view will be sustained by those who are in the habit of making very many qualitative testings of urine, using both Trommer's test and the quantitative solutions of Fehling, and I am glad to be able to quote the very explicit language of Senator, who says (article Diabetes, Ziemssen's Cyclopædia of Medicine, Vol. XVI., p. 963): "Trommer's test deserves to be ranked foremost on account of its certainty and ready applicability."

Fehling's Test.—When Fehling's or Pavy's solutions are used, the following method will be found delicate:

A small quantity of test fluid should be placed in a test-tube and diluted with about four times its bulk of water, then boiled alone for a few seconds. If the solution remains clear on thus boiling, add immediately the suspected urine drop by drop. If sugar is present in any quantity, the first few drops will usually cause the red or yellow precipitate, but if the reaction does not occur, the dropping may be continued until an equal volume of the urine has been added, the mixture being kept hot by repeated application of the flame. If no precipitate occurs, sugar is absent.

If a precipitate occurs on boiling the *test fluid alone,* a new supply may be obtained, or a little more soda or potash may be added, the fluid filtered, and it is again ready for use. The precipitate referred to is cuprous oxid, the result of a spontaneous reduction of the cupric oxid which sometimes occurs when Fehling's or Pavy's solutions are kept for some time. Boiling causes its precipitation, and hence the necessity of heating a solution which has been kept for any length of time, before adding the suspected fluid. All possibility of such source of error may be avoided by keeping the solution of copper separate from that of the potash and potassic tartrate, and mixing them at the moment they are required for use.

In doubtful cases, also, urine passed two or three hours after a meal should be tested, as well as that passed fasting, for the former will often contain sugar when the latter does not.

Quantitative Testing.—In judging of the progress of a case of diabetes under treatment, it is not sufficient to test the urine qualitatively, but a quantitative determination of sugar must be made. The simplest method is the *fermentation method* of Dr. Roberts. In this the specific gravity of the urine is taken before and after fermentation, and the difference in the specific gravity indicates the number of grains of sugar in each fluid-ounce of urine. Then suppose the specific gravity before fermentation to be 1045, and after fermentation 1035, the quantity of sugar per fluid-ounce is 10 grains, which may be converted to percentage by multiplying by .23.

The simplest method of analysis by Fehling's or Pavy's solutions, and one which may be used in the consulting room as easily as the

laboratory, is the following: One cubic centimeter of Fehling's solution is diluted in a large test-tube with four cubic centimeters of distilled water, and boiled as described for qualitative testing. Its purity being thus ascertained, one tenth cubic centimeter of the suspected urine is added from a suitably graduated pipette. Heat is then reapplied, the precipitate examined, and then another one tenth added, the heat again reapplied, until it is found, after proper subsidence, that all the blue color is removed from the cubic centimeter of Fehling's solution. If in doing this, 1 c.c. of urine has been added, the urine will have contained just *half* of 1 per cent. of sugar. If more than 1 c.c., it will have contained less than one half per cent., but more than one quarter per cent. If exactly 2 c.c. are used, it will have contained exactly one quarter per cent. If, on the other hand, but half a cubic centimeter is used, it will have contained 1 per cent., one quarter of a cubic centimeter, 2 per cent., and so on.

If the proportion of sugar is large, as indicated by the specific gravity or qualitative test, the urine should be diluted with nine parts of water, and the result multiplied by 10. In point of fact, most saccharine urines met with in practice require this dilution.

The following table, prepared by the late Professor Wormley, will greatly aid in the estimation of glucose by this method, which is known at the University of Pennsylvania as the clinical method:

PERCENTAGE OF GLUCOSE IN URINE AS INDICATED BY THE QUANTITY OF URINE REQUIRED TO EXACTLY DECOLORIZE 1 C.C. (16 MINIMS) OF FEHLING'S SOLUTION.

Of Undiluted Urine.		Of Diluted Urine 1 in 10	
C.c. Urine.	Glucose Per Cent.	C.c. Urine.	Glucose Per Cent.
0.1 [5 ÷ 1]	5.0	0.4 [50 ÷ 4]	12.5
0.12	4.2	0.5	10.0
0.14	3.5	0.6	8.33
0.16	3.1	0.7	7.14
0.18	2.7	0.8	6.25
0.2	2.5	0.9	5.55
0.25	2.0	1.0	5.0
0.3	1.66	1.1	4.6
0.35	1.4	1.2	4.2
0.4	1.25	1.3	3.8
0.45	1.10	1.4	3.5
0.5	1.0	1.5	3.3

Of Undiluted Urine.	
C.c. Urine.	Glucose Per Cent
0.6	0.83
0.7	0.71
0.8	0.62
0.9	0.55
1.0	0.5
1.5	.375
2.0	.25
3.0	.187
4.	.125

Of Diluted Urine 1 in 10.	
C.c. Urine.	Glucose Per Cent.
1.6	3.1
1.7	2.9
1.8	2.7
1.9	2.6
2.0	2.5
2.25	2.2
2.50	2.0
2.75	1.8
3.00	1.6
3.5	1.4
4.0	1.25
4.5	1.1
5.0	1.0
6.0	0.83
7.0	0.7
8.0	0.6
9.0	0.55
10.0	0.5

If it is desired to determine the quantity in English measures, Pavy's solution may be used, 100 minims measured off into the test-tube, diluted with four times its bulk of water, and boiled as before. Then the urine, diluted if necessary, is allowed to fall into the liquid, drop by drop, the heat being constantly renewed until all the blue color has disappeared; and when this has happened the quantity of urine used will have contained just half a grain of sugar.

Greater precision may be obtained by the burette. Ten cubic centimeters of Fehling's solution are placed in a porcelain capsule and diluted with 40 c.c. of distilled water. Fill the burette to 50 c.c. with urine diluted 1 to 9. The capsule containing the diluted Fehling's solution should be placed on a wire gauze and heated over a gas flame or spirit lamp, when half a c.c. of urine is allowed to fall into the hot solution from the burette. Immediately a yellow or red precipitate will fall. This is allowed to subside, and if any blue color remains more urine is cautiously added, the solution being kept hot, until all the blue color disappears. The titration must be repeated, if necessary, until the exact point of disappearance is

ascertained and noted. If 5 c.c. of the urine are used to decolorize 10 c.c. of Fehling's solution, the 5 c.c. of urine will have contained exactly .05 gram, since 10 c.c. of Fehling's solution corresponds to .05 gram of sugar. If now the urine has been diluted 10 times, the 5 c.c. will contain .5 gram sugar, and 100 c.c. will contain 10 grams or 10 per cent. Pavy's solution may be used similarly.

Test for Aceton.—The accurate study of aceton is best secured by working with the distillate from the urine. By Legal's nitroprussid of sodium test, however, even moderate quantities may be recognized in the urine itself.

To 3 or 4 c.c. of the suspected urine add enough liquor potassæ or liquor sodæ to secure a distinct alkaline reaction. To the mixture add a few drops of a rather strong solution of sodium nitroprussid freshly made by dissolving a few small fragments in a little water, when promptly the whole assumes a red color whether aceton is present or not, said to be due to creatinin. In any event the red color disappears, but if aceton is present, the addition of a few drops of concentrated acetic acid causes a *purple* or *violet red.* If aceton is absent this final change does not occur. The purple color fades in a little while even if caused by aceton.

Test for Diacetic Acid by Chlorid of Iron.—(1) To fresh urine add cautiously a few drops of moderately strong watery solution of chlorid of iron. If a precipitate of phosphates results remove it by filtration, and to the filtrate again add more of the chlorid of iron solution. If a *Bordeaux red* color develops, diacetic acid is probably present. (2) This is confirmed if, after boiling some of the original urine, there is no reaction since diacetic acid is dissipated by boiling. (3) Acidulate a second portion with sulphuric acid and extract with ether. If the chlorid of iron reacts with the ethereal extract and pales after twenty-four to forty-eight hours, and the urine is found to contain large quantities of aceton, further confirmation is furnished.

Prognosis.

The prognosis of diabetes is generally considered unfavorable as to cure though the patient may be maintained in a condition of practical good health for years. Much depends upon the age at which which the disease makes its appearance, the time which has been

allowed to elapse before treatment is instituted, and the treatment itself. Once thoroughly established early in life, or before 25 years of age, recovery would seem to be impossible, while even at this age, if treatment is instituted sufficiently early, much may be done to prolong life. Diabetes is a disease in which the expectant plan of treatment is disastrous. It is a disease which never gets well of itself, and always gets worse if not properly treated.

When the disease appears after middle life, is early recognized and promptly treated, it is ordinarily easily controlled; and although it is almost never safe to declare a case of diabetes absolutely cured, it does happen that recovery is so complete that the patient may be left to his own mode of living. As a rule, however, even persons who have apparently recovered have to keep a watch upon their diet, and should at intervals have their urine examined with a view to sounding, as it were, their condition.

When diabetes depends upon recognized nervous lesions the prognosis is altogether that of the lesion itself.

The cause of death is very frequently some intercurrent or consequent disease, as pneumonia and consumption. The extreme debility which ensues sooner or later is of such a character that there is no power of resistance, and a disease which would ordinarily be trifling, becomes, on this account, often a fatal one. The most usual mode of death is by coma although many cases die of exhaustion. Sudden death is a possible event.

Treatment.

I have already said that diabetes is a disease in which the expectant plan of treatment is disastrous, that it never gets well of itself, and that when left alone it almost invariably gets worse. The importance of a prompt and correct treatment is therefore evident.

From the discussion of the pathogeny of the disease it is also plain that at least an abatement of the most important symptom, glycosuria, may be expected by regulating the diet. Experience justifies such expectation, and it so happens that the abatement of this symptom is almost invariably followed by improvement in all. The treatment, therefore, naturally divides itself into *dietetic* and *hygienic* and *medicinal*.

I. *Dietetic and Hygienic Treatment.*

By far the most important line of treatment, without which indeed no sufficient results have ever been attained, is the dietetic. This consists essentially in the elimination from the diet of such articles as are readily convertible into sugar. It is well known that in the early stage of the disease all the glucose which appears in the urine has its source in the saccharine and amylaceous foods; that they are not oxidized in the blood and tissues as they should be, and that the organism fails to secure the benefit of this important class. Hence, if these foods be excluded from the diet and their place supplied by other assimilable articles, the symptom glycosuria disappears, and the disappearance of this symptom seems to be, for the time being at least, the cure of the disease. For with it disappear also the polyuria, thirst, dryness, etc.

If it were necessary to select a diet absolutely free from sugar and starch it would indeed be restricted, as there are comparatively few articles of food thus constituted. Such are, however, meats of every kind, fresh or salted, including tripe, tongue, ham, bacon, and sausage; soups made from meat without flour; game, poultry, fish, oysters, lobsters, crabs, eggs, in every shape; butter and new cheese, oils and fats. Happily, however, it is not necessary to use articles absolutely free from the unassimilable principles, and in this manner quite a variety of palatable articles may be added to the dietary. Among these are cream, curds, buttermilk, all green vegetables, including spinach, endive, the green leaves of lettuce, dandelion, cabbage, coleslaw, brussels sprouts, cauliflower, oyster plant, broccoli, string beans, watercress, celery tops, asparagus tops, turnip tops, young onions, tomatoes, cucumbers, pickles, and olives. To these may be added unsweetened jellies (preparations of gelatin), and especially a variety of nuts, including almonds, walnuts, butternuts, filberts, pecan nuts, Brazil nuts, but not chestnuts; also, all acid fruits, apples, oranges, lemons, strawberries, etc. Tea and coffee, with cream and without sugar, cocoa-nibs, but not chocolate, are permitted; also, all wines which contain little or no sugar, including claret, Burgundy, Rhine, and still Moselle wines, together with very dry sherry, unsweetened brandy, and whiskey; and gin when re-

quired. The carbonated waters, natural or artificial (the so-called soda-water of the shops), are preëminently suitable.

Water may be allowed *ad libitum,* for water is the medium by which the sugar is carried out of the blood and tissues. Its supply should therefore be liberal, and with diminished sugar-formation comes diminished thirst.

Beer, ale, porter, cider, and the fermented liquors generally, are not allowable because of the sugar they contain. They are less objectionable when fermentation is carried to a high degree, resulting in a more complete destruction of the sugar. This is the case with certain bottled lager beers and English ales.

It is not simply on account of the small quantity of sugar and starch contained in them which renders the vegetable substances named permissible, for many of them contain a good deal of sugar; but these sugars, unlike grape-sugar, are more easily assimilable. Such are preeminently mannite, the sugar of manna, lactin or sugar of milk, levulose or fruit-sugar, and probably, also, inosit or the sugar of muscle. All of these should however be used in very small quantity if at all. In this class also is placed *inulin,* a hydrocarbon and starchy principle found in the *inula helenium* or elecampane, but especially in Iceland moss. Hence, too, the impunity with which milk can often be taken by diabetics, although it contains from three to six per cent. of lactin. On this account, too, mannite and levulose have been recommended for sweetening tea and coffee where this addition is indispensable to the patient. Glycerin is also sometimes used for the same purpose, *i. e.,* as a substitute for sugar, but although less objectionable than sugar, it is not only theoretically unsuitable, but experience has shown it to be so; for glycerin is probably converted into glycogen or sugar in the liver, nearly two molecules of glycerin ($C_3H_8O_3$) being required to furnish one of sugar ($C_6H_{12}O_6$), or glycogen ($C_6H_{10}O_5$). Further, under the careful observation of Dr. Pavy,[1] it was noted that with the use of glycerin the urine increased from 3 and $3\frac{3}{4}$ pints to between 5 and 6 pints, and the sugar from 1100 grains to 3000 grains *per diem* in the course of three days. Its withdrawal was followed by a prompt fall in both the urine and sugar, a return to it by a second increase, and subse-

[1] Pavy, On Diabetes, London, 1869, p. 259.

quent withdrawal by another decline. With the increase in the quantity of urine and sugar, came an increase in the thirst and discomfort; so that it would seem conclusive that the tendency, at least, of glycerin is to aggravate the symptoms, and, therefore, contraindicated.

It will be noted that not only all saccharine substances of animal or vegetable origin, and all vegetables largely composed of starch, as potatoes, rice, and corn, are omitted from the category of admissible articles, but that *bread* also, and all preparations made of wheat, rye, rice, or corn-flour, are conspicuous by their absence. This is found to be a very important omission from the dietary of most persons, and very numerous have been the attempts to devise substitutes for it, with varying success.

Perhaps the best substitute for ordinary wheat-flour is the *gluten-flour*. It was suggested in 1841 by Bouchardat, and was made by washing the ordinary wheat-flour to free it from starch. Although this is not completely accomplished, a quite pure article of gluten may be obtained, containing but a small per cent. of starch, and some starch is necessary, if it is desired to make it rise.

At the present day the purest gluten is obtained as a residue in the manufacture of starch, and an almost pure gluten can be thus made. It is unfortunate that a large number of the so-called gluten flours and breads advertised as pure glutens and used as such by diabetic patients contain very little less starch than the ordinary white bread made of the best flour. In order to determine the comparative purity of the glutens I have had analyses made of a number of those most largely advertised. The analyses were made for me by Dr. Daniel Fetterolf, of the University of Pennsylvania, with the results shown in the appended table.

Leffman and Beam give the percentage of carbohydrates in wheat flour as 71.25 (1901), Richards and Woodman as 70.3 to 75.5 (1900), which is not widely different from that of U. S. Govmt. Ag. Bureau.

Senator gives another method of getting rid of the starch and sugar in bread, as tried by Vogel at the suggestion of Liebig. It consists in converting the starch into sugar by the action of diastase, and dissolving out the sugar thus produced. It is done by treating thin slices of bread with an infusion of malt. The bread is then washed, dried, and slightly toasted.

Another substitute for white flour is the *bran-* or *unbolted flour* deprived of its starch by washing. The bran itself is not wholly

ANALYSIS OF SO-CALLED GLUTEN FLOURS COMPARED WITH WHEAT FLOUR (FETTEROLF).

		Per cent. of Water.	Per cent. of Fat.	Carbohydrate.	
				Moisture and fat free.	As Purchased.
Wheat flour.		13.12	1.04	85.27	74.7
Battle Creek Sanatorium Food Co.'s Products.	Pure gluten meal.			7.38	6.65
	" " biscuit.			7.22	6.55
	40 per cent. gluten flour.			58.96	54.15
	20 " " " "			65.34	59.76
	Nuttose.	49.77	34.25	29.19	15.38
	Granola.	8.72	1.91	57.27	51.77
	Granose biscuit.	7.26		69.21	64.53
Van Abbot's Gluten Flour (London).	Two samples. (1)	11.00	.29	8.36	7.51
	(2)			10.18	9.33
Aleuronot Flour.		9.79	.54	4.29	4.45
Chicago Sanitary Flour.[1]		11.01	5.5	7.09	6.79
Soya Bean Flour.		10.35	3.99	33.12	28.87
Domestic Wheat Gluten.		10.85	0.622	29.07	26.08
Phila. Gluten Flour (Ottinger).		10.11	0.46	32.37	29.42
Pure Gluten Food Co.'s. Products.	Gum gluten (ground).	9.20	0.47	50.76	46.29
	" " (self raising).	9.58	0.531	46.89	42.91
	" " breakfast food.	7.78	0.560	39.67	36.63
Health Food Co.'s Products.	Glutosac (an impure gluten)	11.84	1.1	59.85	52.20
	Pure gluten flour.	8.33	0.99	12.18	11.1
	Gluten bread made from glutosac.	44 27	1.06	68.39	47.07

innutritious, containing, according to Parkes,[1] sometimes as much as 15 per cent. of nitrogenous matter, 3.5 per cent. of fats, and 5.7 per cent. of salts, although, in consequence of its indigestible character, it is probably not much availed of in nutrition. Moreover the salts are washed out in removing the starch which is mixed with it. But it is especially valuable in contributing a desirable bulk to the food of which it forms a part, and by its slightly irritant properties aids in maintaining a proper action of the bowels. These properties may be diminished, and the bran made much more suitable for its purposes by being very finely comminuted. It may be made by the ingenious cook into a variety of more or less palatable cakes. But sometimes, even when most carefully prepared, it is too

[1] Said to be made from an edible species of the pine nut family.

[2] Parkes, Practical Hygiene, 5th ed., Philadelphia, 1878, p. 222.

irritant to be borne. Dr. Prout very early recommended, as a substitute for bread, a compound of bran, milk and eggs, which he declared not unpalatable.[1]

In cases which do not require an extremely restricted diet, some of the flours containing a larger per cent. of starch may be used. Where still less stringency is required ordinary "bran bread" of the bakers, which is really bread made of unbolted flour, and contains the starch along with the gluten and bran may be substituted. Caution must be observed, however, in obtaining this brown bread from bakers, as they often put molasses in it to improve its flavor.

Still another substitute for wheaten bread is the *almond food* suggested by Dr. Pavy. The almond is composed of 54 per cent. of oil, 24 per cent. of nitrogenous matter known as emulsin, 6 per cent. of sugar, 3 per cent. of gum and *no starch*. Chemically speaking, it is therefore admirably adapted for diabetic food, and when the sugar and gum are extracted leaves nothing to be desired. The sugar and gum are removed by treating the powdered almonds with boiling water slightly acidulated with tartaric acid, or soaking the almonds in a boiling acidulated liquid, which may form part of the process for blanching. The boiling and acid fluid are necessary in order to precipitate the *emulsin,* which would otherwise emulsify the oil of the almond. Dr. Pavy speaks very highly of biscuits made of almond-flour and eggs, which, he says, go very well with a little sherry or other wine. I have had some experience with the almond foods, and have found them too rich to be used in large quantity. Dr. Pavy admits that they are found too rich by some for ordinary consumption.[2]

[1] The following are Dr. Camplin's directions for making biscuit of the bran-flour: To one-quarter of a pound of flour add three or four fresh eggs, one and a half ounces of butter, and half a pint of milk; mix the eggs with a little of the milk, and warm the butter with the other portion, then stir the whole together well; add a little nutmeg or ginger or other agreeable flavoring, and bake in small forms or pattipans. The cake when baked should be about the thickness of an ordinary captain's biscuit. The pans must be well buttered. Bake in rather a quick oven for half an hour.

These cakes or biscuits may be eaten by the diabetic with meat or cheese for breakfast, dinner, or supper; at tea they require rather a free allowance of butter, or they may be eaten with curd or any of the soft cheese.

[2] Seegen recommends an almond food made as follows: Beat a quarter of a pound of blanched sweet almonds in a stone mortar for about three quarters

Biscuits made of *inulin,* the starchy principle already referred to on page 280, were suggested by Kuelz.[1] Lichenin, or moss-starch, abundant in Iceland moss, is a variety of inulin and would be the material used for the purpose. Being very cheap it is suitable on this account. Though a starch, it is, according to Kuelz, one of the assimilable starches already alluded to, of which small quantities, at least, do not increase the excretion of sugar. The biscuits are made with the addition of milk, eggs, and salt.

Under the head of dietetic treatment belongs the *skim-milk* treatment, of which Dr. A. Scott Donkin was the chief exponent and advocate. This treatment is based upon the view that lactose or sugar of milk is a material assimilable in diabetes, "and does not in the slightest degree contribute to the formation of sugar;" that in this respect it is even superior to casein, which, however, resists the sugar-forming process of the malady "to a degree immeasurably greater than any other albuminous alimentary substance, so that in all but the most severe and advanced or complicated cases it is complete."[2] With regard to casein, an albuminous substance, I presume no one will dispute, in general, the view taken by Dr. Donkin, although all may not agree with him in assigning to it the highest position in this respect.[3] But as to lactose Dr. Donkin's claims have not been sustained by the experience of others. It is true that in common with mannite, inulin, levulose, fruit sugars and lactose is more easily assimilable than cane-sugar and glucose and I am in the habit of allowing a moderate amount of unskimmed milk to my

of an hour, as fine as possible; put the flour thus produced into a linen bag, which is then immersed for an hour and a quarter in boiling water, acidulated with a few drops of vinegar. The mass is then thoroughly mixed with three ounces of butter and two eggs; the yolks of three eggs and a little salt are added, and the whole is to be stirred briskly for a long time. A fine froth is to be made by beating the white of the three eggs, and added. The whole paste is now put into a form smeared with melted butter and baked by a gentle fire.

[1] Kuelz, Beiträge zur Path. und Therapie des Diabetes Mellitus, Marburg, 1874, Bd. I., s. 145.

[2] Donkin, Diabetes and Food, New York, 1875, p. 132.

[3] For an account of Dr. Donkin's experiments the reader is referred to his communications to the London Lancet from 1868 to 1875; to his work on The Skim-milk Treatment of Diabetes, London, 1871, and the Transactions of the Clinical Society of London, Vol. VII., 1874.

diabetic patients. It may be that in a few cases it acts as Dr. Donkin claims. I know of at least one case in which the patient, a very intelligent physician, declares himself cured by a rigid adherence to it. On the other hand I have known sugar to persist in the urine of a patient until a liberal allowance of milk was discontinued, after which it disappeared at once. I see no advantage in skimmed milk over unskimmed. In fact, by skimming milk we increase the ratio of sugar, while the fat quite suitable for the diabetic is discarded.

In the first stage of diabetes, the dietetic measures above indicated are usually followed by the most prompt and decided results, occasionally by the permanent removal of all symptoms, at others by a continued absence of them so long as a watchfulness over diet is maintained. In a more advanced stage of the disease, in which a more rapid emaciation and loss of strength show themselves, such a regimen is followed by a decided diminution in the quantity of sugar excreted, but it fails to disappear altogether, and a more rigid elimination of saccharine and amylaceous articles must be enforced. Through such stringency, glucose may be kept out of the blood and urine a while longer. Sooner or later, however, in the intractable cases, not only the albumins of food, but also the fixed albumins of the body framework are converted into glucose as though in response to some insatiable demand of the economy which is still unable to make use of the glucose thus produced and the patient goes on starving to death, a very Tantalus, while surrounded with food which under healthy conditions would fulfil every want.

It is to be remembered, too, that even a so-called exclusively meat diet contains also glycogen, as well as undoubted glycogen producers and hydrocarbons in the shape of gelatin, glycerin (in the fat), and inosit. It will be remembered that the experiments of Salomon go to show that glycogen appears in the livers of animals fed on fats alone, the glycerin therein contained being probably its immediate source, and that Dr. Donkin's observations go to show that in aggravated cases of diabetes the ingestion of fat is followed by increased elimination of sugar; so that it is probably impossible to secure a thoroughly non-glycogenic diet, and it is questionable whether, even if it were possible, other urgent needs of the economy would be sufficiently supplied by it. On the other hand, it is evident

that further observation and experiment are still necessary on the matter of diet in diabetes, and that valuable additions to our knowledge may be expected therefrom.

In conclusion, the following summary of articles admissible for diabetics will be found convenient for reference:

Food and Drink.

Shell-fish.—Oysters and clams, raw or cooked, in any way, *without* the addition of flour.

Soups.—All made without flour, rice, vermicelli, or other starchy substances or without the vegetables named below as inadmissible. Animal soups not thickened, beef tea and broths.

Fish of all kinds, fresh or salted, including lobsters, crabs, sardines, and other fish in oil.

Meats of every variety except livers, including beef, mutton, chipped dried beef, tripe, ham, tongue, bacon, and sausages. Also poultry and game of all kinds, with which, however, sweetened jellies and sauces should not be used.

Vegetables.—Spinach, cabbage, cauliflower, brussels sprouts, broccoli, green string-beans, the green ends of asparagus, dandelion, mushrooms, string-beans, lettuce, endive, tomato, coleslaw, olives, cucumber fresh or pickled, radishes, young onions, watercress, mustard and cress, turnip tops, celery tops, or any other green vegetables. Salads made of any of the above-named vegetables dressed with vinegar, oil, salt and pepper.

Vegetables to be especially Avoided.—Potatoes, white and sweet, rice, beets, carrots, turnips, parsnips, peas, and beans; all vegetables containing starch or sugar in any quantity.

Bread and cakes made of gluten, bran, or almond flour, or inulin, with or without eggs and butter. Griddle-cakes, pan-cakes, biscuit, porridges, etc., made of these flours. No pastry permitted unless made of the admitted flours and without sugar.

Eggs in any quantity and prepared in all possible ways, without sugar or ordinary flours.

Nuts.—All except chestnuts, including almonds, walnuts, Brazil nuts, hazelnuts, filberts, pecan nuts, butternuts, cocoanuts. Nut foods.

Fruits.—Acid fruits like plums, apples, lemons, and even oranges

may be permitted in moderate quantity. One of the most frequent causes of aggravation of symptoms is the excessive use of fruits, especially of oranges, and the number allowed each day should be specified.

Condiments.—Salt, vinegar and pepper in moderate quantity.

Jellies.—None except those unsweetened. They may be made of calf's foot or gelatin, and flavored with wine.

Drinks.—Water, coffee, tea, and cocoa-nibs with milk or cream, but without sugar. Also milk, cream, soda (carbonated) water, and all mineral waters freely; acid wines, including claret, Rhine, and still Moselle wines, very dry sherry. Unsweetened brandy, whiskey, and gin. No malt liquors except those ales and beers which have been long bottled and in which the sugar has all been converted into carbonic acid and alcohol.

Ice cream sweetened with saccharin instead of sugar, 2 grams to a quart of ice cream, may be permitted.[1]

Saccharin may be used for all purposes of sugar.

II. *Hygienic Treatment.*

Next in importance to the dietetic is the hygienic treatment of diabetes. This consists in a wholesome life secured by perfect ventilation within doors, bathing, and attention to the skin, together with muscular exercise, and outdoor life.

The diabetic should breathe the freshest and purest air. While the cases are not numerous in which embarrassed respiration results in glycosuria, there are undoubted instances in which this has occurred, as in croup and whooping-cough; and it is well known that asphyxiated lower animals are apt to have glycosuria. And although the glycosuria thus resulting is probably reflex, it can hardly be expected that the diabetic should improve under unfavorable respiratory conditions. He should not, therefore, live, work, or sleep in a confined atmosphere, but secure the most perfect ventilation, spending much of his time out of doors, and sleeping in large, well-ventilated chambers, with windows open, etc. Especially should he avoid exposure to irrespirable gases. Attention to the skin, or skin-culture, haut cultur, as it is termed by the Germans, is most

[1] Such an ice cream is made by Benj. F. Detweiler, 1913 Pine St., Philadelphia.

important to the diabetic. Massage should be practiced daily or on alternate days when possible. He should bathe, unless some special contraindication exists, daily, in tepid or hot water, to which sodium carbonate should be added. The bath should be taken on going to bed in winter, and on rising, or both on rising and retiring, in summer. He should groom his skin thoroughly daily, either after the bath or independent of it on the days on which he does not bathe. The soda softens the skin and facilitates its action by removing the dead epithelium.

Attention to other secretions, particularly the bowels, is of the greatest importance to the diabetic. It is probably partly on account of their action in this respect that the saline and alkaline saline aperient waters, as those of Carlsbad and Marienbad are so useful. The waters of Vichy are not aperient and any good effect they may exert must be ascribed to their alkalinity. To those who visit these springs, a part of the advantage resulting therefrom is ascribable to the other favorable hygienic influences, such as diet, rest, fresh air, massage and exercise, with which they are associated. Independently of these influences, however, I think there is reason to believe that these waters are of service to diabetics. The Vichy waters are more alkaline than the Carlsbad waters, containing 35 grains of carbonates to a pint, while Carlsbad has but 11, but contains twice the proportion of chlorids, 8 grains to a pint, and nearly ten times as much sodium sulphate, or 19 grains to the pint; hence its more purgative quality. Since Carlsbad has the greater reputation it may be that it is through the action of the sulphates and chlorids on the liver rather than that of the alkalies they contain, that these waters are efficient. This is the more likely, as other alkaline waters nearly as rich as those of Vichy, and richer than Carlsbad in sodium carbonate, but without sulphate of sodium, are without reputation. The alkalies, however, increase the effect, and are especially of service where there is acidity.

When the springs cannot be visited, the waters should be used at home when this is possible. They may be taken as at the springs, one or two glasses of the Carlsbad water before breakfast, and of the Vichy half a glass to a glass before each meal. When diabetic coma threatens I increase the Vichy to a glass every two hours or

increase its alkalinity by adding 15 to 20 grains of potassium citrate to each glass. The addition of a little lemon juice to each glass takes away the flatness of taste which characterizes all alkaline waters and which is often complained of.

The only American waters known to me which approach these very closely as to both chlorids and sulphates, are those of Crab Orchard Springs in Kentucky, of which Sowder's Spring contains 25 grains of sulphate of sodium and magnesium, and 7 grains of sodium chlorid to the pint, yet I am not aware that these waters have any reputation in diabetes. Other springs which approach them in the proportion of sulphates of sodium and magnesium are the Estill Springs and Harrodsburg Springs in Kentucky, and the Bedford Springs in Pennsylvania. The latter waters contain a little iron, which may be of advantage. The Vichy waters also contain a trace of iron. The waters of the celebrated Saratoga Springs, in this country, have an undoubted action on the liver, probably through their chlorids, which are in very large proportion, reaching in the Geyser Spring 70 grains to the pint, and in the Empire and Hathorn 63 grains to the pint. They contain no sulphates, according to Professor Chandler's analyses, but the carbonates are in considerable proportion, though much less than in the Vichy waters. In the absence of the Carlsbad and Vichy waters, I would use the purgative Saratoga waters, especially the Hathorn.[1]

Muscular exercise should be taken daily by the diabetic, both by walking and gymnastics. It is likely that glycogen is consumed to a degree in the muscles during their action, and that in diabetes there is an undue accumulation of sugar in the muscles is quite certain. The sense of muscular weariness so characteristic of diabetes is ascribed by some to this accumulation of sugar in the muscles. Muscular exercise was suggested as a remedy for diabetes by Bouch-

[1] Some of the American waters which are most vaunted and advertised as useful in diabetes contain a surprisingly small quantity of either sulphates or chlorids, indeed of any of the ingredients which go to make a mineral water. Thus Bethesda water contains 1.7 grain carbonate of sodium and magnesium to the pint, .14 grain of chlorid of sodium, and 1.1 grain of sulphates of sodium and potassium together, to the pint. Clysmic water about the same. The same may be said of the Poland and Capon waters. It is possible, however, that by drinking very large amounts of these waters, using them as table-waters and as substitutes for all other drinks, effects may be produced.

ardat in 1835. Dr. William Richardson,[1] of London, illustrates by his own case and that of others under his care, its undoubted benefit. It should be sustained regularly day by day, even in wet weather, care being taken to keep the feet dry, while it should never be carried to real fatigue. Dr. R. relates of himself, that at one time he had so little muscular power that he could not walk 100 yards without great fatigue, falling two or three times, and requiring always the greatest vigilance to prevent falling. He began to take exercise regularly two or three times a day, wet or fine. He gradually gained strength, so as to walk five or six miles a day without fatigue. I cannot too strongly urge upon diabetics the following of Dr. Richardson's example according to his method.

Trousseau as well as Bouchardat early advised muscular movements, and Kuelz in 1875 also strongly advocated them. On the other hand, it is even more important that extreme fatigue should be guarded against, especially by those in advanced stages. Dr. Richardson reports two cases of sudden death after long journeys, and I have known several such.

For a similar reason venereal excesses should be avoided, being peculiarly exhausting to one already weakened by diabetes.

III. *The Medicinal Treatment.*

Like all diseases in which treatment by drugs is relatively inefficient, diabetes has its full share of reputed remedies, most of which are useless. This dare not, however, be said of all.

In the first place I would call attention to the natural waters already referred to as adjuvants under the head of hygienic treatment. What was said of them there, might with equal propriety be said here.

The only drugs which have any positive and direct effect in controlling the symptoms of diabetes mellitus are opium and its alkaloids.

It seems that *opium* was used for diabetes as early as the second century, by Archigenes. It was also used by Ætius in the fourth century, A. D., and in the latter part of the eighteenth century and beginning of the nineteenth, by Rollo, Frank, Tommasson, and especially the English physician, Pelham Warren, in 1812.

[1] Richardson, op. citat., p. 91.

It is certainly an efficient agent in diabetes, but its use is united with disadvantages in the locking-up of the secretions which it causes. Aperient remedies should therefore be used with it, and very suitable are the natural aperient waters, including the bitter waters, Friedrichshalle, Apenta, Hunyadi Janos, Racoczy, Püllna, etc. Dr. Pavy[1] is a strong advocate of the use of opium, and has been astonished at the highly successful results. He has seen a patient entirely relieved under its use, and the use of it alone. It was given in increasing doses until the quantity reached *nine* grains in a day. At first the glycosuria returned after its discontinuance, but on returning to its use the disease finally disappeared not to return. There was no restriction of diet whatever. As much as sixty and ninety grains have been given in the twenty-hours by McGregor.[2]

Morphine may, of course, be substituted for opium, but the favorite preparation at the present day is *codein.* It has the advantage over the other alkaloids and of opium itself in not locking up the secretions so much and in producing in a less degree the unpleasant symptoms of opium. Numerous reports attest its great value. My plan in giving it is to begin with one quarter of a grain three times a day, adding a quarter of a grain daily until the desired effect is produced or until a dose of ten grains a day is attained. I may say, however, that I have very seldom reached this quantity, two to five grains a day being the more usual dose. Either such doses produce all the effect desired or satisfy one that further dosage is useless. Thus in one instance, by gradual increase I attained the enormous dose of over 50 grains a day without either good or bad results. If the sugar entirely disappears, as it sometimes does under the use of codein, the dose should be gradually reduced.

Next to opium in efficiency is *arsenic.* The most convenient preparation is Fowler's solution because of the facility with which the dose may be changed. As the result of some experience I have adopted the method of giving small doses long continued rather than to aim at the physiological effect by larger doses. Three drops of Fowler's solution after each meal is the more usual dose, although even this may be too large in certain cases. On the other hand, v.

[1] Pavy, op citat., p. 275.

[2] McGregor (London Medical Gazette, 1837).

Leube has given arsenic in doses of one third grain (presumably arsenious acid) three times a day with advantage. In lieu of Fowler's solution arsenic may be given in the shape of arsenious acid in doses of one thirtieth grain which affords the opportunity of combining it with other drugs, as strychnin and iron tonics which are often indicated.

The rationale of the effect of opium and arsenic is undetermined. According to the older view that the symptoms of diabetes mellitus are the result of an over-production of glucose, opium may be said to act as a sedative to the exaggerated function. If, however, the phenomena of the disease are the result of a defective combustion of glucose, it is not evident how opium does good. On the other hand, the good effects of arsenic are best explained by the later views which ascribe the glycemia and glycosuria to a deficient combustion, since the effect of arsenic is to stimulate oxidation.

Similar in their action to opium, when efficient, as they sometimes are, are the *bromids* of sodium and potassium, more especially in connection with nervous disorders due to mental overwork or psychical disturbance. The bromids were suggested by Begbig in 1866.

For a time considerable popularity was enjoyed by a combination of bromin and arsenic known as Clemens' solution of bromid of arsenic, of which the dose is from three to five minims three times a day. Clemens' own method of using the bromid of arsenic was as follows:

The patient being put on a nourishing meat diet, the solution is administered at first in single-drop doses diluted with *much* water, say, one drop of the solution three times a day in a tumbler of water. After this has been kept up for about eight days, the harrowing and annoying thirst of the patient will generally be greatly relieved. The dose of the solution is then gradually to be increased to three drops, thrice daily, each dose being administered in a tumberful of water. After about fourteen days, the amount of sugar in the urine will become less. When this point is reached, the dose is again gradually diminished until the single-drop doses are reached again, at which rate it may be continued for years without injurious effects. It is only necessary, besides, to observe the usual rules of diet suitable for diabetic patients, with the additional precaution that

neither sour food nor raw fruits be eaten about the time when the medicine is to be taken.

Through a like sedative action if any must the *coal-tar derivatives* antipyrin, antifebrin and phenacetin act. Great efficiency was claimed for these by the French physicians in the last decade of the last century, and I at one time thought I secured results in a certain class of cases in doses of ten to fifteen grains given three times a day on an empty stomach. Their efficiency is said to be increased when combined with an equal dose of sodium bicarbonate, a nauseous dose which is resented by many stomachs.

The *salicylates* have had warm advocates and in arthritic and gouty cases they may be of service. According to Van Noorden it is especially in neurogenous cases that the salicylates are useful by quieting the irritability of the central nervous system.

On the same principle, that of oxidation or combustion of glucose, the *alkalis* have long had a reputation. Mention has been made of this property when speaking of the use of mineral waters, especially those of Vichy, in the treatment of diabetes. These waters contain 35 grains of alkaline carbonate to the pint. By alkalinity it is held that glycogen is converted into glucose and glucose into carbonic acid and water. This is apart from the effect of the alkaline carbonates in neutralizing the organic acids which accumulate in the later stages of diabetes and become active in producing the symptoms of diabetic coma. Especial efficacy in the former direction is claimed for *lithium,* and L. Martineau[1] called attention to the fact that all the mineral waters which have attained a reputation in the treatment of diabetes contain either *arsenic or lithium,* or both, however much they may differ in composition in other respects. Reasoning thence Martineau suggested a combination of these substances as follows: Dissolve 3 grains of lithium carbonate in a quart of distilled water and add to this solution a tablespoonful of solution of sodium arseniate made by dissolving 3 grains in a pint of distilled water. This quantity (a quart) containing 3 grains of lithium carbonate and about one tenth grain of sodium arseniate should be drunk during meals and last for at least three meals. Martineau also directs that if the patient be thirsty between meals he should drink nothing but

[1] Les Annales Medico-Chirurgicales, March, 1887.

this water. I have, however, seen edema of the face result from the free use of this solution and the possibility of such an event should be borne in mind. Martineau reports 67 cures out of 70 cases treated, in some of which no regard was paid to diet. The proportion of cures is so large as compared with the treatment of others as to discredit its value. It is important, however, to add that Martineau holds that this treatment is thus efficient only in cases of *arthritic* diabetes, by which he means cases with arthritic symptoms, "either articular or in the form of biliary or urinary lithiasis or as cutaneous eruptions." The treatment certainly deserves a trial. It should be mentioned that the attention of Martineau was first called to the use of artificial lithiated arsenical waters by Professor Rouget, with whom Martineau saw a case in consultation seemingly cured by this treatment.

Now and then one sees a case of cure reported from the use of *iodid of potassium.* This may happen where the diabetes is due to the impingement of syphilitic brain tumors on centers which preside over the glycogenic functions.

Ergot is a remedy which has had some reputation, and at one time I thought I was obtaining good results from its use. Any effect resulting from it might be explained by its contracting effect on blood-vessels. The fluid extract is the most convenient preparation, as it admits of easy graduations in its dose which should be increased to at least a fluid-dram three times a day if any results are to be expected from it.

A similar organic substance for which good results are claimed, but which has been disappointing in my hands, is *jambul,* the syzgium jambolinum or Java plum, of which the bark, seeds and fruit or rind of fruit are used. One may begin with the fluid extract of any of these in 10-minim doses, increasing rapidly to a drachm or even more. The powdered seeds have been given in 10- to 30-grain doses. It is said to produce active diuresis in some cases. Its clinical results may be said to be confirmed by experiment, in which, in diabetes produced in dogs by the administration of phloridzin, the excretion of sugar was diminished 50 to 90 per cent. No rationale has as yet been assigned for the favorable action of jambul in diabetes. It will be remembered that phloridzin diabetes is supposed to be due

not to any influence on sugar production or combustion, but to a leakage of sugar through the renal cells which in health have the power to retain the sugar in the vessels until consumed in the normal way.

In illustration of the difficulty in ascertaining the real value of a remedy may be mentioned *nitrate of uranium*. As far back as 1877, my classmate J. Y. Dale,[1] of Lemont, Penna., called attention to this drug, claiming remarkable efficiency in the treatment of diabetes. He prescribed it in doses of one grain three times a day, increased if necessary, to three, either in pill, powder or solution. He always used it, however, in connection with appropriate diet. In 1880, Dr. H. Augustus Wilson published in the Medical Bulletin of Philadelphia the results of treatment by this remedy, accompanied by a record of volumetric analyses, from which it appeared that there was a decided reduction in the quantity of sugar excreted. The dose was half a grain increased to a grain three times a day, but the diet was restricted. About this time I also tried the drug in several cases, without and with a selected diet. In the former it was without effect, in the latter there was no effect which could not be accounted for by the diet.

In 1895 Samuel West, of London, called attention to this drug, reporting to the British Medical Association two cases seemingly benefited by its use. The next year he reported to the same association five cases in which the results were not so favorable. In 1897 Ebenezier Duncan[2] read a paper before the British Medical Association at its meeting in Montreal, in which the remedy again appeared at great advantage. Encouraged by West's results I made another trial of the remedy, but could seldom give more than 5 grains at a dose because of a resulting diarrhea, except in one case associated with constipation when a dose of 15 grains was attained. It was without any effect.

It seems hardly possible that conclusions by physicians as experienced as those named should be entirely erroneous, and it

[1] Boston Medical and Surgical Journal, 1877.

[2] Treatment of Diabetes Mellitus by Nitrate of Uranium, British Medical Journal, October 16, 1897. At this meeting the above views were expressed by the author in the discussion on this subject and concurred in by Dr. Saundby.

may be there are certain cases that are favorably influenced by uranium as by jambul. A French pharmacist of Bordeaux, Pesqui, prepares a wine of uranium, an elegant and agreeable preparation, which is highly lauded by patients and even physicians who have used it.

Lactic acid was recommended by Cantani as a substitute for sugar, for the purposes this substance serves in the normal economy. Adopting the view that in health sugar ingested is converted into lactic acid in the liver, he proposed to furnish the lactic acid already prepared to the latter organ, and thus, by giving it a rest, effect a cure. Senator, also, is inclined to favor its use, but on another ground,—the theory that sugar is normally converted into lactic acid in the intestine, and that in diabetes the normal conversion may be interfered with. This is obviated by giving lactic acid itself, whereby this important ingredient is more directly furnished to the blood, where, as claimed by Scheremetjewsky,[1] it is completely oxidized and becomes a force-producer. Therefore we must not look to a reduction in the quantity of sugar eliminated under its use, but regard it as a source of energy, the patients getting the same advantage from it as the healthy individual does from sugar. They are said to gain in weight, become stronger, etc., and if they belong to the class in which the sugar disappears from the urine under an exclusively animal food, the disease may, by the use of lactic acid at the same time, be wholly suppressed, and a condition of perfect health take place without excessive ingestion of food.[2] Cantani recommends that from 75 to 150 grains of the acid daily in from eight to ten fluidounces of water. Larger quantities sometimes cause diarrhea and pains in the joints, which disappear after its omission. A medical friend, who has apparently recovered from diabetes, used in conjunction with Carlsbad water and a pill of iron, quinin, and arsenic, 30 drops of lactic acid three times daily.

On account of its contained lactic acid *buttermilk* becomes a suitable food for the diabetic. So also does *matzoon* or *zoolak*, a fermented milk in which sugar of milk is converted into lactic acid by fermentation. Glycerin was also recommended as a substitute for

[1] Scheremetjewsky, Sächs. Acad. Sitzungsb., 1869, p. 154.

[2] Senator, loc. citat., p. 999.

sugar by Schultzen on the supposition that sugar in health is decomposed into glycerin and aldehyde of glycerin. But it has already been explained that glycerin is easily convertible into sugar, and that this conversion probably takes place in the intestines, while the experiments of Pavy and others have shown that glycosuria increases under its use. It is, nevertheless, not impossible that in the early stages of diabetes, glycerin is assimilable, and it may be used in moderate amount for sweetening purposes, but from what is now known of its properties and chemical composition, it does not seem a rational remedy for the disease.

It might be expected that *cod-liver oil* would be a valuable remedy, or rather food, in diabetes. For while most experimenters deny that glycogen is ever produced under a diet of pure oil, those who claim that it is admit that, in the earlier stages at least of diabetes, all fats are assimilable. Cod-liver oil is one of these whose tonic and roborant properties have been too often tried to be any longer doubted. When well borne by the stomach, therefore, it may be early administered with the expectation that the general health and strength of the patient will improve while the excretion of sugar will diminish. The further indication for its use by the presence of phthisis in so many cases of diabetes, and the results of experience where phthisis is absent as well as when it is present, confirm the propriety of placing it in the category of adjuvants to the dietetic treatment. It is generally accepted at the present day that the association of alcohol in the shape of whiskey or brandy with the oils favor their assimilation.

Among other substances for which efficiency has been claimed may be mentioned tincture of iodin, turpentine, salicylic acid, benzoic acid, salol, benzosol, guiacol, creasote, oxygen, ozone, permanganate of potassium, brewer's yeast, whortelberry (myrtillum Jasperi) and testicular juice. The whortelberry in the shape of pillulæ myrtillæ Jasperi is one of the remedies much advertised in Germany, as a cure for diabetes.

In the treatment of all cases of diabetes, in the earlier stages, at least, we should first ascertain what can be done with diet variously restricted in connection with a proper hygiene; and as long as the diminution of sugar from the urine can be thus accomplished medi-

cines specifically intended for the cure of the disease being always of uncertain value should be omitted.

Treatment of Complications.

The only complications requiring special allusion as to treatment are pruritus and diabetic coma. *Pruritis.*—This is a symptom so intensely annoying and at times resists treatment so stubbornly that the physician should be provided with numerous resources to combat it. In the first place treatment of the diabetes itself by measures intended to remove sugar from the blood and urine are a part of the treatment for this troublesome symptom, since the sugar in these two fluids is the direct cause of the eczema and the itching. The treatment added to this consists solely in local measures. In the first place, absolute cleanliness of the parts invaded, attained by frequent washing with soap and water followed by thorough drying tends to relieve the troublesome symptom. When this does not suffice the next remedy I commonly use is *boric acid* in solution an ounce to a quart of water applied after the thorough washing referred to, and in the case of women injected into the vagina as well. Sometimes simply dusting the external parts with boric acid after the manner of powdering infants will supply the needed relief. A solution of creolin, teaspoonful to a pint of water applied as the boric acid solution, including vaginal injection, may be tried. *Sodium sulphate* in the proportion of an ounce to a quart may be similarly employed. Solution of acetate of lead 20 grains to the ounce, and the officinal *liquor plumbi subacetas dilutum* are soothing applications. Tumenol-sulphone in 5 per cent. solution is also recommended; also weak solution of corrosive sublimate 1–3,000.

Other local applications are the following: (1) Boric acid ℥ij; morph. sulph. gr. viij; glycerin f℥ss; water f℥viiss. (2) Corrosive sublimate 1 part; starch 100 parts; alum 20 parts; water 2,500 parts. (3) Liquid cosmolin f℥ij; powdered boric acid ℥iv. (4) Precipitated sulphur ℥iss; glycerin f℥ss; lime water and camphor water of each enough to make f℥iv.

As a last resort in pruritus *nitrate of silver* may be used in the proportion of 20 grains to the ounce, making daily applications, and

extending them also into the vagina. Though sometimes painful they are generally ultimately effectual.

Treatment of Diabetic Coma.—While treatment is commonly useless after coma is once established, threatening attacks may be averted and occasionally remarkable temporary improvement has been produced. Whatever may be the correct theory of coma, the treatment based on the view that ascribes the symptoms to an "acidosis" due to the acetone series in the blood seems to be the most effectual. It consists in measures intended to alkalize the blood or to neutralize the acidosis. To this end I immediately place threatening cases on a diet of French Vichy and milk, giving four ounces of each every two hours or oftener, as determined by the thirst of the patient, adding also 20 grains of sodium bicarbonate or of potassium citrate. Or a drachm and a half or two drachms may be added directly to a bottle or two of Vichy or Neuenahr water and the whole consumed in 24 hours. Magnus Levy reports a case in which a boy aged 13 years was twice brought out of coma by the administration of 200 grams or a little over seven ounces of the bicarbonate of sodium, and another patient, a girl aged 12, recovered from fully developed coma after the administration of 100 grams per day, and showed no signs of coma during the nine weeks she remained in the hospital.[1]

Where coma actually exists this method of treatment is, however, too slow and soda solution must be introduced by hypodermoclysis or intravenous injection. A solution recommended is 1500 c.c. (50 oz.) of normal salt solutions, 7.2 grams (say 100 grains) of sodium carbonate, and 4.6 grams (say one drachm) of sodium bicarbonate. After the injection of a pint (500 c.c.) by Koetnitz, striking changes occurred. The patient revived enough to answer questions, but did not open his eyes. I have seen similar results follow a hypodermoclysis of normal salt solution alone, which may be used instead of the alkaline solution just mentioned when the latter is not obtainable. Whatever the relief thus obtained, sooner or later it

[1] Quoted by F. W. Pavy in his paper on the Acetone series of products in connection with Diabetic Coma, reprinted from the London Lancet, July 12, 19, 26 and August 9, 1902. Magnus Levy's paper appeared in Archiv für experimentelle Pathologie und Pharmakologie, 1899, Band XIII., p. 180, and ibid., 1901, Band XIV., p. 399.

fails and the patient perishes because the treatment only neutralizes the effect of the acids referred to and does not diminish its production.

It is important that the bowels, which are apt to be constipated, should be thoroughly regulated, mercurial purges being preferred.

It should be remembered that according to some authorities the proteid diet tends to favor diabetic coma. As to this I am sure I can not do better than quote Von Noorden, who says: "I can only say that in the case of a thing upon which so little calculation can be made as the occurrence of diabetic coma and in view of the fact that coma has been observed under all forms of diet, we should be very careful how we use the word favor. Only an extensive critical comparison of statistics which has never yet been made, could give objective support to this opinion, and put to one side the subjective judgment of the physician theoretically disposed to one or other view. Such cases prove absolutely nothing."

On the other hand, experience teaches also that whatever the diet at the time this accident supervenes, a change to an opposite food is desirable, that is if it be a strict proteid it should be substituted by a carbohydrate and *vice versa*.

The most recent measure of treatment suggested for diabetes mellitus is the transplantation of pancreas, based upon experience in treating myxedema with thyroid extract. It is well known that the internal administration of pancreas has failed. Two efforts at transplantation are reported by James W. Allan in *The Lancet*, May 14, 1904. Both were unsuccessful. In one case the pancreas was found atrophied at autopsy.

SECTION II.

THE OCULAR MANIFESTATIONS IN DIABETES MELLITUS.

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The following division of diabetic ocular affections suggests itself:

Primary lesions of the eye and its appendages.

Secondary lesions, that is, those which result from intracranial affections.

The disturbances and diseases of the visual organs in diabetes may further be divided, as Hirschberg has suggested, into those which possess lesions easily demonstrable clinically, and those which do not possess lesions of this character.

I. Affections of the first class manifest themselves in the form of:

(*a*) Diseases of the lids, orbit, conjunctiva and cornea.

(*b*) Diseases of the uveal tract, that is, the iris, ciliary body and choroid, and of the vitreous.

(*c*) Diseases of the retina and optic nerve.

(*d*) Diseases of the lens.

II. Affections of the second class manifest themselves in the form of:

(*a*) Disturbances of accommodation and the pupil reflexes.

(*b*) Pareses and paralyses of the external ocular muscles.

(*c*) Alterations of the static refraction of the eye.

The secondary affections, namely, those which result from intracranial disease, manifest themselves in lesions of the cornea and the fundus oculi, in changes in the visual field and palsies of the ocular muscles.

Diseases of the Lids, Orbit, Conjunctiva and Cornea.—The liability of diabetics to furunculosis finds its expression, in so far as the eyelids are concerned, in the development of styes, ulcerated

blepharitis, edema and even gangrene (Koenig). In the same category should be placed the occasional occurrence of phlegmon of the orbit, as reported by Lagrange,[1] and herpes zoster. Of these conditions persistent eruption of styes is the most significant, and there are cases on record, for example, a striking one by Groenouw,[2] in which this condition led to the discovery of sugar in the urine. Anderson[3] has suggested that there may be a diabetic conjunctivitis; but though a diabetic might have a persistent conjunctivitis, the relationship between cause and effect is not established, and the same is true of scleritis, as Knies maintains. The subconjunctival hemorrhages which are so significant a sign of chronic nephritis have also been seen in diabetes.

Purulent varieties of keratitis in diabetes have been well described by Von Graefe, Panas and Wiesinger.[4] Superficial inflammation of the cornea is ascribed by Galezowski to the same affection.

Diseases of the Uveal Tract.—According to Leber's[5] investigations, iritis in diabetes, often but not always bilateral, assumes usually a definite form with a fibrinous exudate in the pupil space and a small hypopyon, that is, a yellowish-white exudate at the bottom of the anterior chamber. Sometimes the iritis appears in the so-called serous type, with the deposition of small dots on the posterior surface of the cornea and an involvement of the uveal tract justifying the term irido-choroiditis, or uveitis; sometimes hemorrhages take place, not only in the anterior chamber, but also in the vitreous. I have seen cases of iritis in diabetes with recurring hemorrhages in the anterior chamber. Terson[6] states that the so-called "quiet-iritis" of Hutchinson, which is usually a gouty symptom, may be present in diabetes, while Hutchinson himself maintains that iritis occurs in diabetics chiefly when they are also the subjects of gout.

Iritis is not infrequent in diabetes, comprising 5 to 6 per cent of

[1] Archiv d'Ophth., VII., 1887, p. 65.

[2] Graefe-Saemisch, Handbuch der Gesammten Augenheilkunde, Zweite Auflage, Lief., XXXVII. and XXXVIII., p. 359.

[3] Ophthalmic Review, Vol. VIII., 1889, p. 33.

[4] Graefe's Archiv f. Ophth., XXXI., 2, 1885, p. 203.

[5] *Ibid.*, p. 183.

[6] Journal des Praticiens, 1903, I., 15, 705.

the ocular manifestations of this disease. Complicating or following the iritis, cyclitis, vitreous opacities, choroiditis and glaucoma have been observed. The prognosis, in the absence of severe complications and in the presence of proper treatment, is quite good, and the pupil exudate and hypopyon may quickly disappear. Occasionally the disease is intractable, especially when complicating eye operations in diabetics. Patients with iritis otherwise unexplained should always, as Schirmer insists, be subjected to strict urinary examination. Very interesting are the alterations in the iris which have been observed in diabetics, manifesting themselves particularly in edematous swelling, vacuolation and proliferation of the pigment layer of the posterior surface of the iris.

Diseases of the Retina and Optic Nerve.—*History.*—The occurrence of retinal lesions in connection with diabetes, usually called diabetic retinitis, has been known for a long time, the first case having been reported by Edward Jaeger in 1856. At that time it was held that the diabetes was probably not alone responsible for the retinal lesions, which were provoked by a coexisting albuminuria. In 1869, Dr. Henry D. Noyes, of New York, carefully studied a case of diabetic retinitis and definitely proved that renal disease was absent, and therefore that to the diabetes should be charged the retinal condition. Subsequently numbers of cases of pure diabetic retinitis were collected by Leber, Hirschberg, Lagrange and many others.

Varieties and Symptoms.—Systematic writers, notably Hirschberg,[1] have recognized the following varieties of so-called diabetic retinitis:

(*a*) *Central Punctate Diabetic Retinitis.*—According to Hirschberg, this is the typical variety of the disease and is thus described: At the posterior pole of the eye numerous white points, spots and stripes appear, which irregularly surround the macula, but do not form a star figure. Aggregations of these spots are seen between the disc and the macula, in the area between the superior and inferior temporal vessels, and they are within the nerve fiber layer. Beyond

[1] Deutsch. med. Wochenschr., Nos. 51 and 52, 1890, and Centralbl. f. prakt. Augenheilk., Vol. 15, 1891, pp. 18–24, 51–58, 68–77. Consult also Schöbl, System of Diseases of the Eye, edited by Norris and Oliver, Vol. III., p. 509.

these vessels the lesions occur in single spots. Where they exist they remain unchanged; their number may increase but they do not tend to coalesce. Between them minute hemorrhages are often evident. The nerve-head is normal, or practically so, the blood-vessels show no signs of gross disease and the intervening retina is not opaque or edematous.

(*b*) *Hemorrhagic Diabetic Retinitis.*—According to Hirschberg, with comparatively normal looking blood-vessels and unaltered nerve-head, hemorrhages, punctiform or of greater dimensions, are scattered over the retina; rarely they are of large size and appear suddenly. Sometimes the hemorrhages are in the far periphery and escape detection. The white spots are wanting. Hemorrhagic glaucoma may also occur.

(*c*) *Atypical Diabetic Retinitis.*—Hirschberg has also described in this disease retinal pigmentation with contraction of the visual field and night blindness, resembling pigmentary degeneration of the retina, but is not satisfied that the affection is certainly caused by diabetes.

Some authors are quite unwilling to apply the term "typical" or "characteristic" to any of the types of retinitis associated with diabetes, and believe with Schweigger that while many forms of ocular disease appear during the course of glycosuria, none of them bears the same relation to it that albuminuric retinitis does to chronic nephritis, or syphilitic retinitis to syphilis. Certainly the punctate central retinitis must be uncommon, and in general terms the retinal lesions seen in diabetes comprise small and large hemorrhages, and white spots of exudate, not specially associated with changes in the retinal vessels and nerve-head. The white spots sometimes arrange themselves in zone-like areas above and below the macula, resembling the so-called circinate retinitis, and may be massed in the central region of the retina. A number of authors call attention to the tendency, not admitted by others, of the hemorrhages to burst into the vitreous. A few examples of proliferating retinitis, with the formation of vascular veils in the vitreous, have been reported, for example, by J. Herbert Fisher, and I have seen this condition in one case of advanced diabetes. Embolism of the central artery of the retina has been recorded (Galezowski), and hemorrhage into the

sheath of the optic nerve. When albuminuria complicates diabetes, there may be a combination of the retinal lesions of the two conditions, to which the term *albuminuric diabetic retinitis* has been applied.

Frequency and Time of Occurrence.—Statistical information is too imperfect and contradictory to state with accuracy the frequency of retinal lesions in diabetes. Groenouw's[1] tables record a percentage varying from 20 to 36 per cent. In general terms, the disease must have existed for a prolonged period before the retinal lesions appear, but Hirschberg thinks that in all cases of long-standing retinal changes probably exist. Diabetic retinitis is rare before the forty-fifth year of life, and when seen in children, for example, in Culbertson's patient aged six years, other complicating factors are present. Doubtless as Dodd suggests,[2] its development is aided in persons of advanced age by changes in the retinal vessels naturally present at that time of life.

Pathology.—In general terms, according to Leber, the retinal lesions depend partly upon a changed condition of the blood and partly upon an alteration in the vessel walls permitting a diapedesis of the red blood corpuscles and a transudation into the retinal tissue. Nettleship and Mackenzie[3] found the following lesions in diabetic retinitis: Hyaline degeneration of the intima of the retinal vessels; varicose swellings in the nerve-fiber stratum; and swelling of the other layers due to a chronic edema with hypertrophy of the connective tissue framework. Recently Himmelsheim and Leber[4] have shown that there may be in diabetes a combination of retinal and optic nerve disease, particularly a high degree of endarteritis of the central retinal vessel and its branches.

Prognosis.—The ocular prognosis depends upon the character and situation of the lesions which may under appropriate treatment disappear in large measure. Sometimes grave complications occur which destroy or greatly damage vision: renewed hemorrhage or exudate in the macula, vitreous hemorrhage and degeneration, and

[1] Graefe u. Saemisch, Handbuch der Gesamten Augenheilkunde, Zweite Auflage, 37, 38 Lieferung, 1902, p. 337.

[2] Archives of Ophthalmology, XXIV., 1895, p. 210.

[3] Ophthalmic Hospital Reports, Vol. IX., 1877, p. 134.

[4] Graefe's Archiv f. Ophthalmologie, 52, 1901, p. 337.

glaucoma. The vital prognosis is certainly more favorable than that of albuminuric retinitis, and although the appearance of retinal lesions should be regarded as a grave symptom, many of the patients have survived a number of years after their appearance.[1] They may be the precursors of cerebral hemorrhage.

Treatment.—This should include the usual measures for the relief of diabetes—dietetic and medicinal, the various iodids, and locally pilocarpin drops to combat any tendency to increased intraocular tension.

Diabetic Amblyopia and Optic Nerve Atrophy.—Systematic writers have divided the lesions which may occur in the optic nerve under the influence of diabetes as follows:

(*a*) *Atrophy of the Papillo-Macular Bundle or Chronic Retro-Bulbar Neuritis, usually called Diabetic Amblyopia.*—The symptoms of this condition are depreciation of central vision, unassociated with ophthalmoscopic retinal lesions, depending upon the presence of a central scotoma, chiefly for red and green. Usually the peripheral visual field is intact; sometimes somewhat contracted. The scotoma extends moderately in all directions from the fixing point, but is more produced in the temporal direction than elsewhere. Within its area the perception of blue is longest retained, but finally its perception and that of white may be lost and the scotoma becomes absolute. The nerve-head is at first not at all or only slightly altered by some congestion and a moderate blurring of its edges; later there is evident blanching of the papillo-macular area. The similarity of this condition to the so-called tobacco-alcohol amblyopia is evident, and Mauthner maintained that these substances should be held responsible for its development. Now, while it is true that diabetics are more susceptible to the action of tobacco and alcohol on the optic nerve apparatus than normal individuals, as has been well shown by Hirschberg, Leber, and especially by Schmidt-Rimpler,[2] a pure diabetic amblyopia of this nature is not infrequent. Thus, Schmidt-Rimpler, in a collection of 140 diabetic ocular diseases, found 34 examples of optic nerve affection, and in the majority of these a

[1] On this point consult Dodd and Groenouw, loc. citat.

[2] Bericht über die 25 Versammlung der Ophthalmologischen Gesellschaft, Heidelberg, 1896, p. 99.

central scotoma could be demonstrated. Leber has found 28 per cent. of optic nerve affections in diabetic eye lesions.

The prognosis, in so far as sight is concerned, according to Leber, is reasonably good, and vision is restored if treatment of the diabetes is early begun and conscientiously pursued. If the condition has lasted long then the prognosis is more dubious and a permanent atrophy may result. Sometimes, according to Hirschberg, the gravity of the vital prognosis is greatly increased by the presence of diabetic amblyopia.

The lesions in these cases have been well studied by Nettleship, Edmunds and Schmidt-Rimpler and are similar to those found in intoxication-amblyopia, namely, a degeneration or atrophy of the papillo-macular bundle. In the drug amblyopias modern investigation has demonstrated that the toxin acts primarily upon the ganglion cells of the macula and the optic nerve changes are secondary; or else that there is a simultaneous effect upon the nerve-cells and nerve-fibers. Doubtless the same is true of the action of the toxin of diabetes.

Acute retro-bulbar neuritis has been reported by Foerster. Amblyopia without central scotoma and unassociated with ophthalmoscopic nerve-head changes has also been recorded.

(*b*) *Primary Atrophy of the Optic Nerve.*—Simple, progressive optic nerve atrophy, resulting in blindness, has been described by Leber and Schmidt-Rimpler but must be exceedingly uncommon, as Uhthoff has never observed a case of this character which he could certainly ascribe alone to diabetes. Stoewer[1] has published an instance of this form of atrophy which he attributes to diabetes, and suggests that the primary anatomical cause may reside in nutritional disturbances of the optic nerve fibers brought about by the diseased condition of the smallest vessels in the optic nerve apparatus which has been demonstrated to exist in diabetes by Leber, Himmelsheim and Schmidt-Rimpler.

(*c*) *Consecutive Atrophy of the Optic Nerve.*—This is an atrophy of the optic nerve which is associated with, or rather, follows, retinitis, and is probably present in many cases. Indeed, Schmidt-Rimpler believes that the optic nerves of all old diabetics almost always exhibit some degenerative changes.

[1] Klin. Monatsbl. f. Augenheilk., XLI., Bd. II., 1903, p. 97.

Diseases of the Crystalline Lens.—Cataract is a frequent, in the opinion of many observers, the most frequent ocular complication of diabetes. Because a diabetic patient has cataract, however, it does not necessarily mean that the lenticular opacity is due to the disease from which he suffers. It may be attributed, as Mauthner maintained, to concomitant conditions, such as age, impaired nutrition, and other intrinsic influences. Nevertheless diabetic cataract must be admitted, the frequency of its occurrence being variously estimated from 4 to 25 per cent.

It may occur at almost any age: in childhood, in young persons, and in the aged. In the young its development is often rapid, from a few weeks to several months, and it appears when ripe as a bluish-white soft cataract, usually bilateral, not unlike that which follows contusion of the globe. It is to these quickly developing lenticular opacities in young persons advanced in the disease that Schweigger would limit the name diabetic cataract. In old diabetics the course of the lens changes does not differ essentially from that of ordinary senile cataract.

Many theories have been advanced to explain the origin of diabetic cataract, but none of them are very satisfactory. It has been suggested that it is due to the presence of sugar in the lens, which acts as an irritant on its fibers; to chemical alteration of the media which surround the lens, notably the aqueous humor, that is, that the sugar in the aqueous humor is converted into lactic acid and directly affects the lenticular tissue; to dehydration of the lens by loss of fluids from the tissues generally; and to a general marasmus which the disease has caused. It is not improbable that the degenerative changes which occur in the iris and ciliary body, or, in general terms, in the uveal tract, may bring about lenticular opacities, as Deutschmann has suggested. Wilder thinks that the lens is readily affected in diabetes because it is an epiblastic structure, and therefore liable, as are other epiblastic tissues, to degenerative changes in this disease.

An interesting fact in regard to diabetic cataract is that it sometimes spontaneously disappears, that is, during the course of the general treatment. Pigmented cataract, the pigment being of unknown nature, has been described by Perles in diabetes.

The treatment of diabetic cataract does not differ from that of the

ordinary varieties, and other things being equal, its extraction meets with fair success, although iritis and suppuration are complications to be dreaded.

Alteration in Accommodation and Pupil Reflexes.—A common ocular symptom of diabetes and one, moreover, that may appear in an early stage of the disease, is failure of accommodation, or, as it is sometimes called, *premature presbyopia.* The amplitude of accommodation may be diminished from one to three diopters, even when the refractive defects are properly neutralized. Necessarily this is difficult to demonstrate in elderly subjects whose range of accommodation is naturally limited, and it may not at all be evident in the presence of myopia, while it is more pronounced if the eye is hyperopic. Should the failure of accommodation exceed three diopters the condition may be described as a paresis. In a few instances there has been complete paralysis of the ciliary muscle, or cycloplegia. Ordinarily no special changes in the pupil-reflexes have been noted in diabetes, but there are a few cases on record of bilateral and unilateral mydriasis indicating paresis of the iris. Accommodative weakness has been attributed to the general muscular weakness engendered by the disease, but is perhaps more accurately explained by the presence of a peripheral neuritis, or, as Berger maintains, by the action of a toxin.

Paralysis of the External Ocular Muscles.—Palsies of the external ocular muscles have frequently been observed in diabetes. According to Groenouw,[1] who has collected the most recent literature, there may be ptosis, unilateral or bilateral; palsy of one or all of the branches of the oculo-motor, either upon one or both sides; paralysis of the abducens, of the trochlearis and of the facial, affecting the orbicularis palpebrarum. Although it is usually stated that the oculo-motor or third nerve is most frequently affected, Hirschberg and J. B. Lawford believe that the abducens or sixth nerve is most apt to be involved, and this corresponds with my own experience. These external ocular paralyses may appear at any stage of diabetes, may be slight and pass away quickly, or may have a long duration, and sometimes, especially, according to Berger, such as develop in the late stages of the disease, may be permanent. Re-

[1] Loc. citat.

lapses and recurrences occur, and in a second attack a muscle other than the one originally involved may be affected. Hawthorne has observed an association of abducens palsy and retinal disease, and I have had a similar experience.

These muscle palsies have been ascribed to the action of a toxin upon the nerve, to a peripheral neuritis, and to a lesion, hemorrhagic or degenerative, of the nuclei. Swanzy regards the diabetic orbital muscle palsies as probably nuclear in origin, while Berger, Lawford and others attribute them to a peripheral toxic neuritis. Those of sudden onset may be explained by a hemorrhage. With the exceptions already noted, they are amenable to the general treatment of the disease.

Alteration in the Static Refraction of the Eye.—Hirschberg[1] has especially called attention to rapid development of myopia in middle life, without alteration in the crystalline lens, as significant of diabetes and suggested the term "diabetic myopia." Many examples of this condition have been reported, and its occurrence is strongly indicative of the presence of glycosuria. Sometimes the changes in the refraction of the eye are exceedingly rapid, for example in a case reported by Grimsdale, where a diabetic myopia of 2 D disappeared in ten days coincident with a diminution of the sugar in the urine. The development of diabetic myopia has been attributed to a change in the index of refraction of the aqueous humor, which is highly improbable, and to an augmentation of the refractive power of the lens, which is concerned less with an alteration of the form of the crystalline body than with an increase of its index of refraction. Groenouw points out that the apparently clear lens of diabetic myopia may later become opaque and cataract develop, under which circumstances the development of the myopia must be ascribed to a change in the refractive power of the lens which should be regarded as the prodrome of cataract formation. To explain the sudden changes in refraction Grimsdale suggests that rapid increase of sugar in the tissue gives rise to increased osmosis and swelling of the lens cortex, which by pressure reduces the bulk of the nucleus and increases its refractive power. Reduction in the amount of sugar causes reduction of the swelling of the cortex and the nucleus regains its original

[1] Centralbl. f. prakt. Augenheilk., Vol. XIV., 1890, p. 7.

size. Horner has reported acquired hyperopia in diabetes, which was, however, probably an example of the manifestation of a hyperopia previously latent. Risley has recorded increase in hyperopia during diminution of the glycosuria, with a marked decrease in this hyperopia when the sugar reappeared in the urine.

Secondary Ocular Affections in Diabetes.—A certain proportion of the ocular disorders in diabetes must be regarded as secondary to an intracranial disease. Thus, Thillies,[1] in addition to palsy of the orbicularis with lagophthalmos and consequent sloughing of the cornea, has also described neuro-paralytic keratitis due to a lesion of the Gasserian ganglion or its sensitive root. The same author, as well as others, refers to cases of orbital muscle palsies caused by intracranial hemorrhage, and cerebral disease accounts for some of the optic nerve affections which have been described. This is especially true of the optic nerve atrophies which have followed neuritis of cerebral origin. An interesting defect of the visual field, namely, hemianopsia, has been noted a number of times in diabetes, both with and without other manifestations of intracranial disease.

[1] Abstract Medical News, August 16, 1902.

SECTION III.

DIABETES INSIPIDUS.

If diabetes mellitus be an imperfectly understood disease, still more must this be said of the insipid diabetes or chronic polyuria, for even less is known of its essential or remote causes.

The term is applied to any excessive and continuous secretion of non-saccharine and non-albuminous urine of low specific gravity.

Thomas Willis, physician to Charles II. of England, first separated, in 1674, the two forms of diabetes, the saccharine and non-saccharine or insipid. Unlike diabetes mellitus, diabetes insipidus affects rather younger persons, being rare in those over 50 years of age, relatively frequent in infancy, and most common between the ages of twenty and thirty, as is shown in the appended table from Senator's article in Ziemssen's *Cyclopædia,* of cases collected by Roberts, Strauss, and von der Heijden:

Age.	Roberts.	Strauss.	von der Heijden.
Less than 5 years,	7	9	2
5 to 10 years,	15	12	5
10 to 20 years,	13		19
20 to 30 years,	16	57	23
30 to 40 years,	—		19
40 to 50 years,	15	7	9
50 to 60 years,	—		6
60 to 70 years,	40		4
	70	85	87

I recall but one patient in my own practice who was over 50. Gerhardt holds that more than half of all cases occur between the tenth and fortieth years. It will be noted that a majority of Roberts' cases were between fifty and seventy, failing to confirm the statement made at the outset as to age.

As to the *sex* of those affected, the same peculiarity is common to both forms of diabetes; the insipid form is much more frequent in

males than females, two to three times as many of the former sex being affected by it as the latter.

The disease is really quite rare. Its infrequency may be appreciated from the statement of Dr. Thomas B. Futcher[1] in a recent paper, that out of 356,637 cases treated in the Dispensary and wards of the Johns Hopkins Hospital in Baltimore, there were only four cases of diabetes insipidus or .001 per cent. During the same time —a period of 12 years—170 cases of diabetes mellitus came under observation. The disease would seem to be more common in Europe. Out of 113,600 patients treated at the Charité, Berlin, from 1877 to 1896, there were 55 cases or .048 per cent. In the Zürich Hospital Eichorst found 7 cases among 35,942 patients treated, or .02 per cent.

In my own practice, hospital and private, extending over many years, I have had probably ten cases.

Varieties.—The older observers subdivided diabetes insipidus, basing the subdivisions upon variations in the composition of the urine, but at the present day only two clinical types are allowed and even these are not founded on a very definite basis, so that it is sometimes difficult to say in which category a case belongs. They include the *primary or idiopathic* form and the *secondary* or symptomatic form.

The *idiopathic variety* includes cases in which there is no discoverable organic lesion. Among these are many hereditary cases and cases supposed to be due to cold, sunstroke, alcoholic excesses and infectious diseases. The *symptomatic* cases include those in which there is discoverable lesion, which commonly includes some affection of the brain or spinal cord and their membranes, or of some part of the sympathetic system.

Etiology and Pathology.

As to causes, the same uncertainty prevails as with diabetes mellitus. An examination of reported cases shows association with certain morbid states, such as cerebral disease, including tumor of the brain, sunstroke, cerebro-spinal fever, blows on the head, falls,

[1] Diabetes Insipidus with a report of five cases, Johns Hopkins Hospital Reports, Vol. X., 1902.

exposure to cold, drinking cold fluids, drunkenness, pregnancy, hysteria, emotion, hereditary influence, previous disease, etc., but this does not show causation.

Probably syphilis more than any other disease may be regarded as a cause, and it may be through this agency that hereditation appears to enter so largely into causation. Some remarkable cases of hereditation are reported. Thus Lacombe reported eight cases (five males and three females) occurring in one family through two generations; Gabriel Pain seven cases (five males and two females) through three generations; S. Gee eleven cases (nine males and two females) through four generations.[1] Still more remarkable is Weil's report of 23 cases out of 91 members of a family in four generations, who had persistent polyuria without any other derangement of health. These included the great-grandfather, three children, seven grandchildren and 12 great-grandchildren. Of the 22 subjects 11 were male and 11 female. There was nothing else peculiar in these cases, although Weil believed that they represented a special form of the disease, characterized by its heredity, by marked intensity of some of the symptoms, especially dilatation of the bladder with the passage of an enormous quantity of urine at each micturition.[2]

This much may, however, be said: The proportion of cases, in which diabetes insipidus is associated with brain disease or injuries of the head, taken in connection with Bernard's discovery in 1849 that puncture of the floor of the fourth ventricle above the diabetic center produces polyuria without glycosuria, but frequently with albuminuria, while puncture below produces polyuria only, makes it very likely that central nervous irritation, however induced, is responsible for the symptom.

It should be mentioned that Eckhard[3] confirmed Bernard's ob-

[1] I am indebted for my knowledge of these cases to Dr. Thomas B. Futcher's paper on Diabetes Insipidus with a report of five cases in Vol. X., Johns Hopkins Hospital Bulletin, Vol. X. (1902). The following references are taken from his paper:—La Combe, De la Polydipsie, Paris thesis, 1841; Gee, St. Bartholomew's Hospital Reports, Vol. XIII., 1877; Pain, De la Polyurie chronique, Paris thesis, 1879.

[2] Weil, Ueber die hereditäre form des Diabetes insipidus, Virch. Archiv, Bd. 95, 1884.

[3] Eckhard, Beiträge zur Anatomie und Physiologie, IV., V. and VI., 1869, 1870, 1872.

servation, although his experiments do not locate the center so precisely. Eckhard also showed that the vagus has absolutely no influence on the secretion of urine in dogs and rabbits; and that in dogs, at least, the route in which the stimulus to increased secretion takes place is probably the spinal cord, certainly as far as the seventh cervical vertebra, since section of the cord above this point entirely abolished the secretion of urine, whence it is evident too that the regulating center is above the point of section. It must be remembered, too, that this part of the cord is traversed by numerous fine sympathetic nerve filaments. Peyrani[1] has shown that section of the cervical sympathetic resulted in a decidedly diminished secretion of both urine and urea, while electrical irritation of this nerve lasting for several hours resulted in an increased secretion of urine and urea. Whence it would appear that excitor influence travels through the sympathetic.

On the other hand, section of the greater splanchnic nerve in dogs by Eckhard caused an increased flow of urine on the same side, while irritation of the peripheral extremity of the same nerve caused a diminution and even cessation of the secretion of urine. Again, irritation of the floor of the fourth ventricle after the splanchnic nerve was cut caused a further increase in urine secretion. Whence it is evident that the splanchnics are inhibitory of the act of secretion of urine, while the excitor influence passes through another channel, probably the sympathetic filaments which pass for a certain distance through the spinal cord. In a word, the channels through which increased secretion of non-saccharine urine is influenced are the same as those through which saccharine diabetes results, the difference being that in the latter glucose is added, while in the former it is absent.

That most derangements of this function not caused by central nerve lesions are due to influences exerted through the sympathetic system is more than likely. This will be better understood after reading Rolfe's description of the course of the nerves forming the renal plexus as follows: "It is interesting to trace the course of the nerves forming the renal plexus, as irritation from eccentric or distant sources may play a part in inhibiting the renal nerves. Thus,

[1] Peyrani, Comptes Rendus, 1871, I., p. 300.

the nerves forming the renal plexus are derived chiefly from the solar plexus; as the right vagus and great and lesser splanchnics join the solar plexus, it is probable that branches of these nerves enter the kidney by way of the renal plexus. The splanchnics also send branches direct to the renal plexus; and the left vagus sends some fibers to the left kidney. They contain medullated and non-medullated fibers; and Krause has traced the latter as far as the apices of the papillæ. Their mode of termination is unknown. Physiologically vaso-constrictor, vaso-dilator and sensory fibers have been ascertained. The connection through the vagus brings us into range with the medulla oblongata, and with many organs susceptible of tubercular or syphilitis growths, or of sudden shock, such as chill. The solar plexus may propagate the effect of abdominal new growths or aneurysms."

It is evident how any lesion such as a morbid growth of the abdomen or pregnant uterus or a local injury to these parts through the solar plexus or its peripheral branches so richly supplied to the abdominal organs may cause the polyuria constituting diabetes insipidus.

The immediate cause of the diuresis is a dilatation, first, of the arterioles, and then of the capillary blood-vessels of the kidney, through whose thinned and stretched walls the water osmoses readily, so that the whole act is probably one of increased filtration, although it has been suggested and deemed not improbable by Eckhard that at least in polyuria from irritation of the floor of the fourth ventricle, there is an excito-secretory influence exerted upon the gland-cells, increasing their activity, and in consequence the secretion of urine. But no nerves have ever been traced to the *cells* of the kidney, and while the cells are probably active in separating some of the organic constitutents of the urine, there is every reason to believe that the water, at least, is simply filtered out, while this filtration is stimulated or retarded by various influences. It should be mentioned on the other hand that Eckhard concluded from the investigations referred to that the secretory action of the kidney was largely dependent on the action of specific secretory nerves and only moderately on blood-pressure. The researches of Heidenhain and Grützner seem, how-

ever, to have finally established the filtration theory of Ludwig, so far as water elimination is concerned.

Hence it may be inferred that diabetes insipidus is generally the result of some irritation, either direct or reflex, of this center in the medulla oblongata, or of the sympathetic ganglia in the abdomen, a conclusion which is confirmed by the fact already mentioned, that the largest number of cases associated with any single condition is found in connection with diseases and injuries of the brain, spinal cord and sympathetic nervous system; and still more by the fact that in a considerable number of cases the lesion has been found to be in the medulla oblongata, or the floor of the fourth ventricle. It must be remembered, however, that as early as 1794 Frank reported a fatal diabetes insipidus associated with disease of the intestine; that Schapiro noted five such cases in Eichwald's clinic, and that Dickinson reported a case associated with carcinoma of the liver, although here there was also associated disease of the solar plexus. The polyuria in these cases must have been reflex in origin.

Morbid Anatomy.

The essential morbid anatomy of diabetes insipidus would be the lesions of the nerve centers and their membranes, or of the sympathetic system which may underlie the symptoms. It is scarcely necessary to repeat them, but we may mention traumatic lesions and diseases of the cranial bones and brain, cerebral tumor of any kind as gumma, myxoma or sarcoma, hemorrhage, various syphilitic lesions of the brain and spinal cord, cerebrospinal meningitis, and diseases of the sympathetic system. Stoermer says that statistics show that about 30 per cent. of all cases are traceable to injuries of the brain alone. In only a smaller number of cases is any lesion whatever found.

As a secondary phenomenon and consequence, rather than an essential morbid lesion, is an atrophy and degeneration of the renal substance, which may be trifling or have proceeded to a degree of complete sacculation of the organ. Out of eleven cases in which autopsies had been made, collected and reported by Dr. Roberts in

his work on *Urinary Diseases,* four presented this alteration; in one, the glandular tissue was entirely wanting. In a fifth, multiple abscesses were found in one kidney, the other was hyperemic. In a sixth, there was a tubercular tumor in the left hemisphere at the border of the longitudinal sinus, and another in the cerebellum. In the seventh and eighth cases, fatty degeneration of the nervous tissues of the walls of the fourth ventricle was present; in the eighth, there was also great vascularity of the kidneys. In the ninth, there was a glio-sarcoma as large as a walnut in the floor of the fourth ventricle, filling the entire cavity. In the tenth, there was miliary tubercle at the base of the brain, near but not in the fourth ventricle, and on the upper surface of the cerebellum. In an eleventh, there were no changes in the kidney, except congestion of the Malpighian bodies.

As a secondary lesion may be mentioned dilatation of the bladder. Duponchel[1] reported a case in which the organ attained a capacity of two quarts. It will be noticed that nervous lesions when present are found more frequently in the vicinity of the base of the brain.

Symptoms.

These are not numerous. The *enormous secretion of urine,* of almost spring-water-like clearness and of specific gravity often as low as 1003, is the most conspicuous symptom, but more annoying, probably, is the *extreme thirst* which always attends it. Thirst is commonly regarded as secondary to the polyuria, but a few well-authenticated cases are reported in which thirst would appear to have been the initial symptom. Such was Nothnagel's[2] case, that of a man 35 years old who was kicked in the abdomen and fell, striking his head in the neighborhood of the right ear against a piece of wood. He was not rendered unconscious, but became dizzy. Half an hour later he became intensely thirsty and drank three liters of water and three hours elapsed before the first urine was passed.

The above may be said to include all the essential symptoms, others which may or may not be present being rather their consequence.

[1] Duponchel, La Semaine Medicale, December 3, 1890.
[2] Nothnagel, Virchow's Archiv, Bd. 68.

Very constantly among them are *dryness of the skin* and absence of perspiration. The health is otherwise often perfect.

Occasionally there are *derangements of digestion,* and sometimes also the *appetite is large,* as in diabetes mellitus. Always, the effect of increased discharge of water by the kidneys is to increase the rapidity of tissue-metamorphosis and to wash out thoroughly the urea and extractives from the blood and tissues, so that it might be expected that there would be some increase of appetite on this account.

In addition to the symptoms detailed, there occur at times *dryness of the tongue, epigastric and lumbar pains, headache, diarrhea, debility, impairment of mental faculties and of sexual function. Constipation* as contrasted with diarrhea is the rule. This is explained by the abstraction of fluid from the alimentary tract as from everywhere else. The patient is spare or emaciated. The debility is sometimes extreme. At other times the patient works hard. In some instances there is the most extraordinary *tolerance of alcoholic drinks,* while at others there is an *exaggerated susceptibility* to their influence. A very *slight lowering of the body temperature* has been observed, amounting, however, to but a few tenths of a degree, and is never below 97° F. This slight lowering has been ascribed to the refrigerant effect of cold drinks, which are constantly ingested. The tendency to boils observed in melliturıa is not found in diabetes insipidus. On the other hand, high arterial tension is found at times in the insipid as well as the mellitic form.

In advanced stages of the disease *edema* of the ankles sometimes occurs.

The *knee-jerks* were increased in four out of five of Futcher's cases.

These symptoms may occur suddenly in the midst of apparent health, or they may supervene upon or be superadded to others, chiefly of a nervous character, which may be the result of the same nervous lesion causing the polyuria. Such symptoms are headache, restlessness, irritability, more rarely convulsions, delirium, paralyses, indeed any one or more of the great variety of symptoms which result from organic or functional nervous disease. Sometimes these symptoms succeed upon the polyuria, or are increased by

it. It is certain that the milder nervous symptoms are sometimes the result simply of the inconvenience and annoyance caused by the two cardinal symptoms, polyuria and thirst. The patient is kept busy, as it were, night and day, in passing water. It is not surprising that such a patient should be fretful and irritable, and that sooner or later his health should be broken if the symptoms are not relieved.

The *duration* of the condition is very various. Sometimes it continues through life with no inconvenience except that from the constant diuresis and thirst, and no disadvantage when the latter is supplied. Dr. Willis records a case lasting fifty years. On the other hand, it is seldom of brief duration; indeed, there is needed a certain chronicity in order to admit it in the category of diseases. One case is reported as terminating fatally in seven weeks. Under prognosis will be found some further information as to duration, but it may be said, in general, that most cases which terminate unfavorably and most which recover completely, do so within a year.

Complications.—The disease has *no complications* except such as are its cause or its results. Among the latter is occasionally dilatation of the pelvis of the kidney and atrophy of the organ itself, due to pressure of the accumulated urine, and resulting in a sacculated kidney. Its symptoms are almost always influenced, and sometimes even cut short, by intercurrent disease, especially of a febrile character, or even by a profound physical impression, as long-continued suppuration after a blister. Thus Willis[1] cites the case of a young man who had thirst and diuresis up to 18 years of age. At that time he was attacked with pleurisy, and a blister was applied which suppurated for 25 days. With the healing of the blister disappeared both the pleurisy and the diabetes. Dr. Roberts[2] cites a case which had existed "in intensity" for 18 years, in which an attack of acute rheumatism treated with nitrate of potash suspended it completely. Kuelz, Charcot, and Lacombe record cases in which temporary improvement occurred during varioloid, and Senator[3] of similar improvement during pneumonia, and again in the same man during erysipelas. On the other hand, Dickinson[4] records a case in

[1] Willis, op. citat., p. 24.
[2] Roberts, Urinary and Renal Diseases, 3d Am. edit., 1879, p. 202.
[3] Senator, op. citat., 1031.
[4] Dickinson, op. citat., p. 205.

which scarlatina supervened without effect on the symptoms. The disease has been known to occur during pregnancy and to disappear with it, while in other instances it has been uninfluenced by the latter condition.

Physical and Chemical Characters of the Urine.

As to the quantity of urine passed, it is enormous, exceeding often the amount passed in saccharine diabetes. As many as 43 liters (90 pints) daily are recorded by Trousseau in a patient 24 years old. One fourth this quantity is common. It has been said, even, that the quantity secreted sometimes exceeds that ingested, but this is impossible, at least for any length of time, unless water is absorbed from the atmosphere, which is not impossible. In point of fact the water excreted is always a little less than that ingested, either as drink or in the solid food.

As the quantity of urine excreted increases, or its normal acidity diminishes, its color disappears and its specific gravity declines. In one case under my care the specific gravity was scarcely 1001, while the urine in moderate bulk was absolutely colorless. Again, a faint greenish tinge is exhibited by the urine in bulk.

As to the other constituents of the urine, it may be said in general that they are all increased, except possibly uric acid. Thus the *urea* is increased to three and even four times its normal amount,—70 and 72 grams (1080.10 and 1110.96 grains) are recorded by Senator, in an adult, and 30 grams (462.9 grains) by Dickinson, in a child of 8 years. Such increase is probably due to increased albumin ingestion. In a case reported by Da Costa[1] the urea was diminished. More frequently it remains normal in amount.

With regard to *uric* acid, its estimation is difficult, on account of the extreme dilution of the urine, but analyses go to show that it may be diminished, or remain within normal limits.

Sulphuric and *phosphoric* acids are both increased, and especially, according to Dickinson, the combination of phosphoric acid with the earths, lime and magnesia.

The same is true of the *chlorids,* which are increased for the same reason as urea, sulphates and phosphates.

[1] Transactions of the College of Physicians of Philadelphia, 3d series, Vol. I., 1875, p. 139.

Of abnormal constituents, *inosit* has been found, and it is said *albumin* very rarely, but care should be taken not to confound the polyuria with small albuminuria of a contracted kidney with an albuminous polyuria in which there is no organic disease of the kidney.

Dr. Futcher, in the paper referred to, reports the results of urinalyses which are the most recent made in connection with this disease. His results do not differ materially from those above stated.

Unlike the urine of saccharine diabetes, that of diabetes insipidus rapidly decomposes, becomes putrescent, and at the same time turbid with bacteria. A further peculiarity of the secretion of urine is that an increase does not rapidly follow the ingestion of fluid as is the case in health, but ensues at an interval, and is kept up during a longer period. This is ascribed to the *constant* dilatation of the renal capillaries which is supposed to exist in diabetes insipidus, as compared with the *alternate* dilatation and contraction which occur in health in the reflex accommodation which is always taking place between the ingestion of fluids and their secretion by the skin and kidneys. In health the ingestion of an undue amount of fluid is promptly followed by dilatation of the renal or cutaneous capillaries or both, and the transudation of an increased amount of urine or perspiration or of both. If, on the other hand, the quantity of liquid ingested is small, these two sets of capillaries remain contracted and the water is retained in the economy. In diabetes insipidus, on the other hand, the renal capillaries are always dilated, and are always therefore in a condition to permit the transudation of water, while they in turn cannot respond as promptly to the ingestion of fluid as they do in health. A longer time, therefore, intervenes before the increased secretion takes place, while it is also longer kept.

Some of the accounts published as to the quantity of water consumed and excreted are almost incredible, yet they seem well authenticated. The following illustrative instances are condensed from Dr. Willis' work on *Urinary Diseases.*[1] A small artisan, 55 years old, had had constant thirst with commensurate diuresis since he was 5 years of age. From the age of 16 he had drunk, on an aver-

[1] American edition, Philadelphia, 1839, p. 23.

age, no less than two pailfuls daily. While in the Hôtel Dieu, to which he was admitted for an injury of the knee, he drank on an average 33 pints of water every day, often swallowing two liters or about two quarts at a draught. He passed daily about 34 pounds of urine and 1 pound of feces. He otherwise enjoyed good health, and was the father of several children.[1]

Again, a French woman, aged 40 years, had been afflicted from her birth with a drought beyond example. She drank every day nearly two pails of water, and was eventually driven from home by the ill-treatment she received in consequence of this expensive habit. At 22 she married a cobbler. She drank four pailfuls a day, and became the mother of 11 children, drinking more when she was pregnant and least when out of health. When 40 years old she was examined by a scientific commission, and drank in the presence of its members 14 quarts of water within ten hours, and voided 10 quarts of nearly colorless urine.[2]

Dr. Dickinson reports the case of a farmer, 51 years old, in good general health, and equal to severe farm labor, who usually drank a quart of water at a time, and repeated the draught sixteen or eighteen times in the day and night, passing about as much urine as he drank water. In one night, under observation, he passed between 5 and 6 quarts of urine which was without sediment.[3]

I have now under my care a young man of 22 who has had diabetes insipidus for 10 years. He passes sometimes eight pints of water at a single sitting, and as much as 19 pints from 9 A. M. to 4 P. M.

The above cases show also the extreme duration in some instances, and the otherwise excellent health enjoyed by them. Very little serious disturbance seems to result as long as water is supplied to quench the resulting thirst. In extreme cases patients have even been known to drink their own urine. Dr. Dickinson had two cases which did so.

An extraordinary flow of *saliva* was met in one instance by

[1] This case was reported by M. Boissat, in the Recueil de Sedillot, Tome LXXX., p. 164.

[2] This case was reported by Mr. Maxwell to Dr. S. F. Simmons, who published it in Medical Facts and Observations, Vol. II., p. 73. It was last seen in 1791.

[3] Also from Medical Facts and Observations, Vol. II.

Kuelz[1] along with polyuria in a hysterical girl of 18 years, from whom as much as 525 cubic centimeters (17.72 ounces) were collected in twenty-four hours, while the quantity ranged during four months from 360 to the former amount. The quantity of urine passed during this time ranged from 6,000 to 7,800 centimeters (200 to 260 ounces). The increased flow of saliva is explained by the fact that in some of the experiments of Eckhard,[2] Loeb[3] and Gruetzner,[4] puncture of the medulla oblongata was followed by ptyalism.

Diagnosis.

The diagnosis of diabetes insipidus is very easy. The persistent thirst, polyuria, and absence of sugar from the urine are pathognomonic. It is simply necessary to be sure of these, to make the diagnosis positive. The only possible error is mistaking the polyuria of chronically contracted kidney of *interstitial nephritis* for that of diabetes insipidus. This I have known to occur from overlooking the presence of a very minute quantity of albumin. In addition, however, to the fact that a careful examination for albumin will discover it in the urine of contracted kidney, the quantity of urine is never inordinately large, nor is the thirst extreme; so that it would seem only necessary to mention the possibility of such an error in order to avoid it.

Hysterical polyuria may be mistaken for diabetes insipidus; but hysterical polyuria is usually of short duration or intermittent, and there are added the other symptoms of hysteria.

Prognosis.

It is extremely rare for a case of diabetes insipidus to terminate unfavorably unless there have been also present symptoms pointing to serious nervous lesion, that is, it is not fatal by the virulence of any symptoms peculiar to it. Patients generally die of intercurrent disease. On the other hand, recovery is almost as infrequent as

[1] Diabetes Mellitus and Insipidus, Marburg, 1875.
[2] Eckhard, Beiträge zur Anat. und Physiol., IV., p. 191.
[3] Loeb, Eckhard's Beiträge, V., p. 1; and Dissertation, Giessen, 1869.
[4] Gruetzner, Pflüger's Archiv, VII., p. 552.

death. According to Dr. Roberts, of 67 cases collected, 16 are reported as complete recoveries, and 14 ended fatally, nearly an equal proportion. The remaining 37 were still in progress. In cases of recovery or death, the duration is comparatively short. Of the 16 recoveries, in 9, the duration was less than a year; in 1, four years; in 2, eighteen and nineteen years, and in the remainder some years. Of the 14 fatal cases, 9 terminated in less than a year, 1 *in seven weeks,* 2 in two months; the other 5 survived for periods varying from eighteen months to twenty years. Of the 47 cases in progress only 5 had continued for a year or under. The remainder had continued for periods ranging from something over a year to fifty-nine years.

These results seem to be tolerably independent of treatment. It may be said, therefore, that, as a rule, cases that last more than a year are apt to continue, but ordinarily only require to be furnished with an abundance of water to keep them tolerably comfortable. According to Dr. Dickinson, cases from drunkenness are very apt to run a severe and rapid course, usually terminating fatally within a few months, and one terminated thus in two months.

The disease appears to me altogether less serious than diabetes mellitus. This I infer to be the opinion of Roberts and Dickinson. It certainly is that of Senator, who says "it is rather a troublesome than a dangerous complaint." But Trousseau and Da Costa are inclined to consider it more serious than diabetes mellitus.

Treatment.

The treatment of diabetes insipidus would naturally resolve itself into the treatment for the disease of which it is the symptom, than of the symptom itself; but as the former is very frequently undiscoverable it must consist mainly of efforts to diminish the secretion of urine, and with it the thirst. Syphilitic disease should be treated by the iodids, and the frequent instances of improvement while taking the iodid of potassium suggest strongly their syphilitic origin.

It is generally conceded that there should be no restriction in the drinking of water or other harmless fluids, for the diuresis is not so much caused by the large ingestion of water as the thirst is caused

by the diuresis. To cut off the supply of drink must therefore result in a draining of the tissues to their disadvantage, and a corresponding increase in the thirst. It should be mentioned, however, that one or two instances are reported wherein improvement seems to have resulted from such restriction. To relieve the diuresis is therefore to relieve the thirst. Rational remedies to this end would seem to be *astringents* and other drugs which tend to produce contraction of the capillaries and arterioles. But experience does not seem to sustain expectation in these respects, probably for the reason that the lesion which causes the capillary dilatation resides elsewhere than in the kidneys themselves. Da Costa[1] reports a case of recovery from the use of *ergot* in dram doses of the fluid extract three times daily, increased after ten days to two fluid-drams as often. I myself[2] have found the symptoms to subside under the use of gallic acid after I had failed with full doses of ergot. Reasoning from the reputed action of ergot on the arterioles of the nerve-centers as well as those of the kidney, we would expect it to be the more efficient remedy. So it has proved. Among the remedies to be cautiously used is *opium,* which has had some reputation, probably acting as in diabetes mellitus as a sedative to a deranged nervous mechanism.

Trousseau and Rayer claimed extraordinary results from the use of *valerian,* the former using the extract in enormous doses,—two and a half drams a day, which was increased to an ounce daily in one instance. Rayer used the powdered root and the valerianate of zinc; the former at first in 5-grain doses three times a day, increased until two drams daily were given; the latter in pills in gradually increasing doses until 20 grains a day were given.

Reasoning from the effect of intercurrent disease and powerful physical and nervous impressions, Roberts suggests a large *blister* at the nape of the neck or epigastrium, according as the associated symptoms and the anamnesis point to the nervous or digestive system, a suggestion which may be acted upon with advantage.

The *constant galvanic current* has been recommended, and in cases

[1] Da Costa, Diabetes Insipidus and its Treatment by Ergot, Transac. College of Physicians, Philadelphia, 3d ser., Vol. I., 1875, p. 139.

[2] Tyson, Case of Diabetes Insipidus Treated by Ergot and Gallic Acid, Transac. College of Phys., Philadelphia, 3d ser., Vol. II., 1876, p. 180.

of spinal lesion may be of advantage. Seidel and Kuelz have both used it with good results. The former applied one pole of a "strong battery" over the loins near the spine, and the other as deeply as possible over the hypochondrium, upon each side daily for five minutes. In eight days the urine fell from 5,957 c.c. to 4,600 c.c. per diem, in three weeks to 2,300 c.c., and the next month 1,904 c.c., while the weight of the body increased nine pounds.

Kuelz applied one pole of a battery of 30 to 40 cells as high as possible in the nape of the neck, and the other to the loins or epigastrium, the best results being apparently obtained with the positive pole to the nape of the neck, and the negative first to the loins for four minutes, and then to the pit of the stomach for four minutes.

Tonics and *nervines,* such as strychnia, iron, arsenic, salts of quinin, cod-liver oil, etc., are appropriately added to the treatment with a view to sustaining the strength of the patient, which is apt to give way. To these are to be added fresh air, sea air, exercise, and all possible favorable hygienic influences.

Senator says: "Since diabetes insipidus is rather a troublesome than a dangerous complaint, it is advisable in the lighter cases to avoid the administration of drugs, and to recommend the patients only a *careful attention to the skin,* warm clothing, warm baths, frictions, etc., in order to divert a portion of the stream of fluid from the kidneys to the skin." He also advises, in addition, in severer cases, to quench the thirst, not by excessive drinking, but by bits of ice and acidulous fluids. I have already expressed my preference for a treatment in which, under ordinary circumstances at least, the supply of water should be unlimited.

Among other remedies which have been recommended are, in addition to opium and its alkaloids, acetate of lead, tannin, digitalis, belladonna, bromid of potassium, iodid of potassium, iodid of mercury, camphor, jaborandi, lime-water, bitartrate of potassium, adrenal extract, antipyrin, antifebrin, etc. Of these probably none has been so serviceable as *iodid of potassium.* Numerous cases have been reported in which there has been a rapid and almost complete subsidence of symptoms under its use. It has been suggested that the cases thus relieved were due to syphilitic lesions. Bromid of potassium is another remedy whose use has been followed by

temporary good results, probably by its sedative action on nerve centers.

It has been stated that the French school of physicians represented by Dujardu Beaumetz have recommended antipyrin and antifebrin in diabetes mellitus, so these remedies have been advised for diabetes insipidus. Mastovsky[1] reported a case of nervous origin of six years' standing in which substantial improvement followed the use of these drugs.

Adrenal extract has been advised, but the results thus far obtained do not justify any conclusions as to its value.

[1] Medical and Surgical Reporter, Philadelphia, September 19, 1890.

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