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GOUT

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THE
NATURE AND TREATMENT
OF
GOUT.

THE NATURE AND TREATMENT OF GOUT.

By W. EBSTEIN, M.D.,

PROFESSOR OF MEDICINE AND DIRECTOR OF THE MEDICAL KLINIK IN THE UNIVERSITY OF GÖTTINGEN.

WITH ILLUSTRATIONS.

AUTHORISED TRANSLATION BY

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LONDON:

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1886.

TRANSLATOR'S PREFACE.

—o—

Professor Ebstein is so well known as a diligent and careful inquirer into the etiology and treatment of gout and some allied diseases that a detailed account of his method of research and of the results obtained cannot fail to be of interest to English readers. This work, which has already appeared in serial form in the pages of the *Medical Press and Circular*, is now respectfully presented in its more appropriate, and, in fact, its original form of a volume.

J. E. B.

Liverpool, May 1st, 1886.

AUTHOR'S PREFACE.

—o—

Since J. Henle, the fifty years' jubilee of whose doctorate affords me the wished-for opportunity of dedicating these studies to him as a small proof of my consideration and respect, in his "*rational pathology*" declared it to be impossible to give a proper physiological history of gout which permits the symptoms to appear as a *necessary consequence of the uric acid*, thirty-five years have now flown.

In the interval Garrod's work has been published, a work that lays a foundation in more relations than one, and many others have been added to this foundation by other inquirers; but a physiological history in Henle's sense is still wanting.

So long as we are not in a position to prove that the gouty symptoms are a *necessary consequence* of the uric acid, the importance of the uric acid theory in gout is but feebly determined.

The following pages have in the first place the aim of attempting *a physiological history of gout* in this sense *on which the clinical facts are to be founded.* It is then hoped that this work will also further and stimulate *medical practice*, which is, in fact, the ultimate aim of our science.

EBSTEIN.

Gottingen.

THE

NATURE AND TREATMENT OF GOUT.

CHAPTER I.

Views of the Older Physicians upon Gout: their Value in relation to Symptomatology and Ætiology—Humoral Pathology—The Discovery of Uric Acid in Gouty Concretions and in the Blood in Gout—The most Recent Views—Aims and Objects of the Present Investigations.

Gout, which is to the present day designated without any further addition as "arthritis," or, as it were, "inflammation of a joint," κατ' ἐξοχήν, belongs to the number of those morbid processes which from time immemorial have most actively aroused the interest of investigators. In the literature of the subject not only is the standpoint for the time of the complicated teaching regarding human tissue change up to a certain point reflected, but it permits a glance into the multifarious views which in the changes of time have been held concerning the nature of pathological processes in general. As all endeavours to thoroughly explore the nature of morbid processes are without significance, and as experience shows, expire in fruitless and joyless speculation, so long as they are not based on a firm foundation of physiolo-

gical investigation; so the inquiries into the subject of gout in general remained sterile until the period of the awakening of the scientific method in pathology generally. In the meantime some of that which has come down to us from the older observers in the matter of symptomatology and in relation to many etiological questions is not only of historical interest, but of abiding value. We possess from earlier times some still applicable descriptions of the disease. The men of former days were excellent observers, and in the narrow limits of the positive problems before them devoted special attention to this part of practical medicine; some, like Sydenham, were able to study the whole chain of gouty disorders in their own persons.

With regard to the antiquity of our knowledge concerning gout, our learned Orientalist Professor de Lagarde informs me that, from pre-Grecian time, nothing is known of the disease. In the writings of Hippocrates, however, we find some indications of the existence of gout (podagra) in South-East Europe. The earliest detailed and reliable information of this disease we find in the writings of the Roman physicians of the first and second centuries of the Christian era. The ancients in their classification of the gouty symptoms made use of the seat of the joint affection only. Although they certainly often enough mistook other and particularly rheumatic joint affections for gout, yet the inflammations of the foot, hand, knee, shoulder, and elbow joints described by them as podagra, chiragra, gonagra, omagra, cleisagra, pechyagra, undoubtedly include also true gout. Celsus (10 A.D.) was already employed in the treatment of gout. Seneca, the Stoic philosopher, in the first century after Christ, showed that gout was a consequence of luxurious living. He remarked that females, who at his time were not behind men in dissoluteness of living, were also sub-

ject to gout, from which at the time of Hippocrates they had remained free, and Aretæus of Cappadocia, undoubtedly the greatest physician between the times of Hippocrates and Galen, who was perhaps a contemporary of Seneca, in his model description of the symptoms and course of the disease, repeats the statement of Seneca as to the etiology of the disease, which he could simply confirm. Cælius Aurelianus, in the third century, pointed out the hereditary nature of gout. Although physicians had begun thus relatively early to note carefully the symptoms and etiological relations of the disease, we, in our study of the clinical history of it, usually only go back to Thomas Sydenham (1624-1689). His classical description—a kind of biography of the long-suffering great man, which was written when he had already suffered thirty-four years from the disease—leaves everything achieved before this time far behind. In regard to what he gives us concerning the nature and treatment of the disease, he was under no illusions. With the motto which I, following his example, have placed at the head of these pages, has he plainly pointed out the aims, and has not overstepped those which he marked out beforehand. He has left it to Time as the conductress of Truth to overcome the great difficulties and to explain thoroughly that which was hidden, as well as the method of treatment, in the light of the elements of the disease.

As regards the prime origin of the gouty process, the humoral pathological views have from their convenience in various forms from the earliest times been extensively held. Galen (130-200 A.D.) held that the gouty tophi were produced by the drying of morbidly-accumulated mucus, gall, and blood. How very much these views of morbid humours ruled over the minds of men is shown by the great number of references to them. Garrod mentions that the words which were introduced into

medical terminology by Radulfe at the close of the 13th century, the gout of the English, *goutte* in French, *gicht* in German, *gotta* in Italian, *gôta* in Spanish, correspond to each other, from which is shown the unanimity of the physicians of all nations in regard to their views of the origin of the disease, and that probably they owe their growth to the soil of humeral pathology. The conception was that a peculiar humour was separated from the blood and distilled over into the joint. But what this humour was still remained the great riddle, which was not solved even by the "tartarus" of Paracelsus (1493-1541). Nevertheless has this "tartarus," this "mucous tough essence full of earthy salts," which burns like hell-fire, whence also it has received its name, for a long period held sway over the minds of men. As the product of faulty digestion this tartarus was supposed amongst other things to cause gout, and to attack by special preference the cartilaginous articulations of bones, whence the moist material disappearing, only the earthy salts remained. The great Boerhave (1668-1738), who makes the statement that at his day the literature of gout had increased so enormously that thousands besides himself had already described the disease, adds to the already accepted causes of gout, luxurious living, and heredity, that of contagion. As establishing this view, he states that he has seen women of condition who were married to gouty husbands also become gouty. What wide acceptance this view met with at the time of Boerhave is shown by a little work of Momber, Stadtphysikus of Königslutter. He believes that he had seen a little dog which a gouty individual often had in bed with him become affected by the disease from the emanations that proceeded from its master. The doctrine of the contagiousness of gout later on still found a few followers, but it is now quite neglected. Moreover, Boerhave and his

disciples van Swieten (1700-1772) and de Haën (1704-1776) favoured the humoral mechanism in the etiology of gout. For de Haën was of opinion that the sharp gouty earth passed over into the blood and was driven into the lymphatic arteries, whence it could not pass into the veins nor into the sweat vessels, being in part too thick and in part too hard. At the same time, the cause of the gouty poison was sought in disturbance of digestion, and with the frequency with which it occurred in those who lived well this was the cause that lay nearest. *Indigestio viscerum merito pro origine proxima hujus morbi habetur*, says Van Swieten in his celebrated Commentaries. Raicus held that the gouty materies, which acted as a styptic in so far as it was not expelled, crept into the meseraic glands, and then became mixed with the blood. Gouty dyspepsia up to the most recent times has played an important *rôle* as the cause of gout with Cullen, Sutton, and Todd amongst others. From a clinical point of view G. Musgrave did good service by his studies on anomalous gout, of which he recognised no less than seventeen forms, the significance of which he summed up in the sentence: "People are ill with articular gout whilst they die of anomalous gout." In the meantime, however, no advance was made in knowledge of the real nature of the disease.

The discovery of uric acid by the Swedish chemist Scheele in 1776, and the proof by Wollaston in 1787, that the gouty concretions contained uric acid even did not place the significance of uric acid in gout in the true light. C. Scudamore, in his well-known and much-quoted work, in 1816 pointed out that gouty concretions were present so rarely and in so few individuals that no theory could possibly be built upon their presence, and that still less could the final cause of the disease be sought in them. Henle also, in the absence of actual material

bearing on the influence of uric acid on the occurrence of gout, looked upon the uric acid deposit (1847) as something accidental, whilst he sought the point of origin of gouty inflammation in an inner, perhaps central, nerve affection. Then it was a performance worthy of recognition when Garrod—whose work on gout appearing in 1860 will for all time remain as a foundation on which to build, and the full importance of which will be more and more recognised—in 1848 first brought forward proof that urate of soda was present in the blood of gouty individuals in abnormal quantity. From this time forward could we speak of an arthritis uritica. In the place of humours, atra bilis, tartarus, and of gouty earth, came uric acid, a distinctly characterised chemical compound, which could be made pure and could be experimented with. But this path of experiment has not been traversed, and the connecting link between uric acid and the gouty process thus remained unexplained. The uric acid dyscrasia could not explain the gouty symptoms. Not only did the pathogenesis of articular gout remain in darkness, but so did also the nature of so-called anomalous gout. The views of Garrod that (1) the primary fault lay in a diminished power on the part of the kidneys to excrete uric acid, whence arose a general accumulation of uric acid, which Gairdner and many others accepted; (2) that the alkalescence of the fluids was diminished in gout, showed themselves altogether insufficient to explain the gouty symptoms; for they were not able to explain what they should have done—viz., why at the very outset in certain typical spots in cartilage, often long before the kidneys themselves become affected, the urates, as acid urate of soda, are deposited in the form of crystals. One would have expected rather that as the stasis of uric acid must be general owing to the diminished power of the kidneys to excrete

it, that deposits of urates would have been demonstrated in many other localities, especially if the view held by Garrod and some other observers be correct, that the diminished alkalinity of the fluids favours the excretion of urates in the form of crystals.

As now physiology strove to explore thoroughly the place and mode of formation of uric acid, a new theory was added to almost every hypothesis bearing on the pathogenesis of gout. Thus Charcot laid the blame on an increased formation of uric acid in consequence of functional disturbance of the liver. Cantani held that the uric acid originated in the cartilages themselves, and looked upon the uric acid dyscrasia of gout as the result of a disturbance of nutrition of the articular cartilage, of the ligaments and tendons adjoining the bones. I shall have to return to these hypotheses in the course of this work. In view of this great number of open questions, the solution of which cannot be brought about by way of hypothesis, it seemed to me necessary to examine whether the many problems afforded by the subject could not be more nearly approached by way of experiment and of anatomical examination. The succeeding pages give account (1) of my investigations on typical affections of organs in arthritis uritica; (2) on gout in animals, and the attempts made by myself to produce deposits of urates in the animal body; and (3) on the action of uric acid and its compounds, as well as of some of the chemical bodies nearly allied to it on the animal system. As to the results of these investigations, I shall finally discuss the nature of human gout, its clinical symptoms, and the problem of its therapeutics.

CHAPTER II.

Pathological Anatomy of the Typical Tissue Affection in Arthritis Uritica of the Human Subject.

1. *Gouty Kidney.*—Views of Todd, Garrod, Virchow, Charcot, Cornil and Ranvier, Dickinson, and others concerning it.—My own researches, from which the result is obtained, that along with the crystalline deposit of urates amongst the numerous changes to which the kidney is subject in gout, necrosing and necrosed patches are the only ones that are typical.

2. *Gout of the Hyaline Cartilage of Joints.*—Views concerning the anatomical relations of gout of cartilage, in particular those of Garrod, Bramson, Charcot, Cornil and Ranvier, Rindfleisch.—My own researches and methods of research, amongst others the examination of fine sections of gouty cartilage in polarised light.—My investigations conducted me to the result that, just as in the kidney, necrosing and necrosed patches are present in gouty cartilage.

3. *Necrosed and Necrosing Patches in other Connective Tissue Substance.*—A, in fibro-cartilage; B, in tendons; C, in loose connective tissue—subcutaneous and intermuscular cellular tissue.

4. *Résumé, Conclusions, and Consequences of the foregoing Observations.*—The necrosing and necrosed patches are primary, and in fact—as will be shown later—are caused by the separation of (neutral) urate of soda in the tissues. The secretion of crystalline urates is secon-

dary. This only takes place after the tissue is completely destroyed, and thus in the patches that are necrosed. In typical gout patches, *i.e.*, tissue necrosis with deposits of crystalline urates, afterwards, as in all other dead tissues, deposition of lime salts may take place. In the neighbourhood of typical gout patches, which consist of necrosed tissues and the urates that are deposited in them, a reactionary inflammation developes, generally early, of greater or lesser extent.

I.—Gouty Kidney.

It is a fact generally known, that in arthritis uritica the kidneys very frequently undergo certain changes which to some extent are so characteristic that from them alone we are able to diagnose the disease.

Concerning these gouty changes, we know that they first consist in contraction of the organ, produced by inflammatory processes, and secondly—and this is typical and characteristic of gout—as in all organs, so also in the kidneys, in crystalline deposits which are composed of urates, and principally of acid urate of soda.

Whilst these interstitial inflammatory processes extend with tolerable uniformity through the whole kidney, it may be looked upon as the rule, so far as regards the above-mentioned uric acid deposits, that they will be mostly found in the papillary portion of the kidney. This rule is, however, no law, as Charcot has assumed it to be; for I know from my own observations, and a communication also exists from Litten, from which it is indubitably shown that these urates may be found in the cortical substance, although not in such quantities as in that of the medulla.

Amongst the numerous observers no unanimity at present prevails as to which of the tissues of which the

kidney is composed the separation of the urates takes place in. Todd expresses himself with uncertainty, and only conjectures that the streaks which are visible along the tubuli uriniferi, and which consist of urate of soda, fill up some of these tubules, and Garrod, who at first inclined to a similar opinion, was led by his own researches to the conception that the crystalline secretion in gouty kidney was often embedded in the interstitial—*i.e.* the fibrous—substance of the kidney. In one case of gout Virchow laid stress on the occurrence of urate of soda in the dilated tubules of the medullary substance, and a similar standpoint has been taken by Charcot and Cornil and Ranvier. All the observers give as the starting point of the crystalline deposits of urate the lumen of the tubules, and further that these are blocked up by them.

The two last-named investigators, in their "Manuel d'histologie pathologique," thus summarise their view: that the urates are met with either in the tubules of the pyramids, or in the straight ones of the cortex, and that the increasing deposits at once attack the neighbouring tissues, that the voluminous concretions surround a group of neighbouring tubules which are filled up with urates to the same extent as the surrounding tissues. Lancereaux similarly assumes that the deposits of urates lie in the tubules themselves, the lumen of which they fill up more or less in the form of rounded masses, or radial bundles. He adds that they gradually destroy the urinary tubules. E. Wagner has also quite recently stated that, like most of the before-mentioned observers, in contracted lead kidney he has always found the uric acid salts in the interior of the tubules. He remarks that they are apparently absent in the interstitial substance. In the cortex they appeared to him to lie in the destroyed glomeruli. Litten, in opposition to most of his predecessors, states that the uric acid salt in great crystalline

lumps not only fills the lumen of the tubules, but he makes the further assertion that it lies deposited in the dilated interstices of the interstitial substance in the form of acicular crystals and in tufts; he thus found it in the cortical substance, to some extent regularly grouped around the tubules. Finally, W. H. Dickinson, as a result of his own investigations, arrived at the conclusion that the deposition of urate of soda took place within the inter-tubular fibrous tissue of the kidney only. Dickinson says that this portion of the organ is thickened by a kind of chronic inflammation; it contracts and compresses the tubules, and thus arises granular kidney. He at the same time distinctly affirms that gouty kidney developes in this manner under all circumstances, whether the gout be the result of intemperance or of lead poisoning, or whether it arises from any other cause.

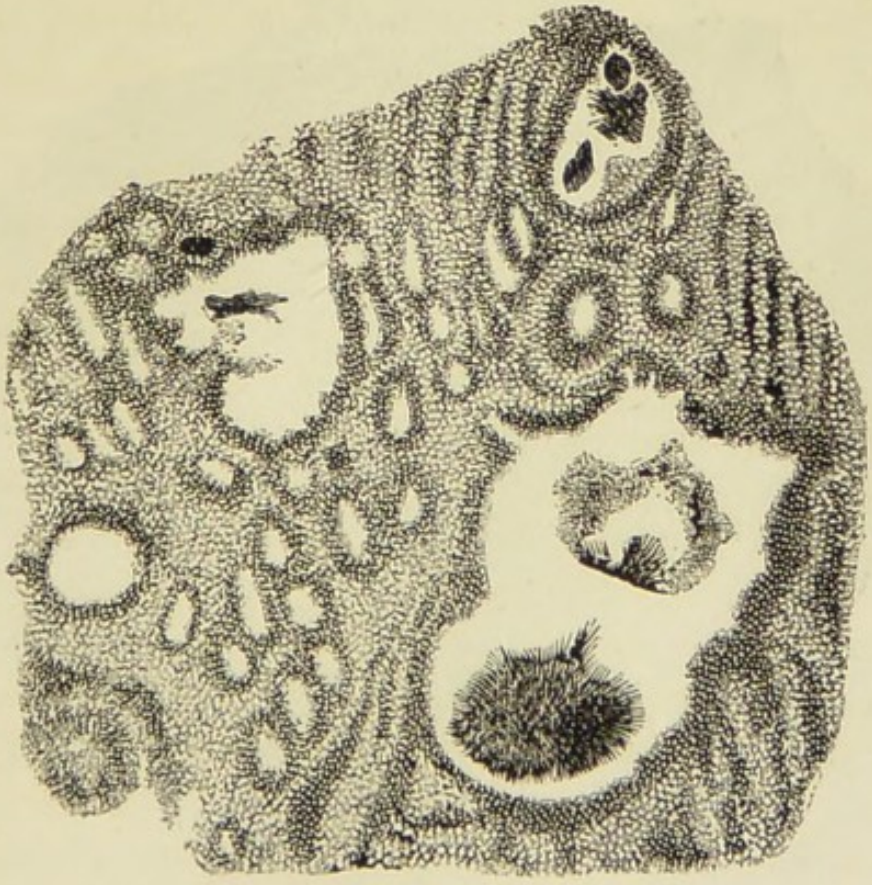

FIG. 1

Upon the basis of the examination of thoroughly typical gouty kidneys, from two cases of gout which had died in my wards, and of gouty kidneys with numerous crystalline deposits of urates that had undergone amyloid degeneration, which my colleague Herr Orth had handed over to me from the Pathologico-Anatomical Institute of this city, I arrived at the results which were made public by me in 1880 in the *Deutsche Archiv f. Klinische Medizin*, which, although agreeing in themselves, were an essential deviation from the views held up to that time. The figures employed to illustrate the text of my publication of that date are here reproduced in figs. 1, 2, and 3. I found in my microscopic investigation, both in the kidneys that had undergone amyloid degeneration as well as in those that did not show this degenerative process, that all the deposits of crystalline urate of soda were imbedded in a structureless and completely homogeneous substance.

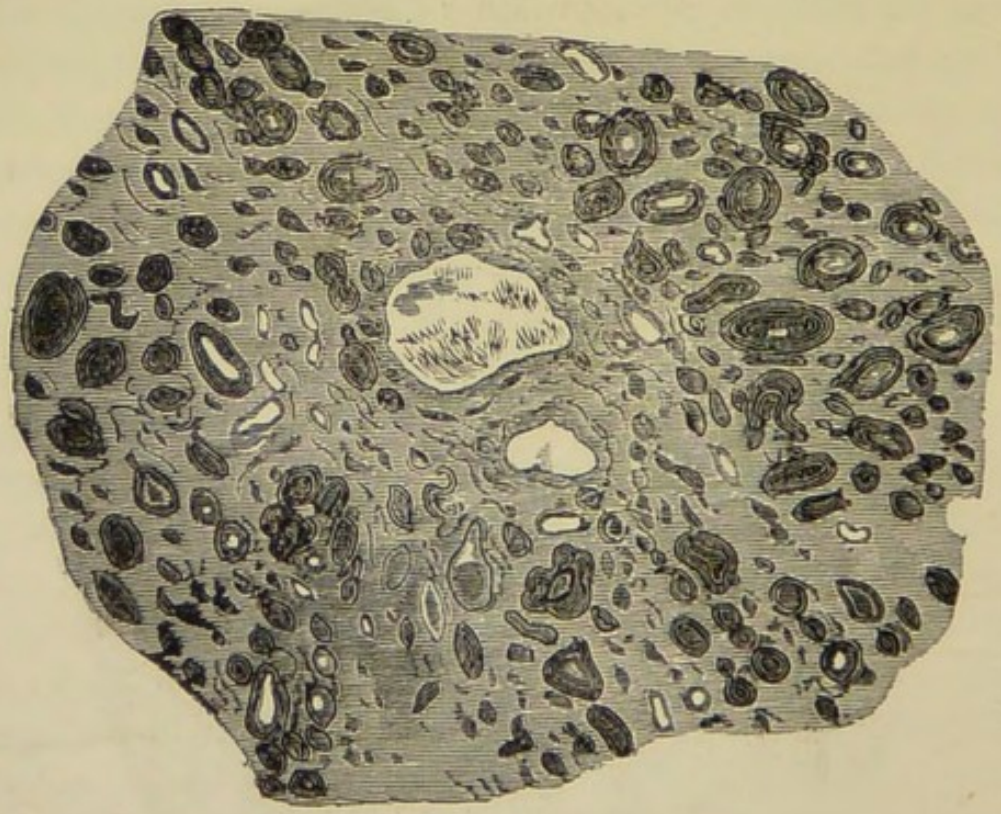

FIG. 2.

For the most part scarcely a cell or a nucleus could be demonstrated in it. Only in very isolated places did I succeed in finding forms which could be taken to be more or less well preserved cells or rows of cells. Here and there, by the aid of high powers, it could even be shown distinctly that the rows of cells were the remains of tubules that had undergone destructive processes. One could say of such places that here the structure had not completely vanished, that a patch of dying, necrosing, tissue had not become completely dead and necrosed. The latter patches consisting of a completely structureless and homogeneous mass, are doomed to a destruction which will gradually complete itself. In this manner hollow spaces are formed which finally in their extent correspond to the size of the patches.

FIG. 3.

That the process in question is a necrosis of kidney structure requires no elaborate proof. There is no other pathological process, besides the necrotic, in which, without a trace of suppuration, a melting down, a circumscribed destruction of kidney parenchyma takes place with disappearance of organic structure, and of the tissues

of which the kidney is composed. Besides this, another condition speaks in favour of the presence of necrotic processes. In the periphery of the patches which are made up of dead kidney tissue, whilst generally speaking there is a very sharp demarcation from the surrounding structure, there is, as is known, in various places a high degree of reactionary inflammation developed, which reaches sometimes a greater and sometimes a lesser extent. No micro-organisms can be demonstrated in these patches.

Most of these necrosed patches I found in the medullary substance of the kidney; they were met with also in the cortical portion, where in particular some glomeruli appeared to have necrosed in an exactly analogous manner. Microscopic examination showed in the Malpighian capsules belonging to the glomeruli affected, instead of the loops of vessels, a structureless, homogeneous mass. A great number of colourless crystalline needles were found in them exactly corresponding to the uric acid deposits in the papillary portion of the kidney, which were repeatedly arranged in groups in these places. In the case of more pronounced enlargement, thread-fibrin-like clots were seen in some places in the homogeneous mass that filled the Malpighian capsules, independent of the crystals.

Now as regards the amyloid degenerated gouty kidney, or more correctly, the gouty kidney that is associated with amyloid degeneration, it has happened to me that in the region of the necrosed patches and their immediate neighbourhood the amyloid reaction did not take place on application of the usual reagents, although this process had reached such a degree of intensity in the remainder of the kidney parenchyma, that independently of the vessels, it had attacked the tunica propria of the urinary tubules and the structure immediately surrounding them.

Neither is there found in any instance at the necrosed patches with amyloid degeneration any small-celled infiltration of the surrounding parts, but simply a very free increase of the interstitial tissue associated with sclerotic thickening.

In the whole of my gouty kidneys concerning which anything had been said up to this time, the necrosed patches were of greater extent than the crystalline deposits within them, and in some of these patches only a few, sometimes practically not any, crystals of urates were to be seen.

I shall have opportunity later on to return to the conclusions which may be drawn from this fact. I will here only point out that the explanation might lie in a not unlikely, but easily-avoided error, in preparation, namely, in examining the object after the crystalline deposits had altogether or in part become dissolved. This happens, for example, very readily if the microscopic sections are kept for any length of time in fluids which dissolve the uric acid compound. After even a short time a marked diminution is observed in the crystalline mass, whilst on the parts before encrusted with the crystalline uratic deposit, instead of the normal structure, necrosed tissue comes into view. Where it is required, therefore, to determine the size o the patches of crystalline deposit as compared with that of the necrosed spots, certain precautions must not be omitted. In the first place the gouty patches must be taken from fresh organs not hardened, and examined in glycerine. For investigation of the further details, in order that the hardening may be successful, the organ, properly cut up, must be at once placed in absolute alcohol. The preparations thus obtained must be examined in glycerine—a fluid which is not adapted for preserving them long—or in Canada balsam, after preliminary treatment with

absolute alcohol and oil of cloves or oil of bergamot, the latter being what I now exclusively use. Finally, in order that the deposits may still be retained in their integrity, only such colouring tinctures should be used as shall not in themselves, nor by the length of time required for successful colouring, act as solvents on the uric acid compounds. To these belong the aniline dyes, which colour very rapidly. In discussing gout of cartilage, I shall have the opportunity, later on, of again returning to the methods of colouring employed by me.

Since this time I have only been able by my further investigation to confirm the observation here made, and already laid down in my earlier work as to gouty deposits in the kidneys. These were made on two further cases of gout. For the anatomical material of one I am indebted to Herr Weigert, of Leipsic. This case, which also afforded the material for my investigation on gout of cartilage, which will be discussed later on, was that of a man, æt. 52, who ten years before had had three attacks of lead colic. Death took place from uræmia. The kidneys contained indeed but little uric acid deposit, but on the other hand the joints, sheaths of tendons, the skin, &c., were much affected. (Letter from Weigert, May 6. 1881.)

The second case was that of a young servant-man, æt. 24, who was variously treated in my wards (from March 26 to April 7th, 1880, and from Nov. 21st of the same year to his death on May 5th, 1881) for chronic nephritis, with consequent acute hæmorrhagic nephritis, cardiac hypertrophy, and the symptoms of acute and chronic uræmia. The patient died in an attack of uræmic convulsions. He had previously been repeatedly dropsical. The post-mortem examination made by Herr Orth revealed, in addition to hypertrophy and dilatation of the left heart, general fatty degeneration of the myocardium, myocarditis fibrosa of the left ventricle, red induration of the lungs, œdema of

the cervical organs, chronic pericarditis, enteritis follicularis, swelling of the mesenteric lymph glands and nephritis uritica. Both kidneys showed an irregular nodulated surface, on removing the capsule. On section the cortical substance appeared to be somewhat diminished. The small quantity of medullary substances, in comparison with the large amount of fat of the hilum was very remarkable. In both kidneys were observed here and there chalk-like specks of urate of soda. The consistence of the kidney was firm. No gouty changes were found in the joints.

In both these cases of gouty kidney, necrosed patches strewn with a crystalline deposit of urate were found, in the neighbourhood of which reactive inflammation had been set up. These differed, however, from the cases previously examined and described by me, so far that in both cases the necroid patches were so thickly strewn with deposits of urates in crystalline form that at first no trace of necrosed tissue was to be seen. When the urates were dissolved, however, where for example, the preparations were placed for some time in a very weak solution of soda, or a solution of carbonate of lithia, or simply in warm water, the necrosed spots stood out in full characteristic clearness and beauty. The reader finds such a necrosed gouty spot of the kidney figured in Fig. 4, in which the crystalline deposits of urates are still visible, whilst Fig. 5 again gives a drawing of the same preparation after solution of the urates. The conditions may have been exactly similar in the case figured by W. H. Dickinson in order to show the crystalline deposits of urate of soda which were embedded in the inter-tubular fibrous structure of the medullary pyramids in a case of advanced gouty kidney. In such case, so long as the incrustation with urates remains, nothing can be seen of the necrosed tissue covered by it.

The question is naturally not materially altered thereby. The only outcome is that in cases of necrosed spots of gouty kidney two forms must be distinguished, in one of which the necrosed spots are completely full of crystalline

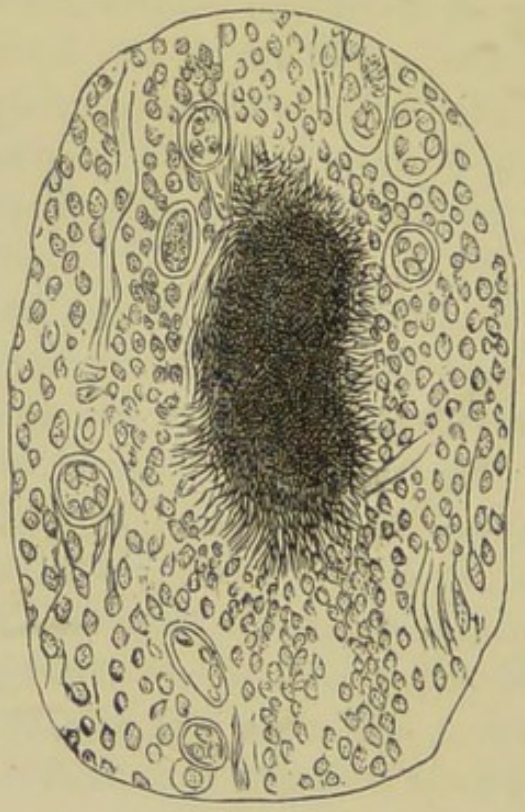

Fig. 4

deposit of urates, the second only partially so. Necrosed gout spots are also met with without deposits of urates in cases in which premature solution of the deposits by faulty manipulation may be excluded. In the meantime, however, these cases, as far as my experience at present reaches, belong to those outer-lying portions of necrosed patches with only partial, centrally lying deposits. By a succession of sections through the whole thickness of such necrotic patches, I have arrived at the views given above, in accordance with which I cannot at present accept existence of necrotic gouty patches in the kidneys, without any deposit of urates. The existence of these two forms

of necrotic gouty patches, with total and partial crystalline deposit, affords an easily comprehended explanation of the fact that after solution of the uratic deposit, such marked and characteristic spots in gouty kidneys have to my knowledge been so completely overlooked.

Apparently up to the present, only patches completely filled with crystalline deposits of urate have been examined, one of which is delineated in Fig. 3. The objection may perhaps here be raised, that the gouty patches of the kidneys figured in 3 and 4, are dilated tubules filled with an amorphous structureless mass, in which are some deposits of crystals of urates. Such an objection can be met on good grounds. I have often put the question to myself, have considered it, and always answered it in the negative. For in the first place, I have never been able to trace the continuity of one of these patches with a urinary tubule, and secondly, I have never been able to demonstrate in them any epithelial covering nor basement membrane, such as are present in the tubules. At least, one of these conditions must be fulfilled in order to support the opinion, that the patches are dilated urinary tubules. I have on the contrary found, as I have already remarked, that in the necrosed patches of gouty kidney the tubules do not dilate, but that they die away and disappear, and that only occasionally in certain stages of the process do indubitable remains exist in process of destruction, and that dilated urinary tubules cannot be demonstrated.

I do not, however, hold the formation of necrosed patches and the crystalline deposit of urates within them to be a *conditio sine qua non* of the gouty process. We shall in the course of our exposition, independent of the necrosed patches described by me, meet with the following conditions in gout :—

1. The kidneys may be found perfectly healthy in

cases of gout, notwithstanding advanced gouty changes in joints.

2. The kidneys may be affected in any way, and with special frequency with chronic interstitial inflammation with contraction of the organ without any deposit of urates.

3. We meet in gout with chronic interstitial nephritis with crystallised urates in the urinary tubules.

4. Necrosed patches, with crystallised uratic deposits, may be associated with crystallised urates in the urinary tubules. I myself have seen the combination.

The presence of crystalline urates in the urinary tubules is not in any way typical of gout. It is, *à priori*, evident that under certain conditions the acids excreted by the kidneys and their compounds may remain blocked up in the urinary tubules. That this is true, both older and more recent observations prove. As early as 1846 Virchow drew attention, not in connection with gout, to the presence in the kidneys of adults of urate of soda in sand-like heaped-up masses, which appeared in beautiful, generally rather long rhombic plates, or rather in columns when it was occasionally observed in the usual dilated parts of the urinary tubules. Garrod then made the further statement, that in the kidneys of three individuals in whose joints no gouty deposits were visible, he had discovered crystals partly composed of urate of soda and partly of uric acid. For the purpose of distinguishing these from the crystalline deposits of urates present in gout, Garrod on the occasion brings forward the following points:—1. They were present in these three cases within the urinary tubules, whilst in gout they are often interstitial, *i.e.*, they are present in the fibrous tissues of the kidney, as if the true gouty inflammation had advanced into the parenchyma of the organ itself; and 2. He observed that the crystals observed within the

urinary tubules were much larger than those met with in gout. We thus see that these differences did not escape the perspicacity of Garrod, although as he himself says, he was not able at the time to give a decided explanation of the question.

The only typical condition in gout I take to be the above described necrosed patches with their crystalline urates and the reactive inflammation that is established in their vicinity. I have never failed to find them in the gouty kidneys which I have up to the present examined. I designate them as typical for the reason that we—of which we shall now speak—regularly find the same necrosed patches also in the pure connective tissue structures when they are the subject of gouty disease.

II.—Gout of Hyaline Articular Cartilage.

How gouty articular cartilage looks is so well known that I am not in a position to say anything new on the subject, and for this reason the reader is referred to the well-known manuals of pathological anatomy. The microscopical appearances are so characteristic that the diagnosis of arthritis uritica by them alone presents no difficulty. But as in the case of gouty kidney, so also in gouty cartilage. No sort of unanimity prevails as to the results of microscopic investigations amongst those observers who have gone more deeply into the question. Apparently insignificant are the prevailing changes, and at the first glance interesting simply as a matter of histological detail; and yet a thorough comprehension of them is of fundamental importance for a correct conception of the nature of the gouty process, which, as is known, has such marked preference for cartilage.

The points of difference regarding which the views of the various observers take different directions may

be formulated in the following questions:—1. In what part of the cartilage, in the inter-cellular substance or in the cellular elements, does crystallisation of the uric acid compounds first takes place, or does it take place in both at the same time? And 2. What influence do the urates deposited in the cartilage exercise upon the cartilaginous tissue?

Let us first glance at the first question.

Whilst some observers, as Birch-Hirschfeld, are of opinion that the deposition of crystals in gouty cartilage may take place quite irregularly, other investigator, as Bramson, Rokitansky, and August Forster, affirm that the urates are deposited in the inter-cellular substance of the cartilage. Bramson found on examining with the microscope fine sections taken from the cartilage of a gouty metacarpo-phalangeal articulation, that the cartilage cells showed no deviation from the normal, but that in the place of the normal connective tissue a mass was present which resembled that found in gouty tendons, and consisting of a very consistent, thick white, groat-like mass, firmly attached to the tissue, and only to be removed by picking it out. Microscopic examination revealed a perfectly amorphous mass, with here and there scattered acicular crystals. Bramson succeeded in treating a fine section through the gouty cartilage in such a manner upon the object glass by means of nitrate of potash and heat that it still served for microscopical examination. He discovered that the purple colouring had its seat in the basement substance, which was the seat of white infiltration. Some well-preserved cartilaginous corpuscles were of normal colour, and were a marked contrast to the surrounding parts. From this Bramson concluded that the gouty cartilage examined by him contained uric acid in like manner as the infiltrated parts of tendons had been shown by him to contain it.

A third view of the subject is to the effect that the cartilage cells themselves, if not exclusively, are still primarily and mainly to be looked upon as the seat of deposit of the uric acid crystals. In the first rank stands Garrod. He has it that if these sections of cartilage containing urates be examined, after being digested with water, whereby the crystalline excretion has been gradually dissolved, they look at first as if the deposit were formed of small crystals separated from each other by clear interspaces, and after further action of the water the mass appears to include the cartilage cells. Charcot states that by the aid of acetic acid, whereby rhomboidal crystals of uric acid are formed out of the crystals of acid urate of soda, the presence of uric acid deposits in the interior of the cartilage cells can be proved. Cornil and Ranvier, who have described the changes produced by gout in joints with particular accuracy and exhaustiveness, distinguish two stages in gouty affections of joints. In the first period according to their description a simple nutritive disturbance is set up in the cartilage which succumbs to the gouty process. They understand by this nutritive disturbance, the commencing infiltration of the cartilage, originating in the cells of the cartilage with the urate of soda which usually crystallises in acicular crystals. This primary appearance of the uric acid infiltration in the cells proves to them that these play an active part in the process. It appears very striking and noteworthy to these observers that these crystals develope in such a solid substance as that of the cartilage, and especially, also that these crystals penetrate the various elements of the cartilage, just as they would a homogeneous liquid. They found that it may happen, if the crystalline deposits are dissolved, that the basement substance of the cartilage is thoroughly freed from urates, whilst the

cells are still occupied by them. Rindfleisch, in his well-known "Lehrbuch der pathologischen Gewebellehre," has declared his complete agreement with these observers, as far as regards this fact communicated by them, and has borrowed the figure given by them as showing the condition of the hyaline articular cartilage in gout. Rindfleisch designates the cartilage cells as the constant centre of the stellate groups of crystals with which the cartilage is strewn. Budd has also expressed himself in a similar, if somewhat reserved, manner when he says, "Cartilage cells (in many instances at least) the original centres within and around which the crystallisation occurs." Rindfleisch in the meantime, however, does not, as do Cornil and Ranvier, assume any active participation on the part of the cartilage cells in the deposition of the uric acid. According to his view the separation takes place in the cavities of the cartilage first, for the reason that there is room for it there first; a hypothesis that will not harmonise with the view, almost everywhere accepted by histologists, that the normal cartilage cells completely fill up the cartilage cavities.

Now that we have brought forward the very various views advocated by different observers as to the localisation of the crystalline urates in hyaline cartilage in gout, we come to the consideration of the second point. This is, as has already been mentioned, the influence that deposition of uric acid salts has upon cartilaginous structure.

With regard to this also the opinions of different observers are very far apart.

Garrod does not consider the influence to be one of much importance, for he states that after digestion of the gouty cartilage in warm water and the consequent solution of the uric acid salts, the cartilage appears to be almost healthy. One thing, however, struck him, viz., that the surface appeared to be somewhat uneven, and

the cartilage substance a little spongy after drying. Charcot expresses the conviction that the fundamental change in gouty cartilage is an infiltration with urates; independent of this there exists in gout no constant change of the cartilage; there is neither segmentation of the basement substance, nor any luxurious growth of cells. On treatment with vinegar he saw the encrusted cells up to a small central nucleus of urate come out clearly and distinctly. Cornil and Ranvier also, as regards the first period of gouty disease of cartilage, decide on this question in a precisely similar manner.

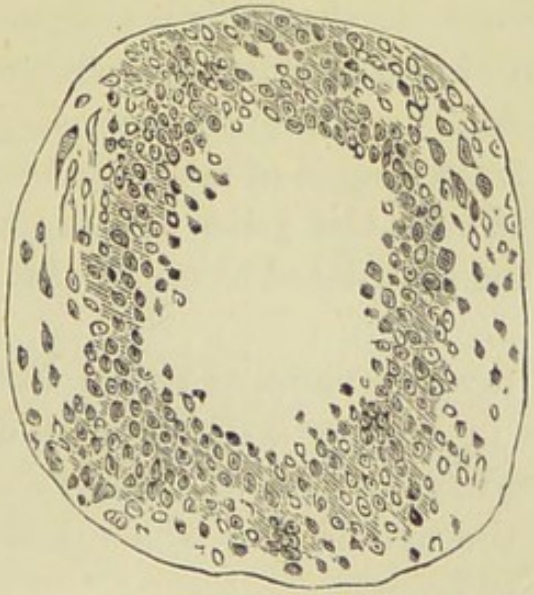

Fig. 5.

On the other hand, however, these two observers lay stress on the irritating action of urate of soda in the second period of gouty disease of cartilage, which, according to their view, is not sharply marked off from the first, inasmuch as inflammatory symptoms develope in the cartilage. This is recognisable on inspection with the naked eye, as the cartilaginous tissue beneath the zone infiltrated with urates is translucent and assumes

an unusual bluish colour. Microscopic examination gave to these observers substantially the following results: they found in the blue-looking parts of the cartilage luxuriant cell growth in the form of pouches, and between them segmentation of the basal substance.

Whilst these changes below the layer of cartilage encrusted with urates are becoming completed, this encrusted layer, as Cornil and Ranvier affirm, goes on progressively, and in consequence of mechanical wear, to destruction. This mechanical wear, according to this view, comes into play for the reason that the layer of cartilage through the incrustation loses its elasticity by virtue of which it opposes resistance to the joint. Cornil and Ranvier conclude that this is the principal factor in the origination of this erosion of cartilage from the fact that these erosions do not form in those joints in which there is but a small degree of movement—for example, in the tarsal joint or in the joint of the cuneiform bones, where in fact the postulated cause of their origination is wanting.

As regards my own views as to the formation of the gouty process in hyaline articular cartilage, they were arrived at from examination of a typical gouty articular cartilage, for the material of which I am indebted to Herr Weigert of Leipsic.

The cartilage at my disposal from the concave upper surface of the tibia was a remarkable paradigm of gouty cartilage. The free surface of it was sown with abundant more extensive and smaller patches, down to such as were only of punctiform extent; the mass where they formed gave even in small traces a well-marked murexide reaction.

Before I proceed to give the results of the microscopic examination of fine sections prepared from this gouty cartilage, I will say a few words on the methods of preparation.

The cartilage was preserved in absolute alcohol, in order to preserve the deposits of urates in their integrity. Both coloured and uncoloured preparations were made use of in part with the deposit of urates retained, and in part, after solution of it. The preparations examined were preserved partly in a 1 per cent. saline solution, partly in glycerine, and partly in Canada balsam. Besides examining them in ordinary light, they were also examined in polarised light, of which we shall speak later on.

The colouring materials employed were—iodide of potassium solution, hæmatoxylin, Grenacher's alum carmine, Weigert's picro-carmine, and aniline dyes, viz., Bismarck brown ♯9^{b} and gentian violet (both according to Weigert's directions), fuchsin, and methyl violet. The urates were dissolved in the manner stated in the description of gouty kidney on p. 19; the precautions to be taken in order to preserve the crystalline deposits are also given

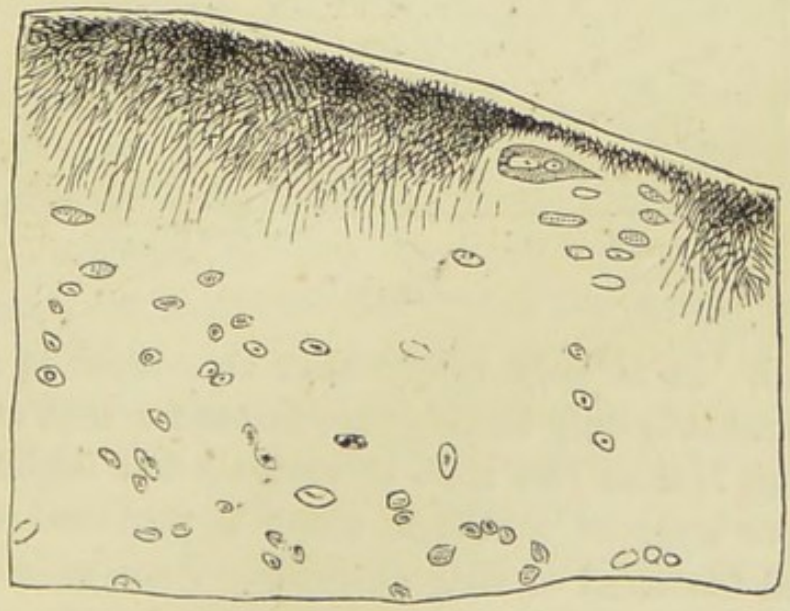

Fig. 6.

at the same place. As was shown even by inspection with the naked eye, the articular cartilage examined by me

displayed the crystalline urates in very varying degrees of richness of deposition in the different parts of the cartilage.

In microscopic preparations of those places where the crystalline uratic deposits were slight or only moderately free, of which Figs. 6 and 7 are representations, it was at once noticed that immediately under the free surface of the cartilage was a layer in which crystals of urates were not present (Fig. 6 and Fig. 7). This layer is in general very narrow, and here and there even with the low power made use of a delicate fibrous texture may be

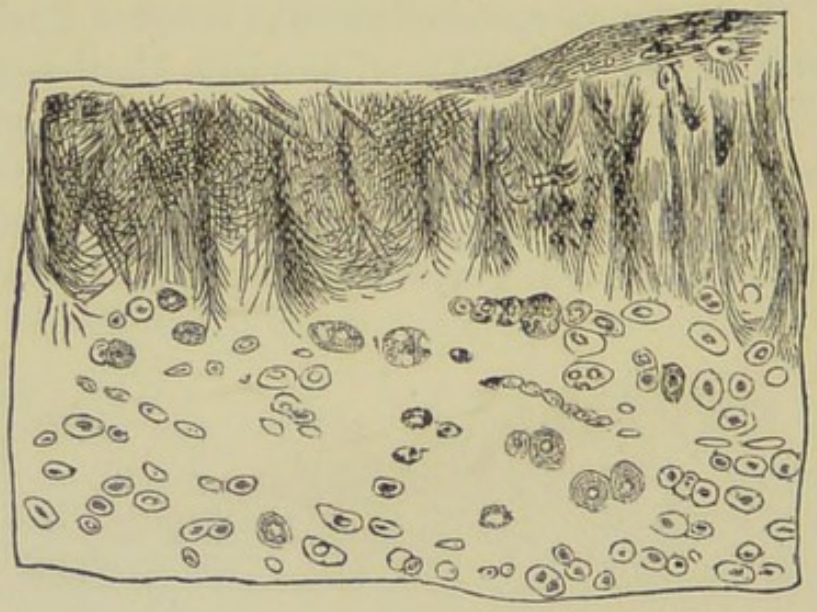

Fig. 7.

observed. It is only rarely that this layer is a little wider, and it is only in very rare instances that one sees, as in Fig. 7, that the zone of crystals first begins below the upper layer of cartilage, which is provided with an elliptical flattened cartilage capsule. I am, moreover, in possession of many preparations in which with complete absence of crystalline deposits of urates in the upper layers of the cartilage they are simply confined to the middle portions of it. It must be described as a regular

occurrence that the deposits of urates are richest and thickest in the upper layers of the cartilage. This condition is shown in Fig. 6 and Fig. 7. They usually, even in those places in which the deposits are of wide extent, only reach to a certain depth in the cartilage without

Fig. 8.

penetrating it as is seen in Fig. 8. That, as Garrod states, they do not occupy more than two-thirds of the cartilage must be designated as in most cases strictly accurate. Exceptions are, however, met with. Cornil and Ranvier report that frequently the whole cartilage of the epiphysis is infiltrated with urates.

That these deposits of urates met with in gout of cartilage are crystalline and consist of needles is known. These needles are in part straight, and in part, as Cornil and Ranvier have already noted, curved, and generally to one side, but occasionally slightly S-shaped (Fig. 7). These observers, and this can be confirmed, have seen needles of a length of from 0·05 to 0·06 mm.

Amongst my measurements I have repeatedly noted needles 0·072 m. in length. The needles frequently form opaque-looking masses or tufts at one or both poles, rounded or oval, formed by the crossing of crystalline needles (Fig. 7). That these correspond to cartilage cells is by no means correct. Occasionally these acicular urates run confusedly through each other, or they arrange themselves in a radiating manner round such a dark nucleus. They very often, however, run vertically, at first parallel, later on to diverge from each other like a paintbrush (Fig. 7). This latter arrangement suggests the thought whether these deposits do not follow the cartilage fibrillæ or their cementing substance. As is known, Tillmanns has succeeded in demonstrating that the homogeneous-looking basement substance of the hyaline cartilage is made up of fibres (cartilage fibrillæ) very firmly bound together by a luting or cement. These very delicate fibrillæ, the cementing substance of which can be dissolved by various reagents, for example, by permanganate of potash in moderately concentrated solutions, by 10 per cent. solutions of common salt, by concentrated solutions of picric acid, &c., lie side by side regularly, if they do not run parallel to each other in all the layers. These formations, which we get occasionally after solution of the urates, have led me to think of the relation of the deposits of urates to the fibrillæ of cartilage. I shall return to these preparations.

Independently of the acicular crystals hitherto described we see in gouty cartilage, and especially, but by no means exclusively in those spots where the crystals lie thick, in the midst of them, small roundish punctiform deposits of urates which, as Garrod has already pointed out, behave like the acicular crystals of urates in the presence of polarised light. Such massy accumulations

of crystals where needles and punctiform deposits lie so thickly together that they can scarcely be disentangled, and which appear on microscopic examination of even fine sections in a falling light as brown or black masses, are met with independently of the above-mentioned circumscribed patches which are illustrated in Fig. 7*b*, diffusely extending over large tracts of the gouty cartilage. The reader will find the delineation of such a section of cartilage in Fig. 8. The disposition of urates is here so abundant that in many places one has great difficulty in distinguishing the individual crystals. In such preparations one is in a position to satisfy oneself that the crystalline deposits do not range above the free surface of the cartilage, although the margin of the tissue (*a* and *a* 1) not infiltrated with crystals figured in 6 and 7 is not everywhere visible.

Now that the mode of deposition and the extent of these deposits of urates in gouty cartilage have been substantially discussed, if we seek to determine their relation to the tissue of the cartilage, in which their relation to the cartilage cells and to the basement substance must be kept in mind, it is at once clear that these relationships can only be studied in a satisfactory manner after the uratic crystals that cover the cartilage tissue have been dissolved. These relations are most beautifully seen in preparations that have been treated with one of the above-mentioned colouring liquids. Colouring is, however, not absolutely necessary to a right understanding of the relationship ; for not only the essential condition, but also a series of more minute details can be recognised in uncoloured preparations. In order to learn the relationship in which the crystalline deposits of urates stand to the tissue of the cartilage, and what influence they exercise upon it, we will first examine a preparation in which the changes are already

so far advanced that extensive necrosed patches have been formed. Such a one is portrayed in Fig. 9. It is taken from the same series of sections as that shown in Fig. 8; the urates are almost completely dissolved out by several hours' digestion in warm water. It has afterwards been coloured in a concentrated solution of Bismarck brown and mounted in Canada balsam.

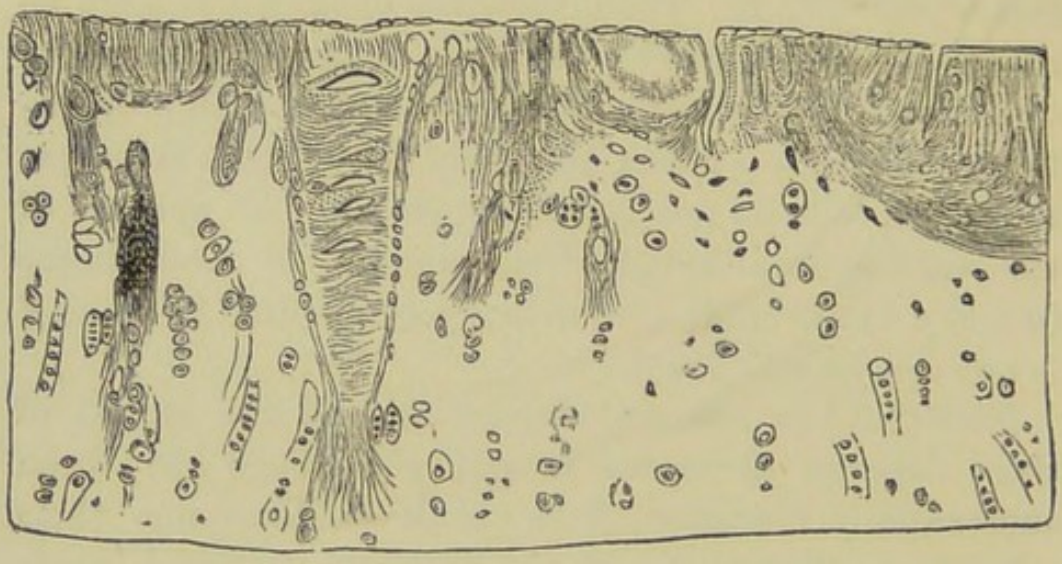

Fig. 9.

The reader sees first in the plate (Fig. 9) on the free surface of the cartilage a very narrow border layer (1) which is covered above by a non-continuous layer of flat endothelium-like cells. In a series of preparations, in consequence of the process of preparation, this uppermost layer had become raised up from the layer below to a greater or lesser extent. Bordering on to this limiting layer lies a pale yellow-coloured zone with a contour mound in the main, but becoming irregular below (2), which is marked off from the surrounding parts by a mostly sharp or at least tolerably sharp line of demarcation. In this pale yellow-coloured zone lay the crystalline deposits of urates before they were almost

completely dissolved out by digestion in warm water. We find residua of them, consisting for the greater part of a punctiform mass in a few places only, which on examination in polarised light prove to be doubly refracting, and which are thus to be pronounced crystalline formations. In this pale yellow-coloured zone the texture of the normal hyaline cartilage is no longer visible; in place of it a textureless mass is seen. Some few roundish rings, 0·009 to 0·012 mm. in diameter, *β*, bring to mind the capsule of the cartilage. I remark here that for the sake of accuracy in the individual details in the case of drawings from low powers, in addition to a large number of precisely similar preparations, I have controlled them with higher powers (Winkel's System, 9 and 10).

Of the elliptic very flat lenticular cartilage corpuscle that lies in the upper layers of cartilage parallel to the surface of the joint no trace is present. As one can easily convince oneself in the figure the pale-yellow tinged zone extends in many places not only into the layer of cartilage that is provided with round cartilage cells, but also in many, more or less deeply into the thicker third layer, in which the cartilage cells have a direction horizontal to the surface, and which is provided with long capsules. In these cell-less regions of cartilage that have been infiltrated with crystalline urates, independent of the destruction of the cartilage corpuscles, the basement substance of the cartilage shows a change of character, becoming fibrous, partly slightly granular, and partly completely homogeneous. The fibres do not by any means run all in one and the same direction, but partly horizontally, partly vertically, and partly obliquely. The demarcation of this textureless zone, in which thus nothing of normal cartilaginous substance is to be seen, and which, when coloured with

Bismarck brown, is distinguished by much clearer tones, is completed, as already remarked, for the most part quite, or almost quite, abruptly. In some places, however, the parts of the cartilage that have lost the texture are less sharply marked off from the surroundings. In those places where the demarcation is complete the basement substance at once shows as dark a colouration as the adjoining normally coloured basement substance Where the demarcation is not quite complete the basement substance is distinguished in the usually rather narrow transition zone by a colouration that is clearer in comparison with the surrounding parts. But there are also places where, as already remarked, no demarcation has taken place, but where a very gradual transition exists between the tissue that has lost its texture and the normal basement substance. When, however, the changes in the basement substance of the cartilage described are complete and the cellular elements have quite disappeared, so that the cartilage structure can no longer be recognised as such, there is at least a certain tendency to destruction. For even if the cartilage structure in this completely changed condition on the whole preserves its coherence, yet one sees in one section of the diseased structure numerous lacunæ. and here and there a breaking up or crumbling of tissue. It has already been remarked that the upper layer is separated from the lower over considerable tracts in these parts. How these necrosed cartilage patches—they must be designated as such—have in general still preserved their coherence is explained by the want of vascularity and the firm texture of cartilage. The breaking down of a tissue after it has been gangrenous depends simply and totally on its contained blood, and the firmness of its texture. We know, indeed, that a necrosed bone, contrary to what takes

place in one that is carious, preserves its smoothness, its coherence, and its usual microscopic texture.

Now when the demarcation of necrosed cartilage tissue from the surrounding parts is complete, the cartilage tissue that lies beyond the textureless patch shows here and there a slightly fibrous character, and follows the lower limiting line of the degenerated part. When the demarcation is more gradual, however, one often finds at the lower end of the pouch-shaped processes a pencil-shaped softening of the basement substance. This takes place for the reason that the patches undergoing degeneration consist of innumerable delicate diverging fibrillæ rejuvenating downwards, between which lies some apparently completely unchanged basement substance, and which is distinguished from the other by its brighter colouration. These pouch-shaped processes have mostly a straight lined border; far more rarely they show in places ampulla-like dilatations (4). One can convince oneself that these pouch-shaped processes have contained crystalline urates by the remains that are here and there demonstrable in them. Nuclei are nowhere to be seen in the walls of the processes.
regards the cartilage cells, I have already mentioned that, in the completely textureless parts nothing more of them is to be seen, and that in some places objects are simply to be observed which at best can be pointed out as residua of cartilage capsule. But in other parts of the cartilage also in which the changes are much less advanced, and which I have designated as necrosing, there are found, and indeed in direct proportion to the intensity of the pathological process, very noteworthy changes in the cartilage tissue, for the examination of which staining and examination with polarised light revealed the most valuable disclosures. These changes permit of being so far grouped together that the cartilage

cells with their nuclei are indeed still present, but the latter are no longer colourable, or that the nuclei of the cartilage cells are as a rule no longer visible, and only the cell contours can be made out, and even these indistinctly, like shadows, or, finally, that in the neighbourhood of the crystalline deposits, on going further off, no cartilage cells are any longer visible, but only a basement substance, generally much less coloured than the surrounding parts. In order to illustrate the changes in the necrosing patches as clearly and distinctly as possible, I have had figures accurately prepared, which represent the changes of gouty cartilage in a much less advanced stage than are depicted in Fig. 9 after solution of the uric acid compounds. I refer to Fig. 10 and 11.

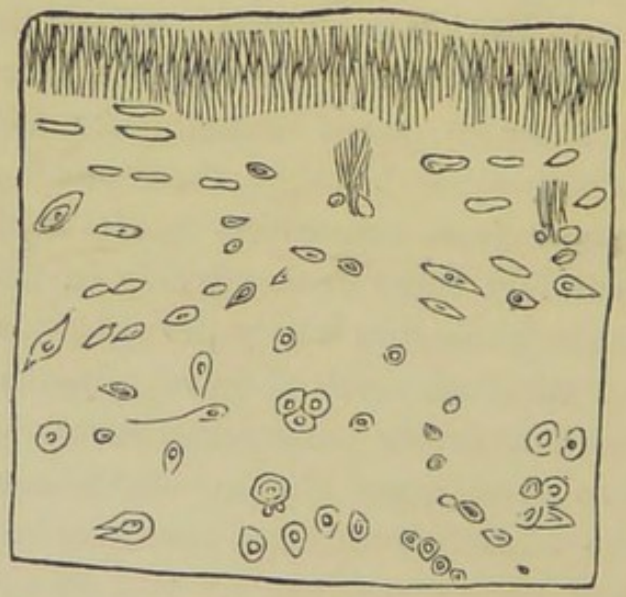

FIG. 10.

In Fig. 10 a preparation is shown from which the crystalline deposits have been removed by digestion in warm water, whilst in Fig. 11 is depicted a preparation which was for some time digested in water acidulated with hydrochloric acid; whereby in place of crystalline needles of urates uric acid crystals have become separated.

In both drawings the above-sketched changes that take place in cartilage in consequence of the gouty process in their various initial phases may be accurately followed in the zone infiltrated with acicular crystalline deposits of urates.

In the preparation here described and illustrated there are frequently present in the neighbourhood of the changes of the cartilage cells peculiar to the gouty process luxuriant growths which have been described by other observers—thus by Cornil and Ranvier—as two stages of gouty cartilage They have nothing in them peculiar

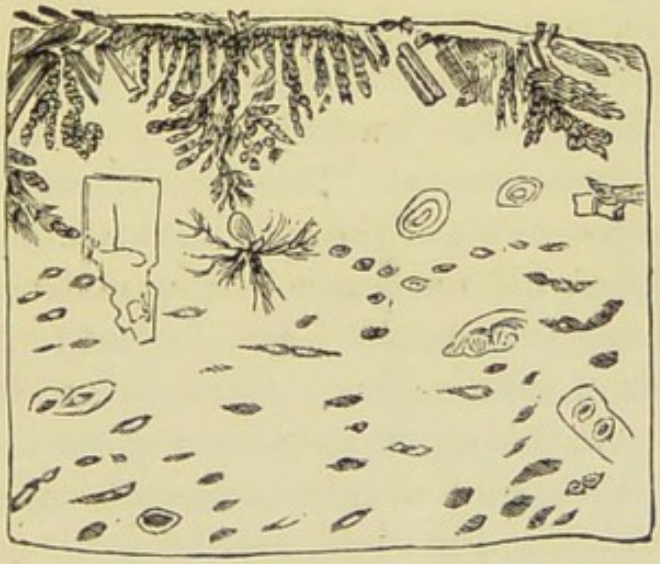

FIG. 11.

to gout; they rather come on in all possible conditions of irritation of the cartilage. I may thus pass over them. They are analogous to the reactive inflammation in the neighbourhood of the gouty necrosed patches of the kidney, where this makes its appearance in the form of a small-celled growth, such as was described above. That the dissolving materials made use of for the uric acid deposit, whether slightly alkaline, or weakly acid, or water alone, are without any influence on the advent of the changes of cartilage here discussed is shown, as may

be here incidentally stated, by the exactly similar treatment of normal articular cartilage, which was undertaken for the purpose of controlling or checking the observations here made.

The illustrations are all taken from sections stained with Bismarck brown. This was done simply that the plates should not be too complicated, so that they might be more easily reproduced. The above-mentioned delineations, when for the purpose of rendering representation easy they rely on the illustrations figured, are yet sketched out with reference to experiences with other staining material. In particular, the behaviour of the nuclei of the cells of cartilage corpuscles in the gouty portion of cartilage was always controlled by staining with Grenacher's alum carmine. This control was of special value to me, on account of the well-known prompt action and reliability of his nucleus-colouring material, and it forms a material and necessary complement to investigation by means of aniline dyes. As regards staining with Bismarck brown, this agent, as is known, has the characteristic that it does not simply cause staining of nuclei. It produces also staining of the basement substance, and I have in part chosen such preparations for illustration in which the staining of the basement substance was particularly deep, in order to show the contrast to the faintly stained necrosed patches. It is not by any means always and in all organs that the necrosed patches of gout are more brightly coloured. In discussing gout of tendons we shall return to this point. Fuchsine and gentian violet were also employed in staining, in order to bring to light any bacteria that might possibly be present in the gouty patches met with in hyaline articular cartilage. I have never succeeded in finding them, however. I remark here, that in examining for this purpose, homo-

geneous immersion was employed (obj. 1-12th of Zeis of Jena).

Amyloid degeneration in the parts of the articular cartilage affected by gout that were examined by me was not observed. I coloured with solution of potassium iodide alone and with this and sulphuric acid. In staining with iodine violet a reddish coloured shade occasionally appeared at the edges of the section. This, however, was of no significance *ad hoc*, as the same colouration was produced in sections made through healthy hyaline articular cartilage.

As regards the significance of the changes just described as taking place in gouty cartilage, there can be no doubt that here, as in the case of gouty kidney, wherever the urates are deposited the tissue is injured, and finally breaks down and dies, and that also, after this has taken place, the necrosed tissue is marked off from its surroundings, for in gouty cartilage, just as in gouty kidney, destruction of the tissue takes place with complete annihilation of the normal texture or structure. What materially distinguishes the process that completes itself in the cartilage from that which takes place in the non-amyloid gouty kidney consists simply in this, that round-celled development can never be demonstrated in the vicinity of the line of demarcation of the completely necrosed parts of the cartilage. The disturbance of nutrition also of the cartilage in gout is completed gradually, and not at a stroke. The terminal is necrosis of the affected parts of the cartilage; the preceding conditions may be designated as necrosing processes. In the neighbourhood of the necrosed patches irritative processes of the cellular elements of the cartilage take place, which consist in their luxuriant development. It is easy to determine the patches of cartilage that are already necrosed; we are able to ascertain this as soon as, so to

speak, the substance of the cartilage is discovered and laid open by solution of the urates. For the study of the area of extension of cartilage the nutrition of which is injured by the gouty process, as well as for the study of the necrosing processes that precede the completed necrosis, staining, as we have seen, gives valuable indications, and especially as regards the nuclei of cells. A still more efficient mode of control than that of staining is afforded by examination of gouty cartilage by polarised light.

This method of examination, as has already been mentioned has already been made use of by Garrod in examining gouty cartilage, but with another object in view. He made use of it for the purpose of confuting Budd, who, in his well-known work, had stated that the deposits of urates appeared in many places granular or amorphous, in others crystalline. Garrod says: "I have made many hundreds of sections through such cartilage from various gouty patients and from various joints, and, although the mass deposited occasionally at first showed the granular form, further examination, particularly with the aid of the polariscope, showed that it always consisted of crystals, and that the amorphous appearance had its origin in the direction of the needles, and not in actual absence of crystallisation."

We can, indeed, easily convince ourselves that Garrod is right, and that all deposits of urates in cartilage doubly refract light, whether they come into view as crystalline deposits or as apparent amorphous points and specks. When the deposits of urates are digested for some time in warm water, whereby they are dissolved, they often have the appearance when examined in ordinary light as if in those places where crystalline needles have hitherto lain amorphous masses were present. Examination of them in polarised light teaches

us that these apparently amorphous masses also refract light doubly, and do this until the last particles are dissolved.

Independently of this, simply in regard to the appearances depending on the power of double refraction of the uratic deposits of gouty cartilage, examination of delicate sections of gouty cartilage in polarised light gave interesting disclosures regarding participation of the cartilage substance even outside the zone encrusted with urates.

For the purpose of control I also examined, at the same time, along with gouty cartilage from the upper tibial epiphysis, the normal articular cartilage of an individual of the same age and from the same locality.

It is now known that if we examine a thin section of normal cartilage taken from the middle and not from the outer border, which does not give so regular an image, and preserved in Canada balsam, by the aid of the polarisation microscope and with crossed Nicol prisms we see immediately below the free surface of the cartilage, corresponding to the lenticular cartilage capsule, a clear line. Next to this is a dark line corresponding to the dark capsule. Then follows a second clear line, which corresponds to the zone of the cartilage, where lie the long capsules arranged in rows and perpendicular to the surface of the cartilage. This second clear line is of lesser luminosity than the first. The transitions between the middle dark and the upper and lower bright band, which shows a straight-lined border, are not sharp, but complete themselves gradually. Ranvier, in his "Traité Technique d'Histologie," has given a very instructive drawing of the appearances described. Examination in polarised light allows us to demonstrate a very marked molecular structure in the hyaline apparently completely structureless substance. We explain this optical behaviour differing in the various parts of the cartilage simply by the various

forms of the cells which lie in them. Whilst the basement substance of the cartilage may be completely homogeneous, the cause named may occasion the various forms of the cells, as well as the single and double refraction of the basement substance. In the superficial layer the cells and the basement substance are compressed from above downwards, and in the layer with the vertical capsules these and the basement substance laterally. This compression in the upper and lower layer makes the basement substance of the cartilage doubly refracting.

In the layer lying between the two, where the round form of the capsule shows that it is equably compressed on all sides, the difference of pressures in the first and third layer is thus neutralised, whence, it is singly refracting. Even if one should explain this behaviour of normal articular cartilage in polarised light differently, this at any rate may be said, that when changes take place in the behaviour of the cartilage some thing in the molecular structure of the cartilage must be disturbed.

Cartilage affected with gouty disease behaves, as my investigations have taught me, differently from normal cartilage.

When, for instance, we examine fine sections of gouty cartilage, infiltrated with uric acid deposit, that have been taken for the reason above stated, not from the margin, but from the central part, and preserved in Canada balsam, in polarised light with crossed Nicols the appearance given in Fig. 12 results. We see, commencing at the free edge of the cartilage, a crystalline deposit of urates, doubly refracting light—with the exception of certain opaque spots, generally not permitting the passage of light—which extends downwards into the zone provided with capsules, lying perpendicular to the surface of the cartilage. These deposits of urates show an irregular border below. After this comes a dark-looking

zone, which is also irregularly marked off below. This extends, especially in some places, and in direct proportion to the greater or lesser magnitude of the deposit of urates, variously deeply into the third layer of cartilage, that with capsules placed vertically to the surface of the cartilage. Exuberantly growing processes in the cartilage cells cannot be verified in this zone, but rather changes, such as have been accurately described. The

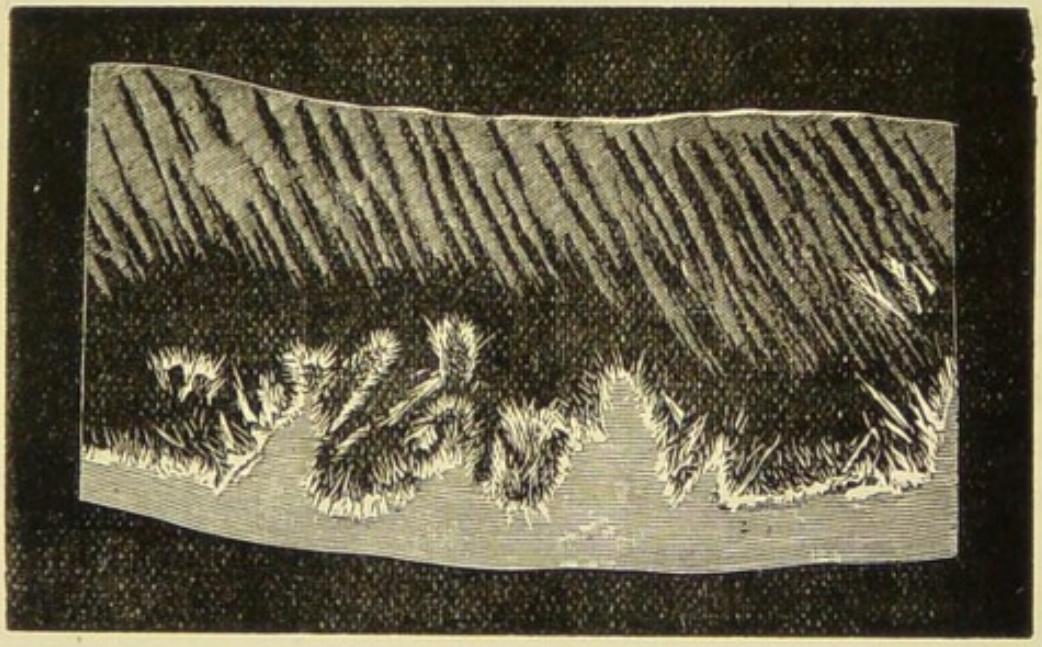

FIG. 12.

changes, therefore, are simply to be referred to the refracting power of the cartilage tissue. One may therefore, say that every deposit of urates is surrounded by a zone of cartilaginous tissue of greater or less circumference, imperfectly, or in general, not doubly refracting. In those parts of the cartilage lying below we again meet with the property normal to cartilage tissue of doubly refracting light.

In this way examination of cartilage affected with gout in polarised light gives a very valuable result, when we have to ascertain with the greatest possible exacti-

tude the extent to which the basement substance of the cartilage has become altered in its molecular structure under the influence of the gouty process.

This changed behaviour of the property of double refraction is, however, not peculiar to gouty disease of cartilage. Ranvier states that the basement substances of cartilage in acute or chronic articular rheumatism, as well as in scrofulous inflammation of joints where the cells of the superficial layer of cartilage are swollen and exuberant, and the basement substance has undergone a certain softening in the corresponding places, no longer doubly refract light. For gout of cartilage, examination in polarised light is of especial value. For this complements the examination by stained preparations in the most effective manner, and confirms the statement that beyond the limits of the deposits of urates the cartilage tissue is injured in its nutrition, and in a manner exactly analagous to that I had occasion to describe in the necrosing process of gouty kidney.

CHAPTER III.

Necrosed Gouty Patches in other Connective Tissues.

Gout is localised in other connective substances far less frequently than in hyaline cartilage. My own material for investigation is from the same case to which I am indebted for the gouty hyaline cartilage.

The literature of gouty disease of these tissues appears to be meagre. Garrod remarks that ligaments, fibrous cartilage tendons, and tendon sheaths, incrusted with urate of soda, exhibit under the microscope an appearance exactly similar to that of articular cartilage, except that in them the crystalline structure is not so regular as in hyaline cartilage and synovial membrane. Rindfleisch, however, like Garrod, notes that in the membranous parts of joints, as well as in the medulla of bones, the clusters of crystals are disseminated without reference to the texture. Whilst, in speaking of gouty affection of hyaline cartilage he expresses the view that formation of crystals of urates takes place in the cells of cartilage, first because there is most room for them; then he remarks, in relation to the regular nodules of urates that form in the membranous parts of joints, as well as in the medulla of bones, and which develope to the size of a pea and larger: "one nvoluntarily wonders at the sight of them, whence space is procured for such voluminous deposits."

I now turn to the results of my own investigations, and speak of

A.—Gouty Disease of Fibrous Cartilage.

As material for investigation I made use of the lenticular cartilage of the knee-joint, in which a large quantity of deposits of urates, in part of considerable size was present. The preparation (balsam preparation) is delineated in Fig. 13, in which the condition under con-

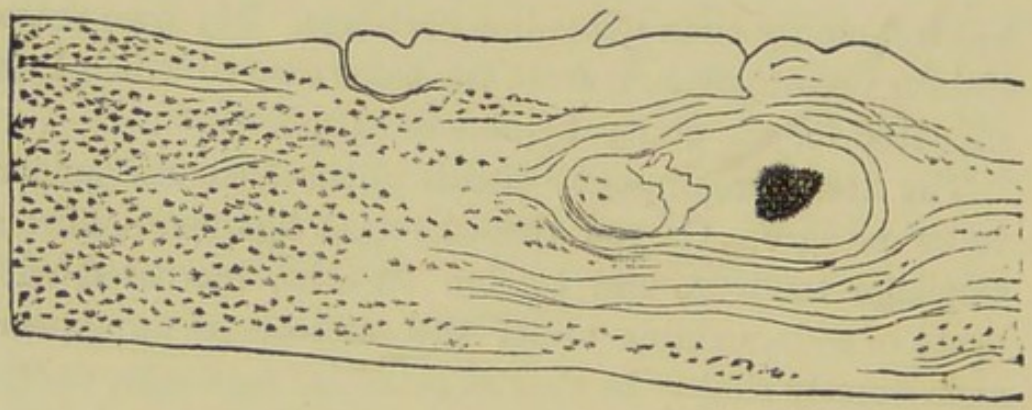

Fig. 13

sideration may be easily demonstrated. The gouty character of the change is immediately shown by the crystalline deposits of urates.

Independent of these, however, further tissue changes are present, completely analogous to those mentioned in the description of gouty arthritic disease of the kidneys, and of hyaline articular cartilage. One sees at the first glance where the healthy fibro-cartilaginous tissue is marked off from the diseased portion. The crystalline deposits of urates, which were very thick and massy, are now principally dissolved out by soaking in warm water, and it is only at one spot that one sees as *signatur* of the process a residuum of urates of quite

typical appearance. This is of roundish form, and composed of a mass of acicular crystals, thickly felted together. At the margin of this conglomerate of crystals a few tips of acicular crystals are seen. This deposit of crystals lies in the midst of amorphous completely structureless substance, that is already sharply defined all round, and is encapsuled from the surrounding parts. In the midst of it a defect is seen, where a part of the substance under consideration has become loosened from its surroundings, and fallen out in the preparation. Besides this patch, that is sharply defined, others are seen, and especially in the parts lying close to the edge of the cartilage, where the limitation in this manner is not yet completed, but the fibro-cartilaginous texture is already completely destroyed. Here, also, as examination of the preparation before maceration in water showed, urates were embedded almost everywhere in crystalline form in thick drifts. These are now completely dissolved out. In this upper portion, just as in the encapsuled patch, no shaped elements are seen, and no method of staining brings out any colouration of nuclei, whilst in the lower portion of the preparation coloured nuclei and some more or less marked fibres can be identified. The textureless patches in the cartilage examined by me were almost altogether limited to the upper part of it; deposits of urates were never sought in vain; others were always present in such thick interlaced masses that many times it was only by their projecting points at the free edge that it could be recognised that these were made of needles. In the parts immediately surrounding the textureless patches just described, freely coloured nuclei are seen. Besides the parts of the tissue that are completely necrosed, necrosing patches are also met with in fibro-cartilage, in which absolute death of the tissues has not yet taken place.

From the preceding we obtain the result that in gouty disease of fibro-cartilage also, besides the deposits of crystalline urates, necrosing patches develope that lead to complete death of the tissues.

I now turn to the description of—

B.—Gouty Disease of Tendons.

When the tendons become affected in gout we find essentially the same gouty patches that we have become acquainted with in arthritic affections of the kidneys, and in hyaline and fibro-cartilage. The crystalline deposits in gout of tendons have this, in the first place in common with gouty affections of fibro-cartilage, that they are distinguished by their bulk and thickness.

I have had two microscopic preparations of gout of tendons delineated, and Fig. 14 represents the gouty patch

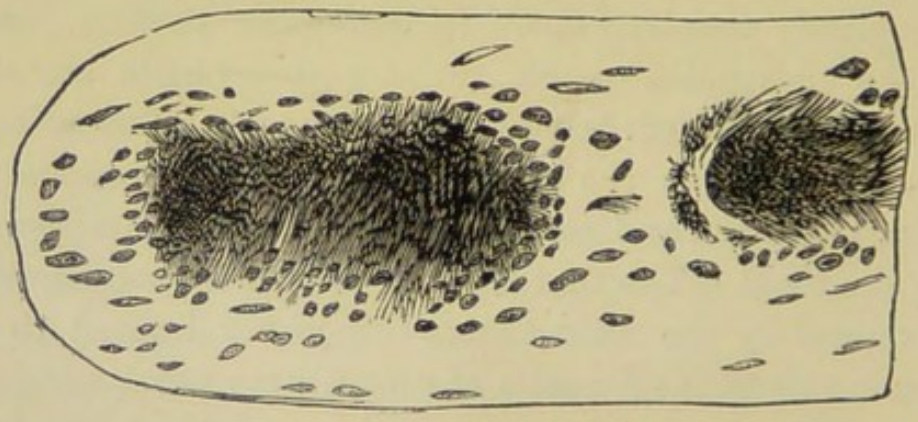

Fig. 14.

of the tendons with the deposits of urates in parts well preserved, whilst Fig. 15 represents the same after the urates have been dissolved out. Fig. 15 shows the changes in transverse section with a low power, whilst the enlargement of Fig. 14 demonstrates these conditions more fully and also longitudinally.

In Fig. 14 we see two gouty patches (*a* and *a*1). The deposits of urates are seen to fail only in the latter, and in this in places only, and in these spots the familiar textural mass comes into view. The first, on the other hand, is composed throughout of thickly drifted, interlaced crystalline urates, only to be recognised at the marginal parts as distinct acicular crystals. In the neighbourhood of this is a tolerably free small-celled growth, whilst in the case of the lower patch this is confined to the lateral parts. Perhaps still more instructive for the determination of the necrosed patches in the tendons in gout is the transverse section slightly enlarged in so far as the whole of the crystalline deposits of urates are dissolved out. Where these have lain the complete textureless mass comes into view. These patches have taken the Bismarck brown staining in various degrees. The main cause of this, as far as my experience goes, is that they take a more intense colouring the more the tissue is beginning to soften. The older the patches, the nearer they are to destruction, the darker they are generally coloured by Bismarck brown. Along with the completely textureless patches, a series is seen in which nuclei are still visible, but are no longer capable of taking the colour, and even some in which a few stained nuclei show themselves in the midst of the textureless tissue. In the immediate neighbourhood of the necrosed, or necrosing patches, for the most part a free small-celled infiltration may be observed. It was only in a few of the patches that I did not observe these. I was many times in a position to remark a striking brittleness, and this was generally in those parts that took up the colouring matter the most in the process of staining. This was recognised on cutting by the section crumbling up at the part affected. Examination of the affected tendons in polarised light affords a very good

method of determining the extent of the necrosed patches, which often spread out beyond the crystalline deposits of urates. As is already known, longitudinal sections of tendons have the property of doubly refracting light. In those parts of the tendons that are necrosed this property is lost; where the Nicols are crossed they appear quite dark.

In gouty patches of tendons, also, we find, in addition to the necrosed patches that are sharply defined from the surroundings, some in which this is not the case, and the reader will easily find both types represented in Fig. 15. But besides this I found places where the ne-

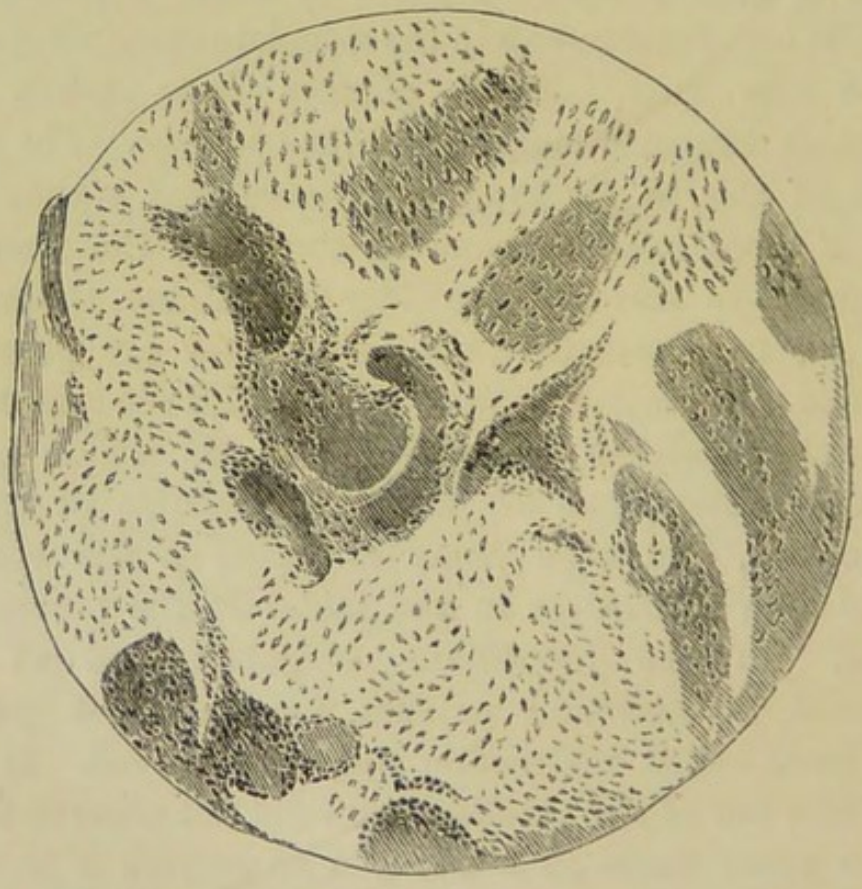

FIG. 15.

crosed process was not as yet complete. I saw these mostly in connection with patches already necrosed, and found in them that all trace of basement substance had

not disappeared; a fibrous character was seen on longitudinal section, as in the normal parts surrounding, the fibres appeared—as a præ-mortal symptom?—to stand out in places perhaps even more distinctly. That the process we had to do with in such parts was really one of necrosis was shown by the corpuscles of the tendons, for these were completely uncoloured, in contrast to those distinctly coloured in their neighbourhood, and even partly already in course of disappearance. I have before me a preparation very well coloured with Grenacher's alum carmine in which these conditions are very distinctly marked.

In the gouty tendons examined by me some yellow-coloured parts, which were mostly found in the immediate neighbourhood of the uric acid deposits, were very noticeable even by the naked eye. Microscopic examination showed that we had here to do with pigmented, mostly indistinct cells, and punctiform detritus of a yellowish brown colour. I wondered at first whether we had here cells, or remains of cells encrusted with uric acid or its compounds. The pigmented masses were not removed however, by maceration in lukewarm water, and I arrived at the opinion that they were residua of hæmorrhages, as the effect of a demarking inflammation particularly intense in many spots, an explanation that had so much in its favour that these pigmented masses were found interspersed in the free small-celled infiltration.

I turn finally to

Gout in the Looser Connective Tissue,

as I have had opportunity of observing it in the subcutaneous connective tissue and in that between the muscles. Such a gouty centre I have had delineated in Fig. 16.

It is not different in any essential form than those already given. For we find here, more or less, copious deposits of urates of the same crystalline character; we see here also the same textureless tracts, which come to light in their full extent when the deposits are dissolved out, which are often of greater extent than the uric acid deposits. In the vicinity of these patches there is generally to be seen a small-celled infiltration, limited, or of greater or lesser extent. As regards the gouty patches of the subcutaneous connective tissue, they were

Fig. 16.

very numerous in the piece of skin examined by me, and were present over a large extent of surface. They completely resembled the patches already described, so that few words may suffice for this description in addition to the two cuts, Figs. 17 and 18, which relate to them. In Fig. 17 is shown a section of subcutaneous connective tissue, taken from a vertical section of the skin moderately enlarged, which appears to consist simply of crystalline deposits, in the immediate neighbourhood of which in certain places is a free round-celled infiltration. In these subcutaneous gouty nodules also the crystalline

uric acid deposits are shown in considerable quantity. In Fig. 18, on the other hand, is represented a vertical section through the skin and subcutaneous connective tissue with a lower power. This instructs us first as to the position and extent of the gouty deposits in the subcutaneous connective tissue, the urates of which have been dissolved by maceration in luke warm water. They are numerously scattered through the whole thickness. Here also, after solution of the urates, an amorphous, quite homogenous texture, and structureless substance

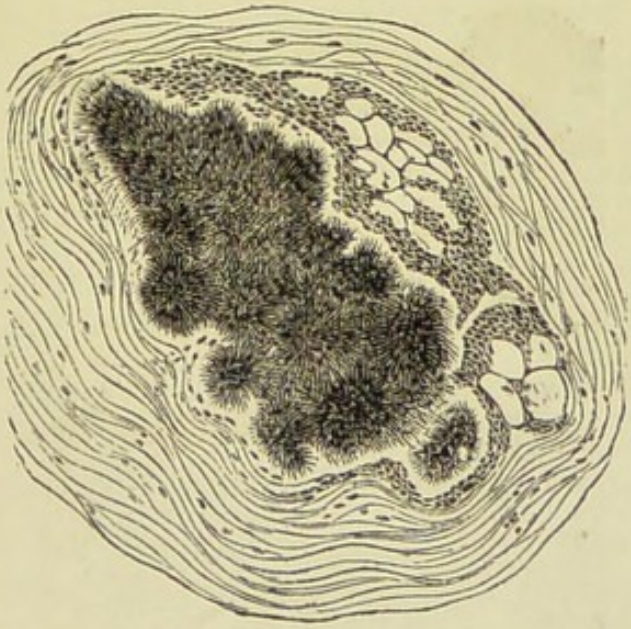

Fig. 17.

has remained, not differing in the least either in external appearance or in reaction from analogous patches in which gout is localised in other tissues and organs. These patches, larger and smaller, occupy two-thirds of the thickness of the subcutaneous connective tissue; neither cell nor nucleus is to be seen within it, nor can either be rendered visible by any kind of staining. But on the other hand we here again observe more or less freely and, mostly so in their immediate neighbourhood, the cells that correspond to small-celled infiltrations.

The smaller of these patches have a regularly rounded form, the larger, on the other hand, show an irregular nodulated form with a rounded off contour. In the larger and plainly older patches lacunæ are here and there seen, out of which the necrosed substance has fallen in the process of preparation.

Wyss has asserted that the gout nodules of the skin have their origin in the sweat glands. In the present instance this was not the case. In the sweat glands lying in the lower part of the cutis no structural changes

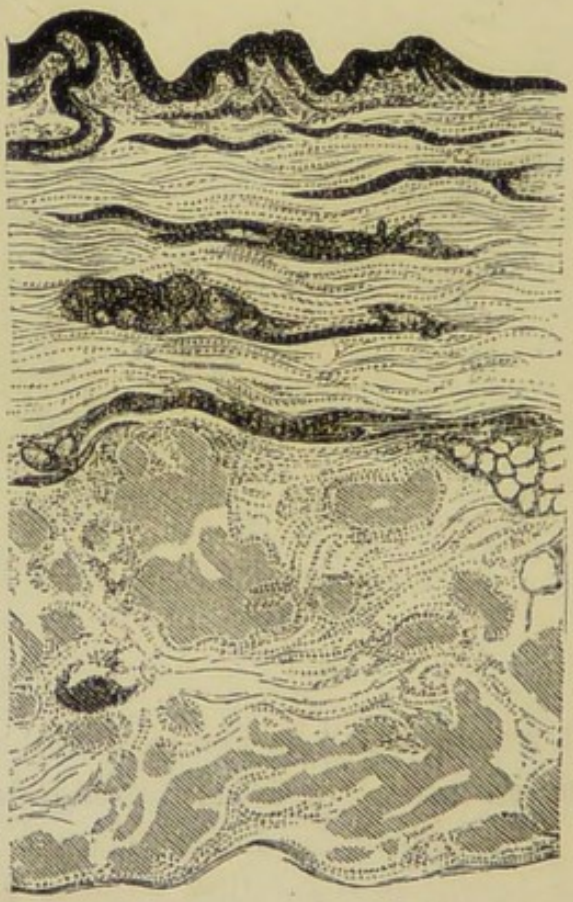

FIG. 18.

were demonstrable, neither were they in the cutis itself. As regards those lying in the subcutaneous connective tissue, concerning which Henle states that they are the larger, I can only say in regard to this point, that no

channel of communication could be traced from the necrosed patches here described, as would have been the case if they had originated in them. I have carefully examined hundreds of sections in regard to this point. As no structure can be determined in the patches, one cannot of course say whether in the places in which they exist, sweat glands previously existed or not. The first striking contradiction which exists between the undoubtedly correct observations of my friend Wyss: that in cutaneous gout uric acid is present in the sweat glands, and mine which, according to the case before us, lays stress on the presence of gouty patches, and along with these crystalline deposits of urates outside the nodular glands, is in my opinion, easily and satisfactorily explained. I mean that here a condition of things exists analogous to that met with in the kidneys which I have already remarked upon in the description of gouty kidney. As uric acid has long been proved, and on many hands to be present in the sweat of gouty subjects, if not constantly so, it is easy to conceive that uric acid occasionally remains lying in the glands as it does in the urinary tubules. Whether the presence of uric acid in the sweat of gouty individuals is something typical, or whether it is present like urea under various conditions, possibly like the latter in health in case of free excretion of uric acid, as far as is known to me we have no decided data. In any case, in my opinion, in the skin as in the other localisations of the gouty processes already described, necrosed patches must be looked upon as typical in arthritis uritica.

4.—Resume, Conclusions and Consequences of the Foregoing Observations.

From the facts hitherto related, regarding the typical

and characteristic gouty tissue changes, so much will be perceived that *independent of the known depositions of crystalline urates, one change is common to them, namely, necrosis of the tissues and organs in those places where the crystalline deposits of urates were present.* I must maintain that necrosis of tissue is something essential in the gouty process as I have never failed to observe it in any case. For me the characteristic of the gouty process is *necrosis of tissue plus depositions of urates in a crystalline form.* When both are met with associated together, one may speak of a formed gouty patch. As is shown by the foregoing, I have been able to verify such gouty patches in the kidneys, the hyaline articular and fibro-cartilage, tendons as well as in the looser inter-muscular and subcutaneous connective tissue, either after preliminary solution of the crystalline deposits or without it, provided the necrosed tissue has a greater extent of surface than the uratic deposit, as appears to be frequently the case. A stage precedes the development of these *necrosed patches*, which can be most beautifully observed in hyaline cartilage and in tendon, which I have designated *necrosing*, where the death of the tissue is not yet complete, and where as far as I have seen, no deposits of urates in crystalline form can yet be demonstrated. If we now ask which is the primary, the necrosing process ending in death of tissue, or the crystalline deposition of urates, I hold that the *disturbance of nutrition is the primary*, and the *crystallisation of the urates the secondary process*, and that before the latter takes place the disturbance of nutrition must have reached an advanced stage; *the tissue must exhibit the symptoms of complete death. I have never yet seen in cases of gout that the urates crystallise in normal tissues.*

When we now seek for the cause of the tissue death in gout, we naturally turn in the first place to the gouty

materies, i.e., to uric acid and its compounds, which specially and perhaps almost exclusively accumulate in the connective tissue and at first in the fluid form. My views in regard to this are identical with those advanced by Garrod. This observer assumes that these deposits are first excreted as limpid liquid, which as it is rich in urate of soda, and this salt is dissolved with difficulty, first takes on a milky appearance in consequence of crystallisation, after which, as the fluid portion is gradually absorbed, the exudation becomes more and more firm, and at last quite hard. I am of opinion that the gouty substance, soluble with difficulty and containing uric acid compounds, is deposited in the tissue in a fluid form, under certain conditions, to be further discussed later on, and in circumscribed places. If this substance is poisonous and capable of injuring the nutrition of the tissues—which will be at first assumed, but will be further confirmed by direct proof—so will the poisonous fluid, like a drop of acid or alkali, act most injuriously on that portion of tissue on which it first becomes active The poisonous action will be less powerful the farther it is removed from this spot. The intensity and extent of the poisonous action will be in direct proportion, not only to the quantity and the greater or less virulence of the excreted substance, but also to the nature of the tissues in which it is deposited. The more resistent the latter are, so much less *cæteris paribus* will the poison damage them. One, and the same quantity, with equal concentration of the solution, will in the case of looser tissues, effect more quickly a more diffusive change, than in tissues of firm texture, which will for this reason offer more resistance to its spread. I have never been able to understand how a series of observers, whilst they ascribe to the urates an injurious influence on the tissues surrounding them, should take up the view that the tissues

exhibit a normal character in the places where these have been deposited. It is at any rate a natural postulate, that the injurious action of mechanical or chemically irritating substances—both these eventualities have been discussed—is most efficient in those places where they first come fully into play. The frequent development of reactionary inflammations in the vicinity of these necrosed patches, has already been thoroughly discussed.

We have, therefore, in the case of gouty patches, to do with the crystallisation of (acid) urate salts in necrosed tissues, the death of which has been brought about by the separation of (neutral) urates in a fluid form. The crystallisation of urates in gouty necrosis is a process for which we have in a certain sense an analogue in petrifications or calcifications, in which lime salts are deposited in tissues in which the nutrient processes are either completely extinguished or greatly reduced in energy. It is thus, without further discussion, quite comprehensible that—independent of the uric acid compounds which after they have effected the destruction of the tissues crystallise in them—that lime salts are also deposited in gout patches as they are in other necrosed tissues. The fact itself was investigated long ago. Lehmann, for example, in the case of a young man, found in the gouty deposit from the metacarpus along with 52·12 per cent. of soda, and 1·25 per cent. of lime urate, 9·84 per cent. chloride of sodium, and 4·32 per cent. of phosphate of lime. I have had the opportunity of observing, side by side, in microscopic examination of the necrosed glomeruli of a gouty kidney, crystalline deposit of urates and sphœro-crystals composed of carbonate of lime.

CHAPTER III. (*a*)

Gout in Animals, and attempts to produce Deposition of Urates in the Animal Body experimentally.

After having discussed in the second chapter the typical affections of organs in arthritis uritica of the human subject, I will in brief report what I have discovered concerning crystalline deposits of the uric acid compounds in the organism of the various classes of animals.

Two groups of facts here come under consideration: 1. Observations on gout and analogous diseases in animals, and observations relating thereto from the domain of comparative pathology; and, 2. The results obtained from comparative pathology in regard to the production of uratic deposits in the animal organism.

We will first turn to the first of the questions before us: 1. Gout in animals.

Apparent rarity of arthritis uritica in animals. Gout in dogs. Guanin gout in pigs. The pathological conditions analogous to gout in birds and reptiles.

Gouty disease is such a rare occurrence in animals or at least such a rarely described occurrence, that my hope of acquiring light on gout in one or other direction, by means of comparative pathology, remained unfulfilled. My colleague, Herr Esser, Professor of Veterinary Medicine in our High School, has never himself observed a case of gout in animals. He also tells me that in the

(*a*) At page 49 instead of *Chapter III.* read *III.*, omitting word "Chapter"

works of Hertwig, Fuchs, Haubner, Pütz, Roell, and Stockfleth, which he consulted at my request with regard to this point, he could find no information respecting gout in animals. In Spinola's work there is indeed a report on gout in old dogs, but the communications of this author do not give the conviction that real arthritis uritica is treated of. Spinola has not drawn a sharp distinction between true gout and the so-called rheumatic inflammation of joints. Gleisberg denies the occurrence of gout in animals generally, and regarding the observations shortly to be mentioned of gout in birds, he remarks concerning the changes in joints that are designated as gouty deposits, that they consist of chalky incrustations of connective tissue growths. Bruckmüller only speaks in a positive manner about gout in mammalia. He mentions very dense deposits partly in the periosteum of the articular ends of bones, partly in the ligamentous apparatus, of a chalky or gypsum-like character, which form by their aggregation uneven glandular nodules the size of a hazel nut, and which are composed of urate of soda. Bruckmüller has himself met with these true gouty nodules in many of the joints of a hound, and particularly in the cartilaginous ends of the ribs.

This observation, the only one known to me as to the occurrence of uric acid gout of the mammalia, is so decided that it outweighs all the opposing and negative data.

The guanin-gout of swine also, described by Virchow, which at any rate stands in close relationship to gout, is plainly an extremely rare occurrence. Professor Schütz, of the Veterinary School, Berlin, to whom I had applied for material for examination in relation to guanin-gout, told me on the 27th of April, 1880, that, notwithstanding endeavours extending over years to procure organs affected with this disease, this had not been possible, and

that he himself had only seen guanin-gout in Virchow's preparations. Virchow found in the muscle flesh (hams) of swine, and also in the tissues constituting the knee-joint, the cartilaginous covering of the tibia and patella in the semilunar cartilages, and the ligamentous part around the joint, multiple, and numerous white, chalky looking deposits in the form of granules and discs, probably from the chemical examination composed of guanin. According to the communications made by Virchow in regard to these diseased pigs, their livers also appear to have been the seats of exactly similar nodules. He was not able to make further investigations on the point. So much, however, results from the investigations of Virchow, that these deposits, with the exception of the difference of their chemical composition, agree in every respect with the arthritic deposits of man. In pigs then guanin concretions are formed in a manner exactly corresponding to that in which gout causes uric acid concretions in man, and it will not, therefore, be going far astray to consider the disease of swine as guanin gout. The observations to be found in literature on gout of birds and reptiles, are rather more numerous than those relating to gout amongst the mammalia. In these classes of animals that excrete uric acid as the mammalia excrete urea, there is developed an affection to a certain extent similar anatomically to gout of the human subject, which consists of depositions of urates in the various tissues of these organs. Charcot has collected a series of examples of this disease which has been designated as incurable, but the number still seems to be scanty enough. The observations of Aldrovandi belong to this subject, who found a "gypsum like" material accumulated on the toes of a falcon. Bertin, of Utrecht, reports a similar observation in regard to parrots. He found in the *Psittacus pandis* a swelling composed of urates in the

neighbourhood of the joints, and exactly similar appearances in the joints themselves and the kidneys. Mégnin has lately related a case of gout in a female parrot, numerous crystals of urates were found in the joints of the foot. Mégnin considers this affection to be not infrequent in birds that move but little. When Mégnin draws this conclusion from his own observations, that gout is not unassociable with a vegetable diet, as the birds live entirely upon grains of corn, the simple rejoinder may be made that with the different character of tissue metamorphosis of mammalia and birds in a physiological condition, the anomalies of it may be at most placed in parallel, and are not by any means to be identified with each other. As regards gout in the amphibia, Pagenstecher observed a case of it in an *alligator sclerops* that died in a menagerie. At the examination made five days after death, he found deposits of urate of soda in the whole of the muscular structure of the animal. It was found principally and in considerable quantities in the common sheath of the tendons, it only exceptionally and in small quantities forced itself along with the sarcolemma of the smaller fibres deep down, lying within the fibrillæ. The kidneys were not changed externally, they were of but inconsiderable size. Internally their passages and also their channels of exit contained pulpy urine of which traces were seen in the openings of the ureter into the cloaca. The function of the kidney therefore had not ceased and was scarcely less active than normal. In the hip-joint besides urate of soda (delicate acicular crystals) free uric acid was found. In the extract of the flesh of this *alligator sclerops*, which was carefully prepared, in addition to urea, strikingly largely quantities of creatinine and uric acid and small quantities of xanthine were proved to be present. The chemical analysis was made by Professor Carius.

Another case of the occurrence of uric acid in the flesh of an alligator is reported by Liebig. The animal was examined in Giessen, and in its flesh a large number of small white needles were present, which under the microscope could be recognised as crystals of uric acid. This was confirmed by chemical examination.

Small as are the results of this investigation concerning the occurrence of gout in animals, they have, however, afforded valuable data for the future investigation of the subject, which will be serviceable for the further progress of our knowledge. In any case careful attention to the chapter of pathological anatomy is much to be recommended.

2. The attempts which have been made to produce experimentally deposits of uric acid in the animal body.

Attempts on birds and reptiles; attempts by Galvani, Zalesky and other investigators. Their results regarding the site of formation of uric acid. Present status of the question regarding the site of uric acid formation. Want of significance of ligature of the ureters hitherto performed on birds, &c., for human gout. My own experiments on fowls, consisting in part of ligature of the ureters, and in part of destruction of the secreting kidney parenchyma by subcutaneous incorporation of small doses of neutral cromate of potash. As by this experiment a stasis of the urine, which consists almost exclusively of uric acid, is produced, we are able to produce experimentally in the various tissues and organs of these animals deposits completely analogous to the gouty patches of the human subject, thus in the liver, in the heart, or in the kidneys. It only succeeds in the latter organ when the kidney tissue is injured in its nutrition by the chromic acid salt. In the stasis of urine produced by ligature of the ureters, no gouty patches are formed in the kidneys. From this it results that the various organs

offer different degrees of resistance to the action of stasis of urine.

I now turn to the results which experimental pathology has given regarding the production of deposits of urates in the animal organism. One naturally choses for these experiments those classes of animals (birds and amphibia) that mostly produce uric acid.

Since experiments have been made by a large number of observers, and indeed with very different objects, in most recent times for the purpose of deciding the site of the formation of uric acid within the system, I shall first mention these briefly as they are not without significance for our own investigations, before I give the results of my own experiments cn this head.

After Galvani in 1766, in order to study the structure of the kidney by a new process of injection, but without being aware of the physiological significance of the experiment, had ligatured both ureters of a fowl from the back, without opening the abdomen, in which he kept the animal alive for some days, these experiments were again resumed in more recent times in the interests of another question, by Nic. Zalesky, the latter seeking out and ligaturing the ureters from the abdominal cavity. Similar experiments, and with a like intent, were afterwards carried out by Chrzonsczewsky, Pawlinoff, V. Schroeder, and Colosanti. For ligature of the ureters Zalesky and Schroeder made use of fowls and serpents. Chrzonsczewsky operated on fowls, as did also Colosanti, Pawlinoff on pigeons and adders, Pawlinoff, and before him Zalesky, in addition to ligature of the ureters in fowls and pigeons, extirpated the kidneys.

Von Schroeder also extirpated the kidneys in serpents and fowls, and excluded the kidney function by closure of the aorta and vena cava, and Pawlinoff stated that he ligatured the vessels of the kidney.

All these experiments which thus had for their aim the elucidation of the part played by the kidney in the formation of uric acid, gave in so far a result thoroughly in accord, as deposits of uric acid salts were demonstrated as present in a series of organs, a discovery which Galvani in the case of his fowls with ligatured ureters had described in a striking manner as follows: "Ejus cadavere dissecto alba terrestris materia conspicitur, quae omnes ferme partes coinquinat, atque membranas potissimun, inter quas praesertim pericardium, quod gypseum, evasisse videtur extima hepatis membrana. Renes vix a naturali magnitudine recedunt, at lobos præseferunt alba materia repletos, quam non est dubitandum urinæ fuisse crassiorem, solidioremque partem." Later observers have added many details to the above. Thus Zalesky found the deposition of urate to be very free in the joints and principally in the larger ones and in older animals, but he states further that he found urates in an amorphous form, not only on the surface, but also in the parenchyma of the liver, in the lungs, the heart, and some other organs in quantities varying according to the longer or shorter duration of life. I shall soon have to go the more closely into these statements of Zalesky's relating to this subject, and exceedingly interesting for the object before us, as my investigations have produced totally different results.

The experimental investigations related have not attained their object according to the intention of the authors concerned, that of determining the site of the formation of uric acid. They have only determined the fact that the assumption of Zalesky was incorrect, that uric acid was formed by the kidneys. The kidneys are really the excretory organs of it, they have no more and no less right to be looked upon as the organs of formation of it, than a number of other organs to which this function has been assigned. They can contribute to the

formation of uric acid, they certainly are not the sole place of origin of it. The experiments of von Schroeder have taught that the kidneys may be extirpated in fowls and serpents, and that by ligature of the aorta and vena cava the functional activity of the kidneys can be completely excluded, and that thus without any participation on the part of the kidneys uric acid is still formed in considerable quantities. Von Schroeder in reliance on a series of physiological and pathological facts, has, although with a certain amount of reserve, denied the uric acid forming function of the kidneys in other classes of animals also. The question where uric acid is formed, and this in the interests of the subject is to be deplored, is still an open one. In the mean time the present position of the question may be here sketched in a few words.

In the normal condition of the hen Meissner looks upon the liver as by far the most important source of uric acid, which is conveyed by the blood from there to the kidneys. But Meissner expressly remarks withal that other organs, such as the spleen and the nerve substance supply a contribution to the uric acid of the urine. In regard to the formation of uric acid in the liver, he relies on the constant occurrence of it, and in considerable quantities, as observed by him in the liver of the domestic fowl, which in common with other observers he has met with in the livers of various mammals, although in lesser quantities than in the livers of birds. Up to the present, unfortunately, the part taken by the liver in the formation of uric acid has not been definitely ascertained, as it might have been as regards the kidneys of birds and amphibia, by the elimination of the liver function.

Ranke believed that he might conclude from his own investigations that the spleen was pre-eminently the place of formation of uric acid. How far it is so has not

yet been proved. That the spleen participates in the formation of uric acid, as was mentioned above, was emphasised by Meissner. It appears that the formation of uric acid is not the privilege of any one organ. Von Schroeder and a number of earlier observers directly combat the assumption that the formation of uric acid takes place exclusively in one organ. Finally, I must here mention another hypothesis, which many observers have advanced independently of each other, and on various grounds, in accordance with which the site of the formation of uric acid is to be located in the connective tissue. As the connective tissue, as is known, is never wholly absent from any organ, the sites of the formation of uric acid would be scattered over the whole organism. Ch. Robin, as far as I know, was the first to distinctly formulate this thought, and he has constantly and firmly clung to it. Charcot communicates literally an expression of Robin's on this point which reached him, according to which the normal fibrous tissue contains uric acid, and that the pathological condition is nothing else than an exaggeration of the normal condition of things. Without noticing this expression of Robin's, Chrzonsczewsky adds to this an experimental histological fact according to which the nodules of the connective tissue are the places of manufacture of uric acid. In the course of the investigation into the origin of the lymphatics in order to ascertain the connection between them and the thoracic duct, Chrzonsczewsky ligatured the ureters of domestic fowls, and subsequently killed them at various intervals. In the earliest stages of the process in the serous lining of the peritoneum, which in order to prevent the solution and decomposition of the uric acid salts, he without any previous preparation at once examined extended in glycerine, he found accumulations of finely granular uric acid, simply in the connec-

tive tissue cells, sometimes only in their nuclei, sometimes in their vicinity also, and sometimes in the anastomosing prolongations of the cells. On the other hand, the lymphatics were not filled with uric acid deposits, neither at that part of the peritoneum that covered the intestinal canal, nor at that which was prolonged over the kidneys. From these investigations, which have been recently confirmed by Colosanti, Chrzonsczewsky draws the conclusion that uric acid originates in the connective tissue, and that it is conveyed thence through the lymphatics. In the meantime, although chemistry may be able to prove the presence of uric acid in normal connective tissue, and although the granules described by Chrzonsczewsky may be actually depositions of uric acid or compounds of it in the connective tissue cells, or in the nuclei of them, this is no proof that uric acid originates in the connective tissue, or in its cellular elements. Bartels, on the basis of pathological investigation, most correctly points out the significance of the connective tissue in relation to the formation of uric acid. His opinion has been frequently reproduced erroneously. For this reason I give his utterances literally. Bartels says: "If, generally speaking, certain tissues are to be looked upon as the place of origin of uric acid in the human system, it would appear to me more probable that it must be those in which tissue-change, and consequently oxidation, proceed with the least degree of energy, and thus the cartilaginous and fibrous tissues, in which, in consequence of absolute absence of blood-vessels, or of their limited distribution with wide interspaces between the capillaries the nutrient fluids are very slowly renewed. In these tissues, in the case of pathological accumulations of uric acid in the blood, and especially in gout, the deposits of uric acid salts are formed. *By this is by no means meant that these substances must have their*

origin in these tissues, only the conditions for their separation from the nutrient fluid are here more favourable than in most others, for the reason that the movement of that fluid is necessarily very much retarded in cartilage and fibrous tissues."

This statement of Bartel's I shall give my adherence to when in the further course of this work I turn my attention to the pathogenesis of the gouty process in the human subject, with the conditions under which it is developed. I shall then return to the part which is to be ascribed to the disturbances of tissue change in the muscles or to the formation of uric acid in them in human gout.

If we now turn to the consideration of the importance of the facts that have resulted from the numerous experiments that were undertaken to bring about the accumulation of uric acid in the organisms of those brute classes the urine of which consists principally of uric acid for the study of gout, all these experiments are without significance for the study of the anatomical changes in arthritis uritica of the human subject as I have described them in the second chapter. For even if it results from them that the symptoms of the disease produced experimentally in birds, &c., have so far certain analogies with human gout, that depositions of urates are found in various structures, with the conception that I have of the typical anatomical changes of arthritis uritica of the human subject, I should set up other explanations of the results of the investigations before I should concede that in certain classes of animals we could produce experimental diseases that had anatomically any proved relation to gout of the human subject. I would thus not only postulate that we by experiment—1, *are able to produce deposition of uric acid salts in the tissues and organs of the animals experimented on; but also*, 2,

that necrosis of tissue can be proved in the places where the crystalline deposits are found; and 3, *that in the neighbourhood of these experimentally produced gouty patches, and indeed as a consequence of them, a more or less extended reactive inflammation is developed.*

Starting from this point of view, a series of investigations have been instituted, and all on the domestic fowl. All the birds, with the exception of one, the history of which I shall especially return to, were not made use of for experiment as soon as they were bought, but were first for several days fed on barley.

I may omit the communication of the complete reports of the investigations, and may limit myself to a comprehensive description of the results of the experiments, the number of which was large enough to exclude accidents. The order of experiment was essentially a double one. (1) The ureters were ligatured partly after Galvani's method, partly from the abdomen. My colleague Marmé has, at my request, had the goodness to carry out all the ligaturing of the ureters. For this I express to him in this place my best thanks. The ligature of both ureters, which was always performed with antiseptic precautions, was kept up for at most twenty-four hours. The ligature of one ureter produced no serious symptoms, only during the first ten hours was the bird somewhat depressed, ate less and no evacuation *per rectum* took place. When the other ureter was ligatured fifteen days later death followed about twenty-four hours afterwards. Section showed complementary hypertrophy of the kidney, the ureter of which was last ligatured and which for fifteen days had performed its function alone. This was enlarged to quite double the size. In the kidney the ureter of which had been ligatured fifteen days no stasis of urine could be shown. (2) Chromic acid salts (neutral chromate of potash) were injected into

fowls with the view either of inhibiting by injuring the kidney substance by means of this poison, the separation of uric acid through the diseased parenchyma of the kidney, or of completely arresting it, and in this way of producing accumulation of urates in the various organs. The expected effect took place in a marked manner. In order to attain this to such a degree as I shall describe later on it is desirable to let the chromic acid salt take effect slowly and gradually. Whilst fowls die quickly if doses of 0·06 grm. of the chromic acid salt be given subcutaneously, they can sometimes be kept alive for weeks with doses of 0·02 gmm., especially if the birds are left at rest for some days as soon as they become drowsy, and the injection is only repeated when they have somewhat recovered. I have thus kept a fowl alive five weeks, during which period 21 injections were made of 0·02 gmm. each of neutral chromate of potash. The later death takes place with comatose symptoms, so much the more typical are the organic changes to be described later on. The fowls always died whilst the secretion of urine was in progress. Mortar-like accumulations were found in the cloaca, which gave the characteristic murexide reaction, and in the ureters and urinary tubules uric acid in the form of the familiar urinary granules could be demonstrated in greater or lesser quantity. Whether the chromic acid salts act in any other way upon the accumulation of uric acid in the systems of the birds experimented on than by damaging the activity of the excreting organs of it, the kidneys, possibly through an increase taking place along with it, of the uric acid production, I am not at present able to say. The fowls emaciate rapidly with these injections, apparently more than corresponds to the diminished ingestion of food. Lessened appetite is noticeable tolerably early. At any rate, this can be determined, that in the domestic fowl, independent of the

poisonous action of the chromic acid salts upon the kidneys and the associated excretion of crystalline deposits of urates in these glands—by means of subcutaneous incorporation of small doses of neutral chromate of potash exactly similar changes are produced as after ligature of both ureters. The greater degree of pathological change in the fowls treated in the way described with chromate of potash appears to be only attributable to the longer duration of life in these than in those in which the ureters are ligatured. In particular I have seen the deposition of urates in the joints, even in the smaller ones as well as in the sheaths of tendons, appear in surprising quantities after administering chromic acid salts. After ligature of the ureters I only noticed this in the larger joints, and here only to a relatively smaller extent in comparison with the effect produced after the subcutaneous employment of chromic acid salts.

I have no need to linger longer on the description of the coarse anatomical condition revealed by my investigations. There is scarcely anything new to be added to the description already given by Galvani of the results of ligature of the ureters, and which have been complemented by Zalesky and others in some particulars. The essential point is that deposits of urates appear in varying quantities and in various tissues and organs of the animals operated on in one or other manner. On the other hand, more minute examination of the organs in which deposition of urates was found afforded results which were quite different from those of Zalesky. It is remarkable that Zalesky in his experiments could only find the deposits of urates in a crystalline form in the serous membranes. I observed that these, even where the individual crystals did not come out distinctly, partly on account of their thicker massing together, partly because apparently punctiform accumulations were also

present, everywhere refracted light doubly. I shall again return to this point. Besides this, however, in the parenchyma of the organs, as we shall soon see, the crystalline urates, in the more delicate development and arrangement, could be demonstrated without any trouble.

My special attention was first directed to the liver. As Meissner was able to demonstrate large quantities of uric acid in the normal liver of the fowl, the thought occurred whether in case of obstruction of the kidney secretion, the liver would be specially rich in uric acid. This proved to be in general correct, although Zalesky affirms that he had found uric acid only rarely in the liver, and then in the form of amorphous deposits. In my investigations the typical condition of the liver was almost constant, although it cannot be denied that in the various instances the intensity varied. This variation stands in direct relation to the abundance of the deposits elsewhere. These, and also those on the peritoneum and pericardium, were most strongly developed. The report of an especially characteristic liver deposit, may here find room in place of many. There reposed on the cut surface of an otherwise healthy looking fowl's liver, a number of sharply defined patches, in size from a grain of sand to a pin head and hempseed, and of a greyish white colour. In fine sections made through the organ hardened in absolute alcohol and coloured with aniline colouring matter, the patches at once became distinct through their paler tint. One was at the same time convinced that independent of the naked eye appearance, many far smaller patches, only visible by the aid of the microscope, were present. I have many times examined livers in which the patches only came to light on microscopic examination. It must also be remarked that in sections through fresh livers made with the double knife, the patches were readily observed. In the case now

described the patches were moreover, as is usually the case, not equally distributed through the liver. Frequently there were found in one preparation eight to ten such patches, more frequently one to two, and sometimes none at all. I have had such a patch delineated in Fig. 19.

FIG. 19.

In general these patches have a roundish, sometimes a more oval form, and they contain, what is at first an almost striking constituent, viz., a more or less massive patch composed of very delicate acicular crystals, arranged to some extent in clusters. These crystals do not always lie exactly in the centre of such patches, but they are generally in the centrally lying parts. These crystalline masses consist, as may be suspected from their appearance, of urates. For when these preparations are placed in luke-warm water, by acidulating this aqueous liver extract with a little hydrochloric acid, the very characteristic uric acid crystals detected in Fig. 20 are obtained, which, moreover, in order to remove all doubts, give the murexide reaction.

After all the crystalline deposits of urates are dissolved in the luke-warm water, in the parts in which they have lain the changes in the liver tissue come into view, which, moreover, are always more extensive than the crystalline deposits. I do not remember a single case in which the crystals of urates had occupied the whole of the patch. This changed liver tissue, in microscopical examination, was sharply marked off from the surrounding normal tissue. The whole patch, independent of the urates, appears to be composed of a completely or almost completely structureless mass, no longer marked off in

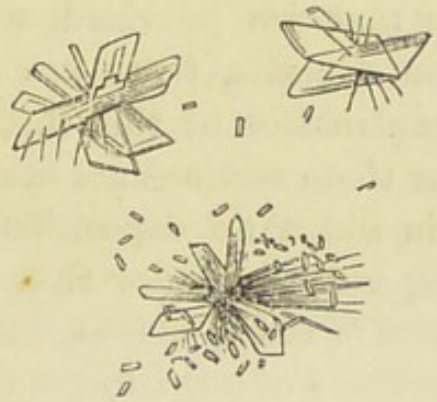

FIG. 0.

acini; of the typical liver tissue not a trace is to be found. Liver cells can no longer be traced in the spaces occupied by these patches. A great number of nuclei are seen in them, some slightly coloured, some not at all. In comparison with the normal nuclei of the liver of the fowl, these appear to be strikingly small. In addition to these nuclei a number of very dark coloured granules are observed scattered through the patches, which in size, in their whole appearance, and in their power of taking up colouring matter, have a certain resemblance to the nuclei granules of the normal liver cells, concerning which I may definitely say that they are really surviving nuclei granules. In the periphery of these patches consisting

of changed liver tissue and crystalline urates, in which, generally speaking, liver cells were no longer to be distinguished, small infiltrations (Fig. 19) were frequently met with. These always appeared as is shown in the figure, of limited extent and mainly in the parts nearest the larger patches. One also finds in the liver, patches without deposits of urates, in connection with which I expressly remark all sources of error were carefully avoided in the preparation, and which I have indicated in describing the gouty changes met with in the human kidney. I have, for example, such a preparation before me stained with gentian violet, in which, besides these patches in the liver that are provided with these most exquisite crystalline deposits, there are others without urates. For an explanation of this there are only two possibilities: either these sections are made through the patches described in which no depositions of urates are present, concerning which we know that they are confined to certain parts of them, or that they are patches in which the disturbance of nutrition of the parenchyma has not advanced to the stage necessary for crystallisation of the urates. Both possibilities may here be in force. For the last mentioned the fact speaks in particular that just in those parts of the patches in which the uratic deposits are visible, the disturbance of nutrition of tissue is farther advanced than in the periphery of the patches where these are absent. If also the demarcation of the patches from the normal surroundings is prompt and sharp, yet in the periphery of the patches more nuclei and granules are to be seen than in the central portions, where in the place of acini a poor structureless substance has made its appearance.

With whatever variety in regard to numbers, these patches develope in the liver of the animals experimented on, whether the ureters are ligatured or whether chromic

salts are introduced hypodermically in the way described. I have only failed to meet with the characteristic condition of the liver in a single case, and in place of it discovered another change which I shall briefly mention here as it may offer "coupling-on" points for future investigations.

It was the case of an apparently healthy bird, which was made use of for experiment, without being first fed a few days on barley. On May 21st, 1881, both ureters were ligatured at the cloaca. The whole course of the experiment had nothing peculiar about it. The bird died with comatose symptoms twenty-one hours after the operation, which was a medium length of time as usually observed in similar cases. At the section it was at once noticeable that the depositions of urates were relatively fewer on the peritoneum than on the pericardium. The cut surface of the liver presented a peculiar appearance, inasmuch, as upon it, very numerous shining, yellow, or brownish coloured points were visible, the size, at most, of a millet seed. In Fig. 21 I have had drawn a microscopic preparation from this liver. The organ was

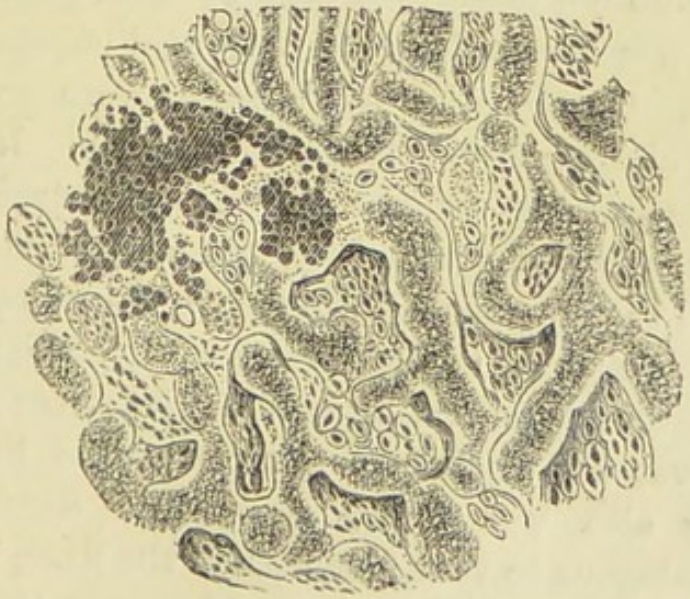

FIG. 21.

hardened in alcohol. The preparation figured here is not stained, and is preserved in Canada balsam. There are two things, in addition to the brownish mass, which I shall return to presently, that strike the eye: the very considerable dilatation of the vessels and the diminution of the parenchyma of the liver itself. As is known in the normal liver of fowls, the acini lie very close together. Here generally speaking they can no longer be distinguished normally. The liver substance consists of a yellow or brownish coloured, more or less, granular substance in which, only rarely, one or more usually very indistinct nuclei are seen. This pigmented protoplasmatic substance, the substitute for the normal parenchyma of the liver, is, as the figure shows, in many places more freely retained, in many much more sparingly, and in many parts distinct decomposition of it may be verified. The larger brown granules of darker colour, partly lying in the protoplasmatic mass, which is the substitute of the liver cells, but which for the most part are grouped into larger deposits, visible to the naked eye, do not become changed by digesting in lukewarm water, whether it is rendered alkaline, or slightly acidified by hydrochloric acid. They do not dissolve either by the employment of alkalies, nor crystallise into uric acid crystals after use of acids. On the other hand urates were contained in the liver, although not in a crystalline form. If a little hydrochloric acid was added to a watery extract made from such sections characteristic uric acid crystals were formed, and the aqueous solution gave the murexide reaction. This change in the liver, to which the name of parenchymatous degeneration must be given, was diffusely extended over the whole parenchyma of the liver. In the kidney also was found a peculiar degenerative process, analogous to that met with in the liver, but only in an insular form and in patches. Moreover, the process

was everywhere less advanced in the kidney, and without the brown shining masses visible to the naked eye described as being met with in the liver. These could only be demonstrated in the epithelium of the kidney of the parts affected in the form of small yellow or brownish granules and isolated.

The accumulation of urates in the liver closely touches upon the question whether the process here described stands in any causal relationship to the ligature of the ureters, and whether the disturbance of tissue change caused by it can, under certain circumstances, set up such a degeneration of the parenchyma. A second such case has never come under my notice in my investigations, and up to the present I have not sought to inquire, whether, and under what conditions, we are in a position to produce such a condition of things experimentally. I intend to pursue the subject further at the earliest opportunity.

Another organ to which I paid great attention in my investigations, was the heart. The deposits of urates visible to the naked eye, which were present in the myocardium, frequently in the form of nodules, some as large as a hemp seed, had already drawn my attention to it. Independent of these, by microscopic examination, many deposits of uric acid could still be demonstrated, which from the small size escaped being seen with the naked eye. If I now examined fine sections made through the heart with deposits of urates upon them, two things have struck me, first that they all refract light doubly, and second, that the accumulations thus shown to be crystalline, appear in far more compact and thicker masses, than the urates in the liver patches above described. The crystals which by transmitted light appeared as very delicate needles and points formed exceedingly thickly matted masses, so that nothing was to

be seen of the tissue lying beneath. Only on examination in polarised light was it seen that in the circumference of the uratic deposit a layer of tissue frequently appeared that did not refract light doubly. But if the urates were dissolved out in the way frequently described, matters took on a different face. Virchow has in connection with his investigation into guanin-gout of swine,

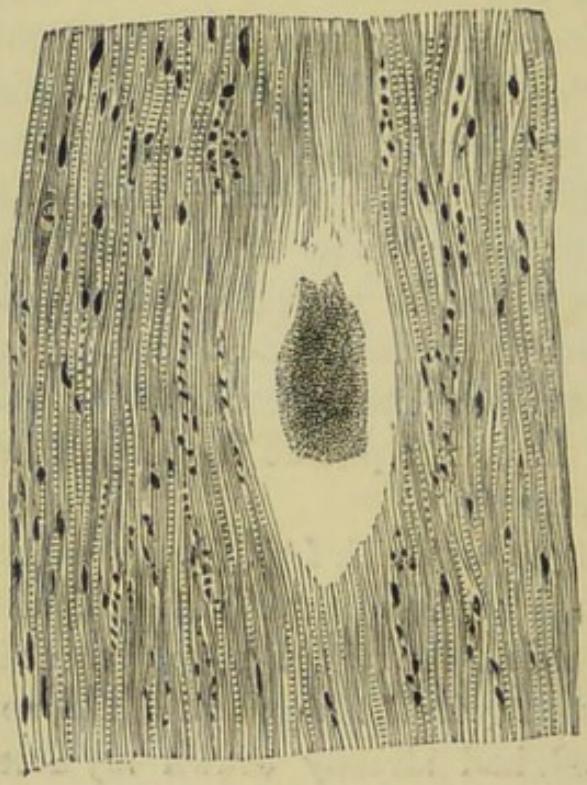

Fig. 22.

examined the muscular tissue after solution of the guanin. He found the muscular tissue *apparently* with unchanged fibres (Primitivbündeln). I will explain the results of my investigation into the changes that take place in the muscular structure of the heart of fowls in uric acid stasis by the aid of two illustrations, Figs. 22 and 23. Both show the increased deposits in the state of incomplete solution, Fig. 22 giving the appearance of a stained balsam preparation with a high power, and Fig. 23 the appearance in polarised light with a weaker power. In both figures

we see first the remnants of urates not dissolved. The uric acid deposits show in Fig. 22 almost everywhere a granular form, but refract light, as is shown in Fig. 23, doubly. In the same figure we see between the doubly refracting remnants of urates and the transversely striated muscular fibres of the myocardium, also doubly refracting, a long oval patch that refracts light singly and not doubly, and that with crossed Nikols looks dark, in the neighbourhood of which, even to the most outer lying border deposits of urates had been present as already remarked. In Fig. 22 we now see around the remnants of urates not dissolved a patch, also a long oval, in which nothing of striped muscular fibre nor of cells, nor nuclei, nor anything of normal structure is to be seen. Particularly at the upper zone of the patch it

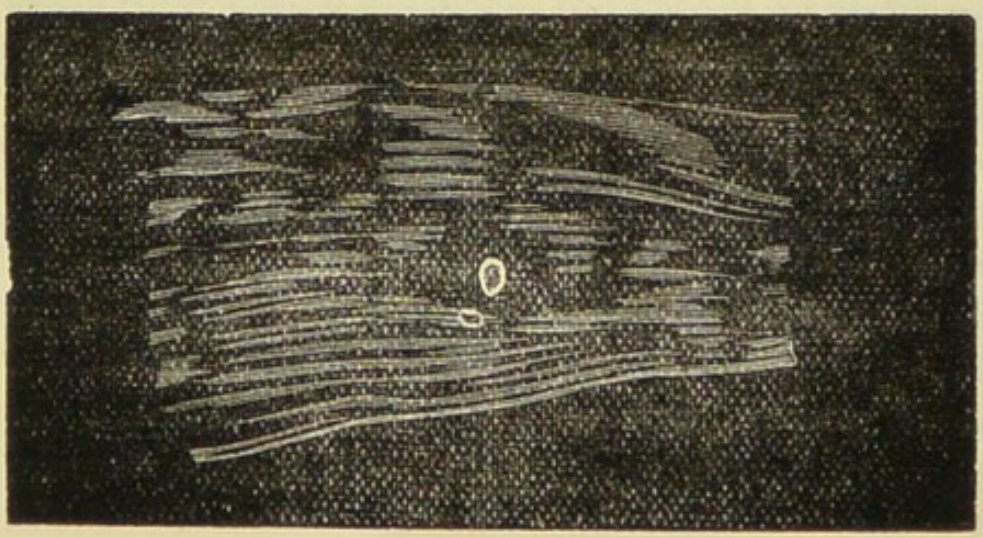

Fig. 23.

is to be observed that the disappearance of the normal structure and texture has taken place gradually, inasmuch as the transition of the normal tissue into the structureless mass can be followed step by step. In the vicinity of these patches in the myocardium we frequently observe small-celled infiltrations of varying extent.

After the changes described as taking place in the

iver and heart in the experiments spoken of, one may safely say that, in consequence of them, and resulting from the experiments—for in the liver of the healthy fowl, as well as in its myocardium, they are not present —morbid processes—disturbances of nutrition take place. On account of the destruction of normal tissue, the gradual accomplishment of which may be followed in the liver, for example; these changes must be designated as necrosing or necrotic. We have seen further that inflammatory processes in the form of small-celled infiltrations may be demonstrated in the surrounding parts. As regards the affections of the sinews and joints in the birds experimented on, I have studied these carefully, especially in one case, in which the deposition of urates n consequence of hypodermic administration of neutral chromate of potash has taken place very abundantly in these localities. The moderate depositions that generally allowed the transmission of light, and also doubly refracted it, I found developed here neither in the proper tissue of the tendons, nor in the cartilage tissue. They were deposited on the free surface of the cartilage in which I could find no further changes, and the same may be said of the tissue of the tendons. The deposits of urates in the tendons were found in the loose connective tissue between the primary and secondary bundles of fibres.

Without losing myself in further details which would not contribute anything material to the solution of the question in hand, I must still add some remarks on the behaviour of the kidneys, which will not, however, touch upon the sufficiently well-known appearances that are formed after ligature of the ureters. I will here only mention that patches as they were found and described in the liver, or in the heart, were never observed in the kidneys. On the other hand, exactly analogous processes

were presented when the secreting parenchyma of the kidney was injured by injection of neutral chromate of potash in the manner before described. These kidneys were distinguished by their remarkable and peculiar patchy clay colour. The changes here spoken of were observed in circumscribed patches of the cortex of the kidney, where in many places they were thick and extremely abundant, between which, still normal looking, or almost normal parenchyma was present. No fatty degeneration was seen in it. In the region of the chromic acid patches, the ordinary structure of the kidney which had never suffered in those cases in which the ureters were ligatured, was completely destroyed. In order to give the reader an idea of these patches, I had five of them drawn in Fig. 24 as they lie together within a narrow space, and in part touching each other.

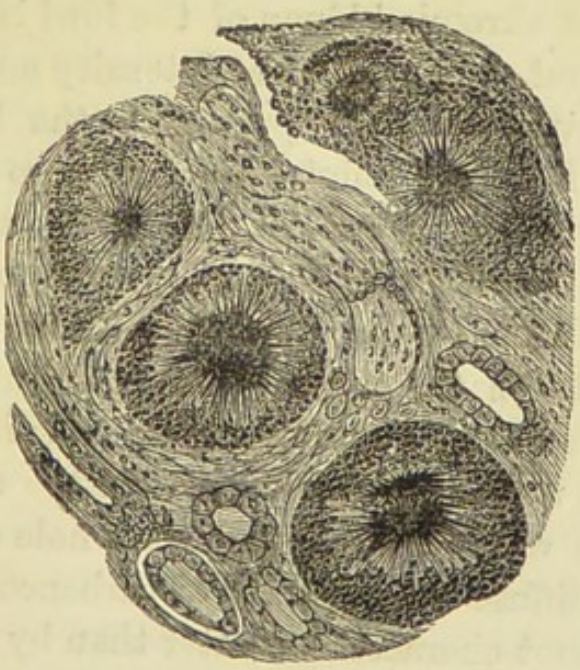

Fig. 24.

Each of these patches shows a more or less abundant deposition of crystalline urates, and in their immediate circumference a very thick small-celled growth, which is

in part sharply, and in part less sharply, defined from the surrounding parts, in which marked pathological changes cannot in any other way be verified. In those spots in which the uratic crystals are deposited, after solution of them exactly similar structureless patches can be demonstrated as have been described in the liver and heart of the fowl. In some places no more of the substance of the kidney was any longer present, than a homogeneous mass at most with some few stained or unstained nuclei. These uratic patches of the chromic kidney of the fowl I have never observed in the region of the Malpighian capsules, but only in the *tubuli contorti*. Very frequently the necrosing and necrosed patches—for the dead and dying parts lay close to and between each other—were of lesser extent than the zone of tissue affected in consequence of reactive inflammation which in the chromic kidney of the fowl is usually early brought about, and is of great intensity and extent.

I have never seen these patches in the kidney of the fowl when I have administered too large doses of the neutral chromate of potash. Such a fowl died in two days after two injections of the chromic acid salt of 0·06 gmms. each. Crystalline deposits of uric acid were found in it, on the peritoneum and pericardium, the ureters were empty and only in the *tubuli uriniferi* were the typical urinary granules met with. On the other hand, there was observed over the whole cortex of the kidney a diffuse wide-spread disturbance of nutrition, which I cannot characterise better than by the statement that the epithelium of the cortex of the kidney was changed in a manner exactly similar to those peripheral parts of the liver still free from deposition of urates, which I have already fully described. This diffuse necrosing process, brought about in this rapid manner, and the consequent injury to the epithelium of the

cortex of the kidney caused by the employment of relatively large doses of the chromic acid salt had sufficed to inhibit the kidney function rapidly, and to bring about the death of the bird from coma, and so far before degeneration of the kidney epithelium, *i.e.*, before its death was absolutely certain, that deposition of uric acid compounds could take place in the kidneys in the crystalline form.

If we now glance back at what has been said we find that the essential outcome of it all is the fact that I have succeeded *in producing by experiment in the domestic fowl, a process which considered anatomically must be looked upon as the equivalent of the arthritis uritica of the human subject as described in the second chapter*, and for this reason, that after ligature of the ureters, or after subcutaneous injection of chromic acid salts: 1. *Necrosing and necrotic processes develope in various organs.* 2. *That in these necrosed patches uric acid salts are deposited in a crystalline form, that in which they are met with of gout of the human subject;* and lastly, 3. *That in the parts surrounding these patches very frequently a re-active inflammation, often very intense, can be proved to exist in the form of a small-celled infiltration.*

That, moreover, the disturbance of nutrition brought about by the experiment in the tissues and organs of the fowls has reached a high degree of intensity, and has apparently led to complete necrosis of them, before the deposition of urates has taken place is evident from the following considerations:—

1. The crystalline deposits of urates increase in direct proportion to the advancing spread of the necrotic process in the tissues. They were never absent when the signs of necrosis of tissue had made their appearance. It was observed for instance in the patches in the liver, when the

parenchyma was in places not yet completely destroyed, the glandular tissue was only in part, strewn into crystalline deposits, and this in correspondence with the necrosed parts. On the other hand, in the myocardium of the fowl in the region of the crystalline deposit the normal structure was completely necrosed. In the narrow peripheral zone of the patches in the cardiac muscle where no crystalline deposit could yet be verified, the normal structure had not yet completely disappeared, and necrosis of tissue was not yet complete.

2. It was only in those fowls in which, in consequence of subcutaneous administration of chromic acid salts, very serious disturbances of nutrition had taken place in the kidneys, that the crystalline deposition of urate could be proved to exist in the kidneys themselves, in the typical form described, or frequently arranged in groups resembling glands. These must, as I have just explained, have suffered in every case to the highest degree, *i.e.*, to complete destruction of the tissue, before this could have taken place. The deposits of urates mentioned are present in the typical form in patches, and they are only deposited in those places when this extreme disturbance of nutrition has taken place, and are not diffusely spread over the whole secreting surface of the kidney. From this, that after ligature of the ureters in fowls, the kidneys remain free from such disturbances of nutrition, and that no such deposition of crystalline urates can be shown, a further conclusion may be drawn, viz., that the kidneys of fowls have a greater power of resistance than the liver and heart of these birds, in which organs we are in this manner able to produce the pathological processes named experimentally. It results, finally, from the deposition of the typical crystals of urates in the necrosed patches caused by chromic acid salts only, that the death of the tissue seems to be a *conditio sine quâ non* therefor. For

the urates to be deposited in the tissues in a crystalline form, a simple disturbance of nutrition is not enough, as this is set up in the kidneys by ligature of the ureters, but complete necrosis of the tissue is necessary. It seems to be quite immaterial whether this necrosis is the result of the action of chromic acid salts or of urates in a soluble form, or of any other poisonous agent.

CHAPTER IV.

The Action of Uric Acid and its Compounds, as well as of some Allied Chemical Substances on Animal Tissues and Organs.

To the facts adduced in the former chapter in favour of the poisonous qualities of the urates, and of the varied degrees of resistance to the poison of the various tissues and organs, further, more extended and complementary proofs are here added. Amongst others for instance, by the introduction of chemically pure uric acid and its soda compounds into the tissue of the cornea of rabbits, infiltrations were invariably produced. Experiments with urea, xanthin, guanin, kreatin, kreatinine, and hippuric acids ran their course as free from reaction as the control experiments made with a 5 per cent. solution of phosphate of soda.

That a causal relationship exists between the necrosing and necrotic processes, as well as the reactive inflammation associated with them, as we have learned to recognise them as typical processes in arthritis uritica of the human subject, and as the effect of experiments on animals, on the one side, and the regular accompaniment of gouty necrosis of tissue and the deposition of crystalline urates on the other, is *a priori* extremely probable.

I have already brought forward my views and the wherefore of them, that the gouty poison first permeates the tissues in a fluid form, damaging them more or less as the conditions present are more or less favourable, and that when the injury has reached the

highest point, and not till then, the uric acid compounds, which frequently form the sole constituents of gouty deposit, crystallise out in the necrosed tissues.

I have also already ventured the supposition that uric acid plays the greatest part in the occurrence of disturbances of nutrition in the tissues and organs, that it alone can produce them, and I have there made known my desire to bring forward proofs of this. This will now be the main object of the following inquiries.

As regards the disturbances of nutrition in the gouty organism, individual observers, such as Charcot, have already noted the disposition to sphacelus. In the following chapter I shall have the opportunity of more closely considering these serious eventualities that come and go in the course of gout, and which have not escaped the older observers. With the matters interesting us at the moment, these have absolutely nothing to do. Of the necrosing and necrosed patches in the organs afflicted with gout, in the sense in which they have been treated in these pages, there has been, as far as my knowledge of the literature of the subject reaches, generally speaking nothing hitherto said.

As regards the other forms of disturbance of nutrition in gout, the inflammations, it is an experience as old as the history of the disease that this remarkable affection is associated with inflammation, and since it has become known, through Wollaston, that the tophi arthritici of the joint consist of uric acid salts the conception has grown with time that these inflammatory processes develope in the neighbourhood of the uratic deposits. But whilst I attempt to fit these necrosing and necrotic processes into the pathology of gout as something general, as a regular occurrence in the various organs affected with gout, I will here at once remark that I consider all these things: gouty inflammations, necrosing and necrosed processes

as closely allied one to another, inasmuch as they originate in a common soil and are caused by one and the same *noxa*. But gangrene is often simply an outcome of the inflammation, and arises when, in consequence of the noxæ in question, the nutrition of the injured tissues is completely interrupted.

If uric acid be looked upon as the foundation of all these disturbances of nutrition we must make the attempt to prove it, for which purpose experiments on animals offer a favourable field. It is a matter of wonder to me, that in our times, rich in experiment, this has not been done. It appears as if the matter were held to be too self-evident although controversy has not been wanting even here.

Garrod finds it quite natural that urates as foreign bodies set up an ordinary inflammation. Rindfleisch says the infiltration of uric acid is plainly an important mechanico-chemical irritant to the parts affected, and Cornil and Ranvier write, in the 2nd edition of the well-known "Manuel D'Histologie Pathologique," "Les cartilages, sous l'influence de l'irritation determinée par la présence de l'urate de soude subissent des modifications, qui doivent être considerées comme de nature inflammatoire." They mean by this the processes of growth in gouty cartilage of which we spoke in the first chapter. For me it has been a thing to be questioned that these investigators have drawn attention to those appearances that are due to the irritating action of the urates that make their appearance in the parts surrounding them only, but not to the part that suffers the most injury from the deposits.

After Braun had already explained that excess of uric acid had no very deleterious action for the organism in general, making reference on the occasion to the experiments of Neubauer, in which rabbits that were fed with 12

grm. daily were apparently quite well; Cantani also has made known his opinion in opposition to that of the above-mentioned investigators against the poisonous action of uric acid. He says, "Excess of uric acid in the blood (actual urate of soda) does not indicate for us the *materia peccans* of gouty irritation, or that which irritates the joints. Neither is it the cause of the local symptoms nor the basis of the local deposition of soda." Up to the present none of these observers has produced proof of the accuracy of his views, neither Cantani for his attitude against the opinion that uric acid has an irritant action, nor the others in favour of it. The poisonous action of uric acid became still more problematical as still other voices were met with in literature more or less favourable to Cantani's ideas. Bartels assumed at once that an increased excretion of uric acid was *per se*, without injurious consequences to the organism affected. He considered that the excretion of uric acid could only produce injurious consequences by the formation of concretions from combination with the salts in the urinary passages. Heidenhain injected sufficiently concentrated solutions of urate of soda into the jugular veins of rabbits, and found that these were mostly deposited freely in all parts of the urinary tubules in the form of finely granular masses, sometimes pale and sometimes darkly coloured. In the cells themselves, which had without doubt excreted the salt, for the Malpighian capsules were completely free from urates, Heidenhain neither discovered any changes, nor is any anomalous condition of cells to be noticed in the accurately drawn illustrations of the changes said to have taken place. Some years ago I caused Dr. Damsch, first assistant at my clinic, to repeat Heidenhain's experiments with regard to the influence of uric acid on the secreting parenchyma of the kidney. These results have

not been published; Herr Damsch has, at my request, shortly grouped them together as follows:—If weakly alkaline solutions of urate of soda are injected into the jugular vein of rabbits it is found fifteen to twenty minutes after the injection partly in the kidneys, and indeed visible to the naked eye in direct light as most delicate white streaks parallel to the course of the urinary tubules, especially in the medullary substance, and partly in the cortical substance, in part in the tubuli recti, and in part in the tubuli contorti.

By microscopical examination the white streaks are seen to consist mainly of amorphous, crumbly masses, looking black in direct light, and lying within the canals. A portion of these streaks is arranged in rows of spherical forms, more or less filling up the lumen of the canals, having a central nucleus, with slight radial markings and strongly refracting light. The glomeruli are always free from this excretion. The epithelial lining of the tubules appears flattened at the place where the cylindrical formations lie, the lumen of the tubules is occasionally dilated, even above the occluding masses. The addition of weak alkaline solutions dissolves these concretions, and after the addition of acids typical forms of uric acid crystals make their appearance in the shape of rhombic plates. If the action of the added alkali is observed under the microscope one becomes convinced that in the situation of the sphæro-crystals *the cellular elements remain with distinct membrane* with nucleus and nucleolus. In the situation of the cylindrical formations, composed of amorphous masses, one finds after solution of the urates a delicate granular substance in which regular round nuclei are imbedded, closely pressed together, and only individual cells are seen to be retained.

If the deposits are dissolved by maceration in water of

30-35 deg. C., and then coloured with Bismarck brown, the cylindrical formations come out distinctly from the intense colouration of their nuclei. These nuclei are smaller than the nuclei of the kidney epithelium and are similar in size and appearance to white blood corpuscles. In isolated spots between the epithelial layers of the urinary tubules exactly analogous strongly tinged nuclei are seen (white blood corpuscles ?).

These experiments teach us that, independent of the excretion of the uric acid compounds administered to rabbits by injection into the jugular vein, by the epithelium of the kidneys, as has been taught by Heidenhain, certain changes take place in the kidneys which are to be looked upon as co-effects of these injections. The uric acid compounds, excreted into the urinary tubules, which, as Meissner has already accurately described, in part completely resemble the urea granules of birds, at one time incrustate a well characterised cell, at another as apparently amorphous masses, a finely granular protoplasmic substance strewn with nuclei. In any case it results in so much that these experiments *produce changes in the parenchyma of the kidneys of rabbits which stand in a causal relationship to the incorporation of alkaline uric acid solutions.* These changes are reparable, for in the case of animals that were killed fourteen days after the experiment residua of them could no longer be traced in the structure of the kidney.

As regards my own experiments on the action of uric acid on the animal organs and tissues, which I will now briefly sketch. Those experiences first of all which the experiments discussed in the previous chapter yielded, were extremely favourable for the conception—1. That uric acid is a substance exceedingly harmful to the nutrition of the tissues of the animals experimented on; and 2. That all organs do not re-act equally readily to uric

acid, *i.e.*, are equally injured by it. The proofs of the correctness of these views are produced without difficulty. Notwithstanding uric acid was always present in the kidneys of fowls, the ureters of which had been ligatured, and it may be said, in large quantities, necrosed patches with acicular deposit could not be demonstrated in them, although they were proved to be present most distinctly in the liver, and still more extensively in the heart. I cannot, indeed, give a more plausible and unobjectionabe explanation of this than that the kidneys of fowls offer greater resistance to the action of uric acid salts than the before mentioned organs.

The experiment with chromic acid salts showed that the kidney substance also loses its power of resistance as soon as the subcutaneous administration of this poison has seriously damaged its nutrition. But one could still raise the objection against all these experiments and their significance that if, as is proved in birds, uric acid forms the principal nitrogenous excretion, yet other constituents are present in the urine that injure the nutrition of the tissues. It could be said, moreover, that in the organism of the bird, whether injured by ligature of the ureters or by the injection of chromic acid salts, still other pathological conditions might be in action, giving rise to inflammatory and necrosing processes.

A method of check was therefore necessary. One had to ascertain whether chemically pure uric acid and its combinations with soda, so far as these relate to the subject, possessed toxic properties as regarded animal tissues.

The following experiments were instituted for this purpose:—The uric acid was in part put into water and shaken up, and partly dissolved by the aid of heat up to the saturation point in a five per cent. solution of phosphate of soda, and, after cooling, filtered. The latter

solutions were neutral or very slightly acid. The reaction had no influence on the results. All the experiments were made with sterilised solutions under antiseptic precautions. Injections were now made into rabbits with such fluids, principally with the last-named uric acid phosphate of soda solution, into the peritoneal cavity, the anterior chamber of the eye, parenchymatous injection into the kidneys, the cartilage of the ear, and finally into the cornea. As regards the last-mentioned attempt, it made as little noticeable appearance of irritation as magnesia usta, which was made use of in the other eye for a control experiment. Just as little was any morbid condition demonstrable in the peritoneal cavity of a rabbit killed three months after injection of uric acid into it. Uric acid in suspension injected into the anterior chamber of the eye disappeared slowly within two weeks, but without leaving any inflammatory appearances visible to the eye. In the place where the uric acid lay, however, a clouding had remained in the lower part of the cornea. Parenchymatous injections into the cartilage of the ear gave rise to circumscribed hyperæmic spots, which remained for some days and then disappeared, leaving no trace. Parenchymatous injections into the kidney, made in such a way that the fluid injected made its way into the kidney, partly by percutaneous injection and partly by laying bare the kidney, resulted, when the animal was killed forty-five days afterwards, in small-celled infiltration of the kidney, extending far beyond the canal track of the puncture. These experiments were only performed in a few cases, as injection into the parenchyma of the cornea afforded a field for experiment in which the action of uric acid could be easily and unambiguously determined. If some of the uric acid phosphate of soda solution mentioned above be injected by means of a fine needle into the cornea, a greyish-white

cloudiness first arises, which, after some hours, so far clears up that it can only be recognised as a slight clouding by an accurately-focussed light. This initial effect is also obtained by injections of sterilised solutions of five per cent. solution of phosphate of soda. In the meantime, the clouding that thus arises disappears in from one to two hours, and none of those changes take place afterwards that are constantly observed to take place when uric acid phosphate of soda is injected into the cornea. With the latter the initial cloudiness that arises does not quite disappear. One hour after the injections still no histological changes are recognisable in the tissue of the cornea. If the development of the process is observed later, the slight cloudiness that remains after the retreat of the initial grey-white opacity increases in intensity in the course of the next few days. In the part corresponding to the initial opacity—*i.e.*, in that to which the fluid has penetrated—milk-white cloudings are developed. A breath-like cloudiness of the corneal tissue that appears in the circumference of these, again, disappears in the course of a week, but the milky cloudings remain. If the milky cloudings of the cornea are now examined microscopically, it will be seen that they are infiltrations of it. Such an investigation made two days after the injection of the uric acid phosphate of soda shows with fine sections of the cornea, of which Fig. 25 is a representation with a low power, patchy accumulation of round cells in the substance of the cornea. In the further circumference of these patches, also, disseminated round cells were found, and in large quantities in the tissue of the cornea. Neither crystalline deposits of urates nor necrosed patches were observed in these spots. If the infiltration of the cornea was now followed in its further course, in the spot where this had established itself a change was seen to take place in the course of the

next few weeks which had the characteristics of a leucoma in an ophthalmological sense, and which, on microscopical examination, showed accordingly that it was composed of cicatricial tissue.

If a suspension mixture of uric acid was injected into the corneal tissue, the effect was almost exactly similar to that described. Only in one case did there take place about one week afterwards a crater-like loss of substance of a pure white appearance, which later on became covered again with epithelium, whilst a depression remained at the spot implicated. That in this case the effect was not due to the particles of uric acid suspended in the water was shown by the control experiments made with *magnesia usta.* Already after a few hours a consi-

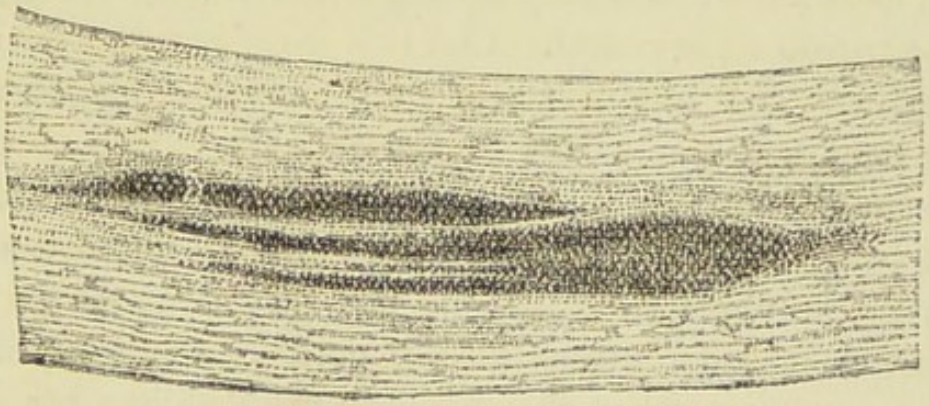

Fig. 25.

derable clearing showed in the place where the magnesia was deposited, and scarcely twenty-four hours afterwards, generally speaking, there was neither any trace of it to be discovered, nor any inflammatory changes to be verified.

These experiments prove *that chemically pure uric acid and its solution in phosphate of soda have an influence* on certain tissues *in a high degree injurious to their nutrition,* which can be most easily and conveniently followed in the cornea. The course of the keratitic process leaves

no room for doubt that it could not have been due to the influence of septic matter; this is also shown without the slightest ambiguity by the simultaneous control injection in the other eye with the same syringe of the solution of phosphate of soda or of the mixture with magnesia in suspension. If I now add to this that parenchymatous injections with a two-per cent. solution of urea into the cornea of rabbits were absolutely without irritation, the conclusion does not admit of doubt *that uric acid has an especial irritant action on the tissue of the cornea of rabbits.*

I have now made similar experiments on the cornea of rabbits with a series of other products of metamorphosis, xanthine, guanine, kreatine, and hippuric acid. The two first, as is known, are very closely allied in their chemical constitution to uric acid. But the experiments were all negative. The hippuric acid only caused a cloudiness that remained some days in the neighbourhood of the puncture. This was not present, however, when the *acid* two-per cent. solution of hippuric acid, which was warmed previous to injection, was first neutralised by soda. All these solutions, after injection into the corneal tissue, cause no other changes than take place after the injection of a five-per cent. solution of phosphate of soda, the effect of which has been described above. The solution of kreatine was neutral, whilst in the case of the kreatinine, xanthine, guanine, the solution made use of was alkaline. Hypoxanthine was, unfortunately, not at my command.

CHAPTER V.

Gout of the Human Subject from a Clinical Point of View.

1. Various divisions of the group of gouty symptoms. Own division into *primary articular* and *primary renal gout. Local and general uric acid stasis.* Primary articular gout by far the most frequent form. With this, even when it reaches a high degree, the kidneys may remain sound to the end of life. In any case, the kidneys become affected much later than the joints. Attempt to explain the genesis of articular gout by the formation of uric acid in the muscles and marrow of bones. *The typical attack of primary articular gout*, an aseptic inflammation. Localisation of it; what assists its development. Why the urates only crystallise out in the necrosed parts. Gouty inflammations and changes in organs in consequence of primary articular gout. Significance of the secondary kidney affection for the occurrence of a generalised uric acid stasis. Relations of calculus and of rheumatic and other articular inflammation to gout. *Ætiology of primary articular gout.* The recognised perverse formation of uric acid in the muscles and marrow of bones is in the majority of cases a congenital and lifelong anomaly of tissue change. Predisposing factors. Inheritance of the gouty disposition, Relations of gout to diabetes mellitus. Course, prognosis, diagnosis, and treatment of primary articular gout.

2. Primary renal gout—*i.e.*, those cases of gout in which the kidneys are primarily affected, and in which the other

organs are only secondarily affected, and usually to a lesser extent or not at all. Arthritis uritica as a condition consequent on nephritis. Relation of lead disease to primary renal gout. Primary renal gout is much rarer and much more dangerous than primary articular gout. Diagnosis and treatment of primary renal gout.

As I now enter upon the clinical questions affecting gout on the basis of the discussions contained in the foregoing chapters, we shall have the opportunity of proving in how far the views advanced clear up the numerous dark points in the question of gout of the human subject. I hope that these investigations will contribute to illuminate much that is problematical in the complicated symptomatology of gout.

Especially since Musgrave drew attention to the multiplicity of, and the Protean changes in, the forms of gout and established various kinds of anomalous gout, many classifications of the symptoms of gout have been attempted. It would be of no value to discuss them all in this place.

Garrod mentions the newer divisions of Cullen, Mason Good, and Hamilton. He himself, however, not contented with these, made a new classification of the gouty symptoms, which the majority of writers at present follow.

He arranges these under two principal forms—1. Regular Gout; and 2. Irregular Gout.

Regular gout, which may be acute or chronic, consists principally in a specific inflammation in or around one or more joints.

Garrod designates those forms as irregular in which serious disturbances of function or inflammations of tissue are observed which are not associated with the joints. They should, therefore, embrace those forms which have been designated as atonic, anomalously loca-

lised, recedent, insidious gout, or as extra-articular gout, &c. Whilst on the basis of my observations, I do not accept the dictum of Garrod that gouty inflammation is always accompanied by deposition of urate of soda in the inflamed parts, I accept Garrod's conception of irregular gout. The deposition of crystalline urates only takes place after the uric acid has destroyed the tissues; if it injures them to a lesser extent, if, for example, it only sets up inflammations of them, then the uric acid combinations, for reasons to be discussed later on, do not crystallise out in the tissues and organs. But these processes are also gouty, *i.e.*, they are caused by uric acid. Both are perfectly regular processes in the course of gout. They find their explanation in the above-explained mode of action of the gouty poison—*uric acid.*

Garrod's classification into regular and irregular gout acts far more confusingly than explainingly for the understanding of the subject; neither has it any significance practically after it has once become clear that the various organs may be damaged in varying extent and intensity by uric acid. On the contrary, I believe that we shall most easily understand the clinical history of gout, its ætiological and pathological relations, the varying course, the things relating to the grouping and sequence of symptoms, and the termination of the disease when we accept *two principal types* in gout, viz., 1. *Primary articular gout*, and 2. *Primary renal gout.* It is common to both that they may be complicated with gouty diseases of various other organs. The first is by far the most frequent form. It affects by preference, but not exclusively, the well-to-do classes of the population. The second form, primary renal gout, is much less frequent. It threatens life much earlier than the first by the disturbances of the renal functions, which are present from the outset, and by the unavoidable conditions

consequent upon these. Here belongs that first gouty symptom in serious kidney disease, especially in inflammations of the kidneys—*nephritis uritica.* The first category of patients, those who suffer from primary articular gout may die without the kidneys being found diseased, the second category often succumb to the gouty process, without the cartilage or any other organ than the kidney being affected.

This classification of gouty diseases has never been distinctly drawn, although, after what Dr. W. H. Dickinson has sketched out in short sharp lines on the basis of his own observation, it lies open to the view. In respect to this Dickinson speaks as follows: –

"The gouty affection of the kidneys may run its course without any other signs of gout.

"The gouty affections of the joints and those of the kidneys are associated as both arising from a common cause.

" When the disease attacks the joints we have the usual symptoms of gout; when the kidneys, the characteristic granular degeneration.

" It appears that in those cases in which the gouty affection is caused by alcoholic drink it attacks the joints by preference, but in those in which it can be traced to lead poisoning, it specially attacks the kidneys.

" The rich man rejoices in a long life with the gout in his extremities; the handicraftsman succumbs to the like disease of the kidneys before his joints are affected."

Before I proceed to a more accurate description of these two forms of gout, I will make a few preliminary remarks respecting the etiology of them. In both forms equally when it developes primarily in the joint or in the kidney, that which sets up the disease process, the essentially active poison is uric acid.

But when uric acid injures the nutrition of the tissues,

an accumulation of it must be present, if it cannot be accepted that the organs of the same individual are variously resistent at various times to an equal quantity of urates. A certain small quantity of uric acid compounds may circulate in our tissues and organs without injury to them, for uric acid is a product of normal tissue change, which, fabricated in adequate quantity and excreted by the kidneys, as far as we know, never, either at the place of its origin or in the organs for its excretion, produces symptoms that have any practical interest for the pathologist.

Bartels has indeed taken pains to prove that increased excretion of uric acid, the amount of which, as is known, varies in a state of health within certain not very wide limits, is *per se* without injurious consequences to the system. Whether this can be borne for any lengthened period without injury I shall not now discuss. In any case, gout does not arise in consequence of increased excretion of uric acid. All observers appear to be at one in this *that the accumulation and stasis of uric acid in the system, in consequence of insufficient excretion of it, is a conditio sine qua non of gout.* Whether the uric acid is at the same time formed in too great a quantity is a question on which up to the present there is no unanimity among investigators. Now one may acknowledge that here, as in other forms of stasis, the stasis may not only be general but local. The general stasis will take place when the excretory organs, the kidneys, act imperfectly, whilst the local stasis of uric acid will take place when the passage of the acid from the places of its formation, of which it must be assumed that there are many, into the fluids of the system, is disturbed, or when some hindrance is present to the movement of the juices containing uric acid. It is thus plain that local stases of uric acid may not only take place in various localities, but from various causes.

In the *first* case, *i.e.*, in that of *general uric acid accumulation, the kidney disease is primary, the accumulation of uric acid in the fluids and tissues secondary.* This manifests itself first in the kidneys, and not unfrequently death takes place in consequence of serious disease of the kidneys, before the consequences of general stasis of uric acid are otherwise manifest. In the *second* case, with localised accumulation of uric acid, the kidneys often remain healthy for a long time, sometimes permanently. The consequences of accumulation of uric acid are, for certain reasons to be inquired into, first made manifest in certain tissues. The typical representative of this form of gout, its most frequent mode of appearance, is *primary articular gout*, which will be first considered.

I.—Primary Articular Gout.

Pathogenesis, Symptoms, Consequences, and Complications.

Until a short time ago, it was generally accepted, and particularly on the authority of Garrod, that even in the milder form of gout, and in the earlier stages of it, the kidneys were seriously implicated. Garrod believed that the onset of an attack of gout might be determined by the sudden cessation of the excretory power of the kidney. Such a one could be developed in consequence of traumatisms, and even of mental disturbances. Garrod's statements, that should prove the diminution of the excreting power of the kidney, are not in a position to do this. He found that during an attack of gout the daily excretion of uric acid was not necessarily increased, but was often markedly diminished, but that the quantity of uric acid excreted on various days was very changeable. The maximum he met with was 0·48 grm., the mean of all his examinations was 0·21 grm. *pro die.* Unfortunately all these investigations relate to hospital patients only. I know of no observations in which the urine of members

of the higher classes was examined during attacks of acute gout. Bartel's statements also relate to one infirm individual, the subject of gout, in whom, during the attacks, the excretion of uric acid was diminished to mere traces. In the case of chronic gout also Garrod found the quantity of uric acid much diminished, at various times very varyingly. Bartel once found 0·225 grm. per day in a patient in the chronic stage of gout. In weighing these facts it is to be borne in mind (1) that Neubauer affirms that in the normal condition the quantity of uric acid– which, like the quantity of urea, depends less on the food taken, than directly on the internal condition of the system—may vary very much, and may oscillate between 0·2 and 1 grm. in the twenty-four hours, as well as further, (2) that the local accumulation also, or, just as well, the diminished excretion, of the uric acid can be explained by the kidneys.

Senator has expressed himself reservedly in regard to the participation of the kidneys in gout. He concedes indeed, that the kidneys in the course of gout, and especially in the atypical chronic form of it, are usually diseased. On the other hand, he says decisively that at the commencement, and when the first typical attacks come on, this is only exceptionally the case. I believe that in primary articular gout the kidneys are only constantly implicated after a longer or shorter period, and that there are cases of primary articular gout, in which the kidneys generally speaking do not become diseased even up to the death of the patient, whilst the joints and also other organs are found affected by the gouty process. On the other side, in the case of primary kidney gout we shall see that, notwithstanding complete freedom from the disease of all the joints, advanced gouty changes are present in the kidney only. I will only relate two such observations of serious articular gout, in which the kid-

neys were found to be thoroughly free from anatomical changes.

The first was the much quoted case of Fauconneau-Dufresne, related by Cruveilhier. It was that of a captain, fifty years of age, who had suffered from attacks of gout, which constantly increased in severity for ten years. During such a particularly violent attack the patient was admitted into the Charité, in Paris, in the beginning of June, 1824. He had diarrhœa, thirst, fever, and was emaciated. With appropriate treatment the pains and fever disappeared; the diarrhœa continued. Soon afterwards the patient died with returning fever and vomiting. The autopsy showed, besides advanced gouty changes in the joints, bones, muscles, cartilages of the ears, a series of extensive ulcers in the descending colon, which increased considerably towards the anus.

The second case to be referred to is one of Bramson's. It was that of a labourer, fifty-five years of age, who had suffered from arthritic troubles for twenty years. The patient was also the subject of phthisis pulmonalis, from which he died. Here, also, although the gouty deposits were very extensive, and extended to the tendons, and even to so-called ossifications of the aorta, the urinary organs were quite normal. This case further shows that this form of gout is not the exclusive privilege of the rich. I will remark further, that the number of cases in which the kidneys remain unaffected till death cannot be very large. This can only be reckoned on when death takes place in a gouty patient in consequence of some complicating affection, and thus before the kidneys have become implicated in the gouty process. We shall have to return to the fact that after a longer or shorter time, even in that form of gout commencing with disease of the cartilage, the kidneys are usually affected.

If we are now compelled to concede, that there are reliable observations by which it is shown that advanced gouty, and especially arthritic, changes may exist, without development of disease in the parenchyma of the kidneys, even after the lapse of ten or twenty years, and if we further confess that an accumulation of uric acid is a *conditio sine qua non* for the development of those gouty affections, which in such cases cannot possibly be referred to disturbances of the function of the kidney, it then becomes certain, in order to comprehend rightly the changes of articular gout that scarcely anything else remains than to refer them to local accumulations of uric acid.

Independent of various other possibilities, those organs might be charged with being the points of origin of such local accumulations, to which the formation of uric acid is mainly attributed, thus the liver, the spleen, and even the nerve substance, and perhaps quite a number of other organs. Pathologico-anatomical examinations respecting gouty diseases of the liver, spleen, and nerve substance have, however, resulted in relatively very little profit. We shall learn later that in the rare cases where one or another of the organs mentioned undergoes demonstrable material change during the gouty process, this takes place in the earlier stages of the affection.

Although there are properly few organs that have not been associated with the origin of gout, the liver at present interests us, especially in this connection, as it is to this that Charcot has recently ascribed an eminent part. This distinguished investigator has taken pains to bring gout into association *with functional disturbances of this gland.*

He represents that in consequence of a disturbance of the function of the liver the uric acid is formed in excess in that gland and accumulates in the blood. That when

the blood is saturated with uric acid from the liver this contributes to the attack of gout. In the meantime, if, according to the clinical symptoms, we have a certain basis for assuming that hepatic disturbances are closely associated with the formation of uric acid, it is not by any means said that the increased formation of uric acid on the part of the liver is a proved—let alone the only—connecting link between gout and the morbid symptoms present along with it.

Although I decline to enter on a detailed account of the various hypotheses that have been put forward on the nature and causes of gout, I will say a few words in reference to those organs to which—as the liver—a greater or lesser participitation has been ascribed in the formation of uric acid.

It has long been questionable with me, and at any rate it is not at all necessary, that all the organs that serve in the formation of uric acid play an active part. In my opinion the uric acid formed in normal or increased quantity in the usual uric acid forming organs may all pass off in the urine, and yet, notwithstanding this, gout may develope, inasmuch as uric acid is formed in an organ in which it is not formed under ordinary circumstances. Of this I shall speak later on. Let us linger a moment on the spleen, to which a certain participation in the formation of uric acid is assigned by eminent investigators. It has never yet been found that this organ has ever been in any sensible way implicated in gout. That increased formation of uric acid *per se* is without any influence on the origination of gout is shown by leucæmia. A combination of the two has never yet been observed, although the fact that the formation of uric acid is really increased in leucæmia cannot be doubted. It is still matter of dispute to what causes the increased formation of uric acid in leucæmia

is to be assigned. In any case we must come to the thought that there is a morbidly increased formation of uric acid without retention of it, whilst we have retention of uric acid, thus in the case of gout, where it is still disputable whether the uric acid is at all formed in increased quantities. If then we assume, in the case of gout in general, no generalised stasis of uric acid in consequence of kidney disease—such indeed is only possible for a certain proportion of the cases—but if we turn whither the facts, at least in the early stages of articular joint compel us, to localised stasis of uric acid, we must, and there remains scarcely any other plausible supposition, seek the causes of gout in the place where the uric acid is formed.

My idea of the cause of the by far most frequent form of gout, primary articular gout, is to the effect that this is to be sought *in the affected extremities themselves*, and in fact *in the muscles and bones*. Clinical and anatomical observations and a series of chemical observations appear to me to speak in favour of this view. The interpretation of the symptoms is effected in this manner with the least amount of forcing.

Clinically, the feeling of weakness, the painful dragging of the limbs, the striking muscular weakness during the attacks, the cramps of the calves of the legs, which often precede the attacks, are well known clinical symptoms, that were specially valued by the earlier observers. The muscular cramps do not limit themselves to the calves of the legs. I observed a gouty patient, sixty-two years of age, from the cartilage of whose ear I succeeded in obtaining the characteristic deposits of urates, in whom before the proper attacks of articular gout the most tormenting cramps of the whole of the muscles of the lower extremities came on, which were in his case far more painful than the attacks of the gouty arthritic affection itself.

As regards the facts of chemistry that may be adduced in favour of the participation of the muscles and bones in the gouty process, we know as far as the muscles are concerned that the number of the known nitrogenised products of tissue-change which are constantly present in the muscles of the mammals is limited to kreatin, which is met with in every kind of flesh and to certain xanthinoid bodies. The xanthinoid bodies are in any case amongst the most prominent of the products of tissue change that are observed in the muscle fluids of the mammalia.

To this group belong, as is already known, *hypoxanthin*, or *sarkin*, *xanthin*, and *uric acid*, to which is to be added as a member apparently less frequently met with, *guanin*. Perhaps to these some other hitherto less known bodies belong. The formulæ of hypoxanthin and xanthin differ from that of uric acid only in that sarkin contains O, xanthin O_2, and uric acid O_3. Guanin can be procured from xanthin by the substitution of O for N H. It is scarcely to be doubted that a genetic connection exists between these xanthoid bodies, so that by continued oxydation hypoxanthin may become xanthin, and this again uric acid. Notwithstanding this, up to the present, none of the xanthoid bodies have been demonstrated in normal muscular tissue by Strecker, Scherer, and Städeler, except hypoxanthin and xanthin. As regards the occurrence of uric acid in the normal muscular tissue of mammals, this, as Meissner has taught, has never been demonstrated, and since the publication of his *grundlegenden* work no observation has appeared that in any way alters matters. The opposing statements of several manuals may, as we shall quickly see, be otherwise explained. Once only has it happened to Meissner to demonstrate exceedingly small quantities of uric acid in the muscles of a fowl fed with beef. On

the other hand, we know decisively that uric acid occurs in diseased muscle. As was stated above, uric acid was demonstrated by Carius and Liebig in the muscles of an alligator. We possess unfortunately so far no chemical examinations of the muscles in gout of the human subject. Such examinations are a great desideratum, and will be made on the first opportunity, which is here, however, not a very frequent occurrence. In the meantime much has been gained in knowing through Neukomm that *uric acid is present in human muscle* in other diseases. Neukomm found *uric acid* in the muscular tissue of the pectoralis and serratus anticus of a girl, æt. 19, who died of typhus, and a remarkable quantity of kreatinin, together with some kreatin; urea and leucin were not demonstrable; from the heart of a female who died of syphilitic cachexia he was able to obtain kreatin, urea, *uric acid*, and xanthin in smaller quantity.

As regards the condition of bone in gout, Bramson in agreement with Marchand found in the apparently healthy bone of a gouty individual (who in addition to this suffered from pulmonary phthisis) in comparison with the bones of a healthy individual a diminution of the earthy phosphates and carbonates. With this fact only verified in two cases, which Bramson seeks to explain by supposing that with the increase of lactic acid in arthritic individuals these earths are carried out of the system by the urine, not much is obtained for our purpose. Moreover, it stands opposed to the investigations of Stokvis on the relations of the urinary phosphates. This observer found in a case of gout that the phosphoric acid in combination with earths was much diminished in comparison with the other phosphoric acids, not only during the gouty attacks, but also in the intervals between them.

The marrow of bones interests us far more on account

of its analogy to the spleen. In the meantime, from the few chemical examinations that are before us we only get the result, that not only, as Salkowski has already shown, hypoxanthin and formic acid together with a higher fatty acid, probably butyric, are present in aqueous extracts of bones in leucæmia, but that also in normal marrow hypoxanthin can be proved to be present as is shown by the investigations of P. Heymann. Whether uric acid occurs in marrow there are no investigations to show as far as my observation reaches. *Can hypoxanthin or xanthin be converted into uric acid in the system?*

Herr Jaffé of Königsberg related to me on the occasion of a conversation on these questions an unpublished experiment performed for the purpose of ascertaining whether sarkin could be converted into uric acid in the animal body. This investigator fed a dog with 0·3 grm. of sarkin which he found again in the urine mostly as such. The uric acid was apparently not increased; a quantitative analysis was, however, not made. Whatever these experiments may yet result in, the negative result obtained will not shake the possibility that sarkin and xanthin may become converted in the system into uric acid, as there may well be certain conditions under which this change may be accomplished. That this cannot be accomplished experimentally by introducing the material into the stomach does not allow the conclusion that this change does not take place in the system.

As regards the muscles especially, as it has been proved that uric acid is really present in diseased human muscle we are on more level ground. It will be our problem now to offer proof that uric acid is present in the muscles in gout of the human subject. If it is allowed to draw conclusions from analogies it appears to be not improbable that when the chemical conditions of marrow are rendered more clear by more frequent examinations uric

acid will be proved to be present along with hypoxanthin, as in muscle. I hold this not simply as a *pium desiderium* that has had its origin in the occasion and in the interest of my hypothesis as to the pathogenesis of gout, but as an almost necessary postulate. For if marrow is to be ranged histologically and functionally by the side of the spleen, about which no one is in doubt, then one should *à priori* be permitted to count on the possibility that the marrow of bones also belongs to the uric acid forming organs.

Whilst according to the foregoing I am inclined to claim for muscular tissue and bone or bone marrow an essential participation in the development of primary articular gout, I deny any active participation to connective tissue which has been placed in the foreground by some authors. I first mention here as the most distinguished and decided of the representatives of this theory Cantani. Amongst the tissues that produce uric acid in gout he places cartilage and the peri-articular tissues (ligaments, tendons, &c.) in the front rank. Senator also appears inclined to the view that at least a part of the uric acid is formed in the cartilaginous tissue; he speaks as follows: "That in cases of gout the depositions take place first and by preference in the cartilaginous tissue and thus in the non-vascular parts, and in the joints lying farthest towards the periphery is to be explained by the fact that at least a portion of the uric acid is most likely formed in the tissues and then conveyed into the lymph; then also perhaps for the reason that this has a lower solvent power than the sanguineous fluid."

I believe, and I have already mentioned the subject, that in the cartilage itself and in the connective tissue no uric acid at all is formed. I look upon *cartilaginous tissue as well as the other connective substances as*

solely or almost solely conducting tracts for the fluids, but not as independent workshops for animal tissue change, and I agree perfectly with Bartels, who says that in the cartilaginous and fibrous tissues only the conditions for the separation of uric acid from the nutrient fluids are particularly favourable. I do not believe that tissues with such little change of fluids are entrusted with such weighty functions. There is certainly no great difficulty in conceiving through what channels in gout a part of the uric acid formed in the muscles and marrow of bones finds its way into the non-vascular cartilaginous tissues. I shall shortly return to this. Another portion of the uric acid formed in the extremities may quickly pass into the blood-vessels, for, as is known, as the investigations of Garrod and Salomon show, uric acid can be proved to be present in the blood, during an attack of gout, but not at other times. The two investigators differ in their results regarding the quantities of uric acid present in the blood during an attack of gout, which Salomon found to be far less than Garrod. As already stated, in regard to the main point, viz., that uric acid is present in the blood during the attack, they are at one. Salomon, in addition, says on the occasion that in the blood drawn in venesection in gout, just as is usual after being digested twenty-four hours in the warm chamber xanthin and hypoxanthin are formed whilst the minute quantities of uric acid disappear. His hope that evidence would be given of some abnormal decomposition, especially an increase of the uric acid present, was not fulfilled.

If I now add a word on the way in which the uric acid compounds reach the articular cartilage, we must assume that they are conveyed to it along with the nutrient material from the adjacent bone. In the marrow of bone itself, in cases of gout, regular nodules of urates have been found. They are retained at the

free edge of the articular cartilage, for a fringe of crystalline urates is first seen appearing just below this in articular gout. It is here that they are met with most freely when in the course of time still larger portions of the articular cartilage are occupied by them.

The opinion of Cornil and Ranvier should not pass unnoticed, which, differing from the view at present in the ascendant, is to the effect that very probably the cartilage is nourished by the fluids given off by the vessels of the synovial membrane, and that it does not receive its nourishment from the bones. But that the urates reach the articular cartilage in cases of cartilaginous gout from the articular cavity is according to the position of things as little to be accepted as that urates enter the cavity of the joint from it. This is shown by Garrod, whose anatomical experience on the subject of gout is very great, who has expressly remarked that even when the joint is affected in a high degree by gout the cavity remains free from depositions, and that relatively large amounts of soda urates are not generally found in the joints.

But in primary articular gout it is not alone the cartilage that is implicated. One thing must be placed in the foreground in the clinical history of articular gout, that in the typical attack of gout independent of the cartilage of the joint, the participation of which *intra vitam* we simply *à priori* assume on the basis of well-grounded anatomical observation—the other parts of it and the encircling cutaneous covering are drawn into the most active sympathy.

Let us analyse the symptoms to be observed in a typical attack of gout:—1. The violent pain; 2. The glistening and tense skin, in which as signs of the œdema present, particularly when the inflammation has ceased, pitting takes place on pressure which only fills up slowly,

as well as—3. The subsequent desquamation which takes place after the inflammation and swelling have passed away. We thus have a group of symptoms strikingly resembling those of erysipelas. As in erysipelas, so also in a typical attack of articular gout, we must assume an accumulation of inflammation-exciting material *in loco affecto*. These two phlogogenic substances are diverse, and are distinguished the one from the other by the fact that in erysipelas the poison is septic, and in gout it is aseptic. That this aseptic poison in the case of gout is uric acid, which accumulates in abnormal quantities in the part affected we may assume to be correct, after our experiments have taught us that chemically pure uric acid and its compounds are able to set up inflammations that run an aseptic course.

Every rapid accumulation of fluid containing urates leads according to this not only to swelling and œdema, but to aseptic inflammation. The facts discussed in the third and fourth chapters have shown us that in regard to this uric acid takes an exceptional position compared to all other products of metamorphosis.

Whilst I premise that in primary articular gout uric acid is formed in the region of the muscles and marrow of bones, and that by the increased accumulation and stasis of this the symptoms of primary gout are originated, the questions occur quite naturally, for it cannot be accepted that the formation of uric acid can be limited to some of the muscles and the marrow of some of the bones—1. Why the fluid containing uric acid accumulates more readily—and 2. Why the fluid containing uric acid becomes localised first, and by preference in the most extreme parts of our bodies?

The assumption that the movement of the uric acid laden fluids becomes obstructed more readily and oftener than that which is normal must be looked upon as

correct and as answerable to the facts. The explanation, therefore, may be sought on several grounds, which I shall explain more fully when I come to the second question, and in the physical condition of the uric acid laden fluids; further, in the peculiar character of the tissues through which the fluids pass, and lastly in the circumstance that in the course of time in the process of gout itself, material diseases of the kidneys, and in the circulatory system set in, which are peculiarly favourable to disturbances of the circulation of the fluids.

As regards the second question, Why do the accumulations take place with especial frequency in the most distant parts of our bodies? the following statement may be permitted.

Like every other stasis, this developes by preference in those parts of the body which are distinguished in general by the slowness of the movements of the fluids. As in our lower extremities the *vis à tergo* is less than in the upper half of the body, it is thus explained, at least in part, why these lower extremities, and especially their most advanced post the great toe, are attacked in articular gout with such marked predilection. I shall return to the other contributory point in regard to this. In the meantime this rule is no law. We see that in the upper half of the body also gouty localisations are not unfrequently developed comparatively early, thus in the hands and fingers, particularly also in the cartilage of the ear, far more rarely in the nose. As regards the nose in particular, I believe the copper nose of gouty people—by which I do not by any means say that it never occurs but under the influence of gout—should not be considered as anything else than a *dermatitis simplex*, or as a *phlegmonosa chronica uritica*, which is kept up by the difficulty there is in getting rid of the uric acid laden fluids from this advanced post. Thus we have here in the speech of

the ancients a *rhinagra chronica*. This in inveterate gout is an oft-recurring inflammatory process, which is to be understood in the same light as the other gouty inflammations of which I shall speak later on.

As regards the typical attack of acute gout, to which I shall again return, clinical experience teaches that, although after the onset of the para-articular phlegmon there is every appearance that suppuration of the joint will take place,—as a matter of fact it does not. For the gouty poison, uric acid, is not a septic, but a chemical poison, to which, indeed, as we shall see later on, sepsis may be added accidentally, an eventuality which fortunately very rarely appears to take place.

In short, the acute typical attack of gout generally terminates in the following manner: After the initial inflammatory symptoms have increased in severity for some days, or even longer, they gradually subside so completely that, to all appearance, no trace remains.

This retrogression of the symptoms may be explained in various ways. Garrod has it that the gouty inflammation has the properties of destroying the uric acid in the blood of the inflamed parts. He reaches this conclusion from the fact that he failed to discover uric acid in the thread experiment of which he was the discoverer in the blood serum obtained from a blister. But the facts upon which Garrod bases his statements are not free from objection, and the destruction of the uric acid in the inflamed parts is by no means proved—if it cannot be excluded. In any case in order to explain the sometimes earlier and sometimes later cessation of the inflammatory symptoms of an attack we must assume that the irritant action of the uric acid ceases, whether as Garrod has it it is destroyed *in loco*, or whether, as is the case in so many forms of stasis, the obstructed circulation of fluids becomes regulated in some way or other, so that the ex-

citors of the inflammation no longer injure the part affected.

Everything that disturbs the movements of the fluids, retards, or interrupts them, such as paralyses and traumatic influences, or other diseases of joints, favours the onset of gouty symptoms, and even the gouty attack itself. Garrod states that when patients who have beforetime suffered from rheumatism become attacked with gout, those joints that have been attacked with rheumatism are usually the first to suffer from the gouty affection. Charcot, in the case of a hemiplegic woman, æt. 40, observed that the cartilages of most of the joints of the paralysed right side were the seat of urates, whilst the joints of the side not paralysed showed nothing of the kind. Only in the kidneys were a few streaks of urate of soda present. This observation of Charcot's, so interesting in many ways, can only be explained by a local stasis of uric acid in consequence of the absence of the muscular influence upon the movements of the fluids in the paralysed limb, for it cannot be assumed that uric acid was formed in the paralysed limb, but not in the sound one. On the whole, the cases are numerous in which an attack of gout has developed under the influence of an injury to the part affected. In a Paris thesis by A. Mousnier-Lompré a series of such facts are collected.

As regards the influence of injuries on the development of an attack of gout, the observations of a colleague of my acquaintance, the subject of primary gout, were particularly instructive. He had the last severe attack in 1875, which laid him up five or six weeks. In the end of 1877 both bones of the lower leg were fractured just above the ankle-joint, recovery from which took place in the course of six weeks. In conjunction with the fracture—thus after an interval of two years—

he had a not very violent attack of gout, which delayed recovery from the fracture but a short time. Since that time has remained quite free from attacks.

If we have, then, determined that by far the most frequently, yea, even almost constantly in the early periods of the gouty process the joint affections leave no visible residua behind in remembrance of the time of the attack apparently so threatening and always painful, as far as the cartilage is concerned the affair takes on quite a different aspect. I will not affirm absolutely and for all cases that the pathological process could not disappear. But in general the disturbance of nutrition does not retire so indulgently as to have been purely transitory, leaving no anatomical changes in the cartilage behind. *Hic fere semper aliquid hæret:* this is not in my opinion that from the fact that a particularly free accumulation of uric acid takes place in the cartilage, neither can it in any way support the hypothesis that uric acid is formed in the cartilage. The excessive disturbance of nutrition of the cartilage in gout, the anatomical substratum of which I have thoroughly described above, takes place in my opinion simply from the fact that from the first the arrangements for the movements of fluids are not exactly of the best. These are easily shown to be insufficient as soon as they are met by any obstacles to the movements of the fluids. Neither is any remedy afforded in the way of compensation. This unaccommodating character of the cartilage for the movement of fluids appears to me to have no other basis than in the narrowness of the much disputed vessels of the cartilage. Although I am aware that many contradictions and dissenting views exist between the individual observers, the number of methods by which the communicating canals between the cartilage cells can be shown increases so much that one is almost forced to the conviction that

the existence of vessels in hyaline cartilage is highly probable; the principal views expressed regarding the vessels of cartilage tissue may here find a place. Arnold believes that the circulation in the cartilage tissue is carried on in the following manner: that the material brought by the vessels of the perichondrium and marrow of bones is carried through the intercellular substance, *i.e.*, through the inter-fibrillary spaces lying between the fibrillary bundles and the reticular structure. From these spaces the nutrient material passes through delicate intracapsular openings running in the capsule of the cartilage into the pericellular space enclosed by this. The cartilage cell is thus surrounded by a layer, although very thin, of nutrient material. Flesch does not consider the existence of presupposed canaliculi for the carriage of nutrient material necessary; at the same time he assumes the existence of cell processes in the capsules, which are filled with a substance belonging to the cells. Spina affirms that he has demonstrated such cell prolongations in the hyaline cartilage, which penetrate the basement substance and communicate by means of offshoots with the adjoining cells. Finally, Petrone holds the cartilage cell to be a nucleus surrounded by a protoplasmatic zone from which offshoots radiate by means of which the individual cells communicate with each other without interruption.

In any case, from all these statements we obtain so much, that the canaliculi in question must be very narrow and that the movement of fluid within them may certainly be easily interrupted. If it is indisputable that the first metatarso-phalangeal joint, if not unexceptionally is yet the most frequently attacked by gout, and especially by the typical form of it, yet in the course of time still other joints are brought within the area of the disease. Later on, next to the joint of the great toe, other small joints of the

feet or hands, so that next to podagra chiragra is the most frequent localisation of articular gout. The knee, elbow, vertebral and hip-joints are more rarely attacked by gout. In the meantime, however, still other joints may be added to the series. In the case of a gouty individual, æt. 54, who has suffered from typical articular gout for the last six years, I saw quite recently a gouty inflammation of the left sterno-clavicular articulation. Whilst thus the larger joints follow the small in the series, necrosed patches, with crystalline deposition of urates, and reactive inflammation in the surrounding parts do not develope alone in the articular cartilage, but also in the synovial membrane, the surrounding tendons, the intermuscular and subcutaneous connective tissue. In the bones also deposits of urates are occasionally observed. S. Wilks states that he has often observed them.

Independent of the necrosed patches in the tendons deposits of urates are met with as my colleague König has pointed out in the sheaths of the tendons also. He has permitted me to make use of the following note: "I have repeatedly observed large collections of free uric acid in the sheaths of tendons. I have a vivid recollection of an old man affected with gout in various joints who exhibited a soft swelling on the extensors of several fingers. The swelling extended on the back of the hand almost to the wrist joint. On incision a pultaceous mass, composed almost exclusively of uric acid escaped, which, as could be determined especially in the finger lay directly on the tendon. The tendons appeared to be normal." I have drawn attention to analogous conditions in my experiments on fowls.

Now, if stasis of the uric-acid—containing fluid in the tissue of the cartilage is especially facilitated by the anatomical structure of the parts, thus furnishing a basis for a special disposition to gouty affections, this

can of course be very much aggravated when still further morbid processes develope or already exist, which at all present obstacles to the movement of the fluids within them. In this connection I may mention the fact noted by C. Hueter that the first metatarso-phalangeal joint is predisposed to gout for the reason that, according to operations on the dead body, simple panarthritis so often attacks this joint in old people. This is not the decisive factor however, for I have many times seen the most violent attacks of gout in young people with the best formed joints. How far the relatively important mechanical action of the joint in walking and standing (a point urged by C. Hueter) is especially effective as a cause cannot be determined with accuracy. At any rate the fact may be adduced in opposition to this that after rest in bed for days, the attack is seen to develope in the great toe often with lightning-like rapidity, as also that it is especially in the night that the attacks of articular gout make their appearance. If a stasis of the fluid circulating in the vessels of the cartilage, holding uric acid in solution, developes as one of the symptoms of an attack of gout, the first effect of this is that the cells of the cartilage are injured in their nutrition, they may die off and they do this frequently in the part where the urate of soda acts with the greatest intensity. In this way it becomes clear why the urates are often deposited first in the cavities of the cartilage.

Whilst thus the necrosis of the cartilage cells is completed, space is afforded for the deposition of the urates.

I emphasise this because this point appeared particularly questionable to Rindfleisch. Later on however, in consequence of the stasis that takes place in the canaliculi, a transudation of the fluids containing urates, takes place into the surrounding tissue, and the tissue of the cartilage becomes damaged more extensively

and with greater or less severity, according to the distribution of the poison, as has been fully described above.

I now turn to one of the most disputed questions in the subject of gout, viz., why it is that it is only in certain tissues, and indeed in certain typical spots, some constantly and others only exceptionally, that the uric compounds are excreted in crystalline form, *i.e.*, as acid urate of soda. Colasanti has thought that the uric acid is deposited in the tissues in the case of birds that have had their ureters ligatured in the form of acid urate of soda, ammonia, and magnesia, he reckons also with the possibility that the urate, at first neutral, is decomposed by the carbonic acid in the tissues (v. Wittich), becomes converted into a less soluble acid salt in which the acid is in combination with several bases, and is deposited in this form.

In the case of gout of the human subject, it has been thought by many since Garrod, and this conception has been defended with much warmth recently by Senator, and also by Cohnheim, that the separation of the urates takes place because in consequence of diminished alkalinity of the blood and lymph the solvent power of these fluids is lessened as regards uric acid. If this view were correct the deposition of urates must naturally take place in a crystalline form in every place to which the urate-containing fluids penetrate, as this lessened solvent power of the blood and lymph would show itself active everywhere, and the same may be said of the carbonic acid of the tissues. But this is not the case as has just been mentioned. For we have amply explained above that the urates excite inflammation in the tissues, that they occasion necrosing processes, without ever crystallising; but that urates always crystallise when the affected parts of the tissues are really necrosed.

Experimental investigations are just as little favourable to the hypothesis of diminished akalinity of the blood and lymph, plausible as it appears at first sight. For Dr. Hofmann tried by bringing about the most favourable conditions by feeding pigeons with acid yolk of egg whether he could not make the blood acid, or whether by deficiency of bases he could not procure deposition of uric acid or of slightly soluble urates in the living animal. In spite of all, the blood remained strongly alkaline, and no depositions either of uric acid or of its salts could be demonstrated either in the articular cartilage or anywhere else.

All the questions relative to the deposition of urates in a crystalline form are resolved in the following simple and satisfactory manner. The urates circulate in the blood in the form of *neutral* uric acid compounds. They crystallise out in the gouty deposits in the form of *acid* compounds, principally as acid urate of soda. To effect this a free acid is necessary, the conditions for the formation of which exist only locally. The free acid is plainly present only in the necrosed parts for the urates only crystallise out in them in gout. We may designate the formation of free acid as an effect of the necrosis. We see for example in the neighbourhood of the necrosed patches in the heart of the fowl, the ureters of which have been ligatured, extensive crystalline deposits of urates. We know that striped muscle after its death shows an acid reaction. Whilst thus the myocardium of the fowl becomes necrosed over a certain area through the action of uric acid, it becomes acid at the spot affected, and the neutral uric acid compounds circulating in the fluids become separated in crystals as acid salts.—So long as the muscular tissue is not dead, and thus has become acid, no uric acid salts crystallise out; neutral uric acid compounds, as easily soluble bodies may naturally be present in solution.—As a second ex-

ample I adduce the following. This shows that tissue necrosis, even when it is not produced by urates may be the causal factor in the crystallisation of urates.

The kidneys of fowls slowly poisoned by the subcutaneous injection of neutral chromate of potash, which we saw die of uræmia after a larger or smaller portion of the excreting kidney parenchyma had become necrosed after the separation of the chromic compounds from the fluids, owe the necrosis of these excreting cells it is certain neither to uric acid nor its compounds. For the kidney parenchyma of the fowl has evidently a great resisting power against the action of uric acid. Although after the ligature of both ureters a large accumulation of uric acid compounds must at first take place in the kidneys, they do not in consequence of this become necrosed; whilst they are not proof against the excretion of chromic acid, inasmuch as necrosed patches develope in them. Now Gergens, who first accurately studied the action of chromic acid and its preparations on the animal system, and especially on the kidneys, has already noted that chromic acid first becomes free again in the kidney in contact with its epithelium. Become free in contact with the epithelium of the kidney, it exerts a poisonous action on it and may cause complete destruction of it. We may assume that the neutral urate of soda accumulated in the fluid of the kidney parenchyma of the fowl becomes converted into acid urate of soda, and crystallises out in the portions of kidney tissue necrosed and rendered acid by the chromic acid.

As regards the crystalline patches of urates in gouty cartilage they are, as we have shown, limited to the necrosed parts of the cartilage. That such parts have an acid reaction may be proved without any trouble on cartilage removed from the body. A piece of blue litmus paper between two freshly cut surfaces of animal cartilage

shows a distinct red colour, so that thus in necrosed acid cartilage tissue, the formation of acid urate of soda, out of neutral urate of soda and the crystallisation of it are clear.

Whilst independent of the necrotic gouty patches, in which by virtue of their acid reaction neutral urate of soda has become converted into less soluble acid urate of soda, the uric acid compounds, *i.e.*, the gouty poison also sets up necrosing and inflammatory processes, the doctrine of visceral gout rises above the problematical and mythical that cling to it so long as it is held with Garrod that that only is gouty, *i.e.*, stands in causal relationship with urates, in which these crystallise out. That there are changes of organs attributable to gout in which no crystalline deposits are demonstrable prominent investigators have placed beyond doubt. A. Charcot amongst others holds that crystalline deposits are not a necessary accompaniment of renal gout, an affection that represents one of the most important types of the disease, and Lancereaux also states that deposits of urates are only occasionally met with in gouty kidney.

Whilst now the gouty process developes in primary gout in the articular cartilage and in the tissues, forming the joint, and in the immediate neighbourhood of these and constantly progresses from stasis of the uric acid in these localities, a portion of the uric acid passes over into the blood in which it may be demonstrated during an attack. In its passage through the various tissues and organs it produces many disturbances and changes. These are known under several designations as wandering, retrocedent, visceral gout. According to the *amount* of the circulating uric acid, the rapidity with which it is separated, the resisting power of the organ affected, &c., it causes in part transitory, slight, or more important functional disturbances, it causes in some cases more serious organic changes in vital organs which naturally, sooner

or later, develope in greater or lesser intensity and extent. It may be fairly assumed that a plus of uric acid is formed in gouty individuals; for if the whole of the organs that usually form uric acid are in activity, which may be well assumed, and if further, in the case of primary articular gout, in addition to these it is formed also in the muscles and marrow of bones, we must necessarily contemplate the probability that there is an increase in the formation of uric acid in cases of gout. The excretion of uric acid, whether increased or diminished, speaks neither for nor against such increased formation, as the augmented uric acid is not necessarily excreted as such, and as notwithstanding no increase in uric acid formation, more than usual may be excreted so far as the further conversion of the uric acid in the system is hindered.

We will now consider a little more closely the principal changes of organs that follow in the train of primary articular gout.

If we first examine the gouty affections of the mucous membranes, we find that catarrh of them is decidedly frequent in the subjects of gout, and I know no ground for remaining sceptical on the point. They are intelligible on the ground of the irritating properties of the uric-acid-containing fluids. The most frequent are the gouty affections of the mucous membrane of the stomach, the so-called "gouty dyspepsia." I accept with Charcot the expression of Ball: "*La goutte est pour l'estomac ce que le rheumatisme est au cœur.*" I have already mentioned above that these diseases of the stomach have been frequently looked upon as causes of gout, a conception for which there is no foundation in fact. In the mean time it is not denied that imperfect stomach digestion, for example by resorption of abnormal products of it, may under certain conditions, unfortunately unknown, assist the development of the gouty process.

I also concede that a gouty glutton and drinker may occasionally acquire indigestions unconnected with his gout. The other mucous membranes also, those of the intestines, of the urinary organs, of the organs of respiration, are often affected in gout. In consequence of the latter emphysema and asthmatic troubles develope, which along with the disturbances caused by gouty affections of the heart give rise to the most tormenting symptoms exhibited by that many visaged disease, chronic gout. In regard to catarrh of the urinary organs I may just draw attention to the so-called gouty gonorrhœa, which is of rare occurrence, and which for the most part, as far as my experience reaches, may be referred to catarrh of the out-let passages of the prostate. Quite recently I saw a man, in consultation, the subject of inveterate severe articular gout, who had been confined to bed for over five months, and in whom without any proper cause, without any urethral affection, hydrocele and acute epididymitis developed on the left side, and had remained stationary for nearly two months. But in what relation this affection, rather disquieting than tormenting to the patient, stands to the original disease, I do not take upon me to decide. The catarrhs of gouty individuals, so far as is known at present have nothing to distinguish them from affections of the mucous membranes that arise from other etiological causes, either in their clinical or their anatomical relationships, independent of their chronicity which is striking in many cases, and especially of their occurrence along with typical gouty symptoms, and particularly of joint affections. Etiology as everywhere so also here, is of very great practical value. Much disputed and, to some extent in most recent times ridiculed, are the gouty inflammations of the eye, a form of disease that has been observed in himself by no less a person than J. B. Morgagni, and which Scudamore has already

mentioned, as a so-called metamorphosis of the disease. It is unnecessary to say that by the use of such a word nothing is explained, only a fresh enigma is propounded. The observation of Th. Leber is very instructive, who describes a peculiar form of acute conjunctivitis, that on two successive occasions attacked a patient simultaneously with attacks of gout. Up to the present as far as diagnosis of the form of gouty inflammations is concerned also, the etiology, and the successful result of certain anti-arthritic methods of treatment are of significance, whilst the form of the pathological processes to the present hour affords no decided definable determining feature. But in practice are we any the better off, for example with a group of syphilitic inflammations of mucous membranes?

For the rest Th. Leber does not doubt, on the basis of his own observations, the possibility that true gout causes ritis and other inflammations of the eyes. In connection with this he recalls an observation where a serious affection of the vitreous came on in a patient who had long suffered from gouty articular pains and gravel that was considerably improved by the use of Carlsbad water and diaphoresis.

It is of especial interest that Mooren has observed congenital eye diseases in three cases of children of gouty individuals an observation which points directly to a disposition towards diseases of the eye in those of a gouty tendency.

Finally, I may here call to mind in connection with the description of the gouty affections of the eye that, as I have already explained, by the incorporation of uric acid n the cornea of rabbits, the gouty process can be originated always in the shape of infiltrations. As in the case of the experiment one must look upon the uric acid as the excitor of the inflammation, so in the

case of gout of the eye one must look upon the uric acid simply as the pathogenetic factor.

I have laboured in vain, exclusive of these corneal infiltrations experimentally produced, which behave in a manner exactly analogous to the gouty inflammations of the human subject, to produce necroses of the tissue of the cornea by incorporation of uric acid into it. Why I have not been successful I cannot say. I consider it most probable that the tissue of the cornea is especially resistent to uric acid; for the conclusion does not seem to me acceptable that the quantity so incorporated was too small, as relatively large quantities of the acid were injected into the tissues of the cornea.

A specially interesting and much discussed field is that of the gouty diseases of the skin, which are far more frequent than the gouty concretions met with in the skin and subcutaneous cellular tissue in unusually severe and inveterate cases of gout. Notwithstanding Hebra to the contrary and certainly rightly so, practitioners have decisively clung to the notion that there are skin diseases of gouty origin, that may be recognised with a probability bordering on certainty from the individuality of the patient, *i.e.*, for the reason that their development has a relation to characteristic gouty symptoms. The standpoint taken by Hebra that dermatology can only reckon skin diseases as being the result of a general disease (blood disease, disease of the fluids, dyscrasia, &c.), when such general diseases develope that, by consideration of them alone, independently of the mere individuality of the patient one is able to deduce the mode of origin, is opposed to a very large series of perfectly reliable observations from the various branches of pathology. Virchow, for example, some years ago proved in regard to cirrhosis of the liver that quite a number of causes acting as irritants of the liver may excite the

process, so that later on no one was any longer in a position to draw conclusions as to the variety of the change, certain special cases excepted. We must in fact assume that under conditions, not as yet clear, the gouty poison may set up interstitial inflammation of the liver. After the assertion of A. Portal was apparently long forgotten, viz., that gout and rheumatism set up considerable indurations of the liver, which depend on accumulations of phosphatic material, Charcot has more recently returned to the interstitial changes in the liver, adding thereby two observations of cases in which undoubted gout-nodules were observed in the fingers and cartilage of the ear. The first case was undoubtedly one of hypertrophic cirrhosis of the liver, whilst in the other chronic icterus simply was observed, the nature of which was not clear. I myself add some pertinent observations. I attended a gentleman, æt. 62, who inherited gout from his father, and who had increased it according to his own statements by good living. He had put a limit to this after he had seen that in gout free living could not be indulged in with impunity. After 1866 the attacks of articular gout occurred more frequently, and in 1879, when I first examined him, he had chronic interstitial hepatitis with moderate enlargement of the organ. This had not given rise to any symptoms of obstruction, and the patient, living on his Tusculum with hard work in his garden, remained in this state in good general health for years, with the exception of typical attacks of articular gout. He has also fairly well recovered from some cardiac and cerebral symptoms which came on in July, 1881, in direct connection with an attack of gout. No kidney symptoms, albuminous urine, &c., had shown themselves up to that time, although the gout, which had then existed for sixteen years, had given rise to frequent, and sometimes serious, symptoms.

Furthermore I have published an observation of a case in which I found crystallised concretions in the midst of hyperplastic connective tissue structure in a case of cirrhosis of the liver in a diabetic patient, which, perhaps, on the basis of their chemical re-action, I must consider as guanin concretions intermixed with hypoxanthine. The man himself has never had attacks of gout, although a son of his, not 30 years old, has already passed through a whole series of typical attacks. One might think in such cases in which cirrhosis of the liver developes in consequence of gout, that the liver affection should be much rather looked upon as the consequence of the slow and continuous action of alcohol beverages, than as the effect of an abnormal quantity of uric acid, as A. Ollivier does with respect to the complication of gout with atheroma of the vascular system. In the meantime, however, the gouty patient whom I observed was not an habitual drinker; and then it is certainly worthy of note that in these cases the cirrhosis was of the hypertrophic form and not that of interstitial inflammation of the liver, the one usually met with in connection with abuse of spirituous liquors. In the case observed by me, even after the lapse of years, absolutely no symptom of obstruction of the portal system was demonstrable. Neither had there been any change in the volume of the liver.

As is known, the kidneys and the circulatory apparatus are far more frequently drawn into sympathy in consequence of primary articular gout than the liver, and this is explained in the following manner:—The longer the articular gout continues, the more frequently the attacks are repeated, the more the exit passages become destroyed in the cartilages, the greater the number of canaliculi that are destroyed in other connective tissue formations also in consequence of the necrotic process

becoming completed in them, and consequently the more the rapid excretion of uric acid from the organism is hindered, so much the more are various other organs damaged by the gouty process.

In this connection the kidneys are specially endangered as organs of excretion. After I had discovered the necrosed patches in the gouty kidneys, I did not permit myself to be led astray into explaining the *nephritis uritica* simply by the reactive inflammation present in the parts surrounding the necrosed patches. I had already resolved in my former publication—(1) that the interstitial inflammation in the immediate neighbourhood of the necrosed patch—and thus especially in papillæ of the kidney, where these patches are mostly found—was only to be looked upon as a consequence of them; and (2) that it appeared to me very doubtful from the way in which the interstitial inflammation spread in the cortex, whether this took place, or at least whether it took place solely, by a continuation of the inflammation along the straight urinary tubules to the cortex of the kidney. The urate-containing fluid circulating everywhere in the kidney, in the canaliculi, in the lymph tracts and vessels, can *per se* produce inflammatory, necrosing, and even necrotic changes in the kidneys, and the urates may, under certain circumstances, even after their separation from the blood, remain lying in the urinary tubules.

By these considerations are explained the various anatomical changes that take place in the kidneys under the influence of gout, and which I have discussed above (p. 23). I have already mentioned that Charcot and Lancereaux have already described gouty kidney without the deposition of urates. That the necrosed patches form by preference in the *pars papillaris* is to be explained simply by the mechanism of the circulation of the kidney. The clinical phenomena of uritic nephritis depend, as in

nephritis generally, at least in their most essential part, not so much on the ætiological conditions as on the anatomical change that these bring about. This corresponds in general, as far as symptoms and course are concerned, with the clinical symptoms of the chronic and, by preference, interstitial nephritis that leads to atrophy of the organ. The gouty changes in the joints may exist a very long time before any kidney disease brings about the lethal termination. Dickinson describes a case, and he does not consider it to be a rare one, where gouty symptoms existed off and on for twenty-six years before death took place from a kidney affection. He is of opinion that this course is observed especially where there is hereditary disposition, and the mode of life is good. I have communicated two cases (p. 110) where, in cases of primary articular gout, the lethal termination followed before the kidneys were affected at all. So much is certain, that the earlier and the more extensive is the destruction of the kidneys in consequence of the gouty process, so much the earlier do the symptoms of general uric acid stasis make their appearance.

As regards the participation of the heart in gout, this plainly may be brought about in various ways. I mention first the functional and transitory disturbances in the form of palpitations, &c., which may certainly be interpreted in various ways. Stokes remarks correctly and with relevancy: "In gout, palpitation of the heart, irregularity, or pain may come on simply as a consequence of functional derangement." In young men such symptoms may be observed as the forerunners of the first or second attack. These retire on the development of the paroxysmal attack. The cardiac accidents are here generally mild and of short duration. Stokes knows a case where disease of the heart followed such an attack. But when repeated attacks of gout have taken place, and

especially in advanced age, in a case of palpitation of the heart in a gouty patient, the physician must always bear in mind possible anatomical change in the organ. The anatomical changes of the heart in gout appear undoubtedly under many clinical and anatomical guises. Stokes mentions dilatation of the heart in consequence of which patients die in a severe attack of so-called gout in the heart, but also frequently of hydrops. Stokes blames antiphlogistic treatment as the cause of this (immoderate venesection) and excessive exertion. In this the principal *rôle* is played by imperfect nutrition of the cardiac muscle by blood rich in urates. That we have generally to reckon on the presence of uric acid in the cardiac muscle is shown at once by the discovery of Neukomm related above (p. 116), who has demonstrated the presence of uric acid in the cardiac muscle. In regard to this, and also the gouty patch in the heart produced experimentally, and described above (p. 84), I may add the suspicion, not by any means too bold a one, whether certain patchy fibrous degenerations of the cardiac muscle in gouty subjects, such as were demonstrated by me in a case I observed, may not be produced by the action of uric acid. That there are also gouty forms of endocarditis—*i.e.*, inflammations of the endocardium which owe their origin to uric acid compounds, may be accepted at once after Lancereaux has succeeded in demonstrating the presence of uric acid infiltration on the cardiac valves themselves. If we concede a gouty endocarditis, nothing can certainly be objected against the assumption of a uritic arteritis.

It is, at the same time also natural that the canals in which blood circulates that is burdened with too much uric acid should show occasional derangements in their nutrition. There are certainly many causes capable of injuring the normal condition of the vessels—syphilis and alcohol amongst many others. That one should not, however, as

Ollivier has attempted, lay the atheromatous process simply to the charge of the excessive use of alcohol, which in gouty subjects plays so great a part, it is not necessary to prove here. For there are so many gouty subjects with atheroma of the arteries who are not only not drinkers, but are thoroughly abstemious people, and who have not suffered from syphilis, that it would be doing violence to facts to maintain such an untenable hypothesis. Just as little as all cirrhoses of the liver are to be attributed to abuse of alcohol, or all cases of acute yellow atrophy of the liver to acute poisoning by phosphorus, just as little are all atheromatous changes to be explained by the same cause. In any case, the toxic action of uric acid makes the generally-accepted view, originated by Garrod, intelligible—viz., that arteritis or irritable conditions of the aorta are occasionally caused by gout. This statement is rather a strange one for Garrod, as he, as I have already mentioned (p. 105), assumes that the gouty inflammation is always accompanied by a deposition of urate of soda in the affected parts. I have shown that necrosis of tissue is necessary for this. It may take place also in the atheromatous arteries of gouty subjects, and, indeed, with consecutive deposition of urates. Bramson found, for instance, in the arch of the aorta some small so-called ossifications that effervesced on being warmed with nitric acid, became yellow, and on further warming turned to deep purple-red. The addition of a little ammonia hastened this change of colour. They thus contained uric acid. Now, I have explained above, in connection with the chromic kidney of the fowl, that the tissue necrosis met with in the gouty patches is not at all necessarily dependent on uric acid itself, even if uric acid compounds are found deposited in the necrosed parts of the tissue. It does not admit of doubt that, as regards the occurrence of gouty patches, two factors may be simultaneously in

action, and, besides the urates, an especially necrosing cause. One may, for instance, conceive that a quantity of urates is present, but not enough to bring about death of the tissues, so that naturally the urates do not crystallise out; but that, notwithstanding the small amount of urates, this takes place immediately as soon as another agent has effected the death of the tissues. How often this second agent is in action I do not know; in any case, the observation communicated by Bramson undoubtedly proves that larger amounts of uric acid compounds must have passed through the vessels. For the rest I am of opinion that in the majority of gouty patches with crystalline urates the necrosis of tissue may be caused by the uric acid compounds themselves.

I will mention further, by the way, that the walls of the veins also may be damaged by the urates, whereby at least in part, may be explained the frequent phlebectasiæ of gouty subjects. That the cardiac complications are not the sole efficient agent is shown by the fact that in the subjects of cardiac disease these dilatations of the veins do not develop in that often really typical manner as they do in arthritic individuals. The affections of the heart and vessels that come on in consequence of gout also threaten the brain in a manner exactly analogous to those other diseases of the vascular system that owe their origin to other ætiological factors, so that a good portion of the brain symptoms met with in gouty people must be looked upon as secondary—as dependent on vascular derangements.

That nervous disorders, however, may be dependent in the most direct manner on the uric acid itself the older observations of Schönlein and H. Watson are adduced in proof, with the necessary reserve, however. The most recent times have afforded this confirmation, that in fact, depositions of urates are not only met with on the

coverings of the brain and spinal marrow, but that they give rise to serious symptoms. In the latter connection an observation of A. Ollivier is of especial value. He reports a case that may be considered one of real spinal gout. It was that of a man 45 years of age, who suffered from severe gouty symptoms. In an advanced period of the disease the patient complained incessantly of a painful feeling as if his neck, his thorax, and his abdomen were drawn together. In addition to this, lightning-like pains darted through the limbs, so that one was tempted to look upon the case as one of tabes. Section showed that upon the outer surface of the spinal dura mater from the 3rd cervical vertebra to the sacrum —and especially freely in the middle part of the vertebral column—and continued along the sheaths of the roots of most of the spinal nerves, many small whitish nodules were deposited, the chemical and microscopical examination of which showed that they consisted of urate of soda. Norman Moore, in the London Pathological Society on December 6th, 1881, demonstrated on the pia mater of the left hemisphere of the cerebellum of a gouty subject, a white plate which contained a trace of uric acid. Ollivier's observation is especially instructive as regards the clinical relations of many nervous symptoms in gout, and sheds light on some much contested observations made at the bedside. For the arthritic paralyses and neuralgias a knowledge of the pathogenesis makes some disclosures. That visceral neuralgias also are met with in gout has not escaped practitioners. Habershon states that cramp of the stomach may come on under the influence of gout. He maintains that in violent gout pains in the stomach are quite independent of indigestion from undigested food, or of inflammations. I have communicated an observation of a case of *insufficientia pylori* in a gouty patient, in regard to which I consider it very probable that it is dependent on a nervous cause.

I have already drawn attention (p. 120) to the fact that the gouty process set up by the uric acid runs an aseptic course. The gouty inflammation, the necrosing and necrotic processes run their course aseptically without suppuration, so far as no other poisonous material is associated with it, whether (1) it be some affection accompanied by suppuration or sepsis, added to the gout, or (2) that the gout comes on as a complication of some purulent inflammation, or (3) whether in some outbreak of gouty nodules in the neighbourhood of joints, the so-called tophi or nodi arthritici, the excitors of inflammation present in the atmosphere set up purulent or perhaps putrid inflammation. Ollivier observed in his case referred to above, that the pus which was found in both metatarso-phalangeal articulations had not sprung from an inflammation of the joint originally purulent but from peripheral gouty abscesses that had perforated into the joint. Independent of the participation of vital organs in gout, of which the complication with diseases of the kidneys and of the circulatory apparatus are the most frequent and the most important, the onset of septic processes threatens the subject of gout which may occasionally terminate life in an abrupt manner. Charcot remarks rightly that gout, like other diseases that set up profound changes in the blood like *nephritis albuminosa* and *diabetes mellitus* have a special disposition towards phlegmonous affections of a severe kind, and towards gangrene. Charcot reckons amongst the diseases belonging to the gouty diathesis, gouty anthrax, the graver phlegmonous and erysipelatous affections as well as dry gangrene. We must add that upon the mucous membranes also ulcerating phlegmonous and gangrenous affections come on in gouty people. Cruveilhier has observed the like affections more pronounced towards the anus in the intestinal mucous membrane of a gouty individual whose case has been

briefly referred to (p. 110), and who showed no other changes except advanced gouty ones in the joints, bones, muscles, and cartilages of the ears. I have already communicated an observation which belongs to this category. It was that of an emphysematous patient, 63 years of age, with intense bronchitis, who four years before was said to have had attacks of gout. After the patient had been fifteen days in the klinik, and felt somewhat better, an intense attack of podagra came on suddenly in the night, to which chiragra was added after two days. In five days the attack of gout completely passed away. But directly following this very violent pleuritic pains come on. On the same day a moderately large pleuritic effusion was demonstrable. The patient succumbed to this after rather less than two days. The autopsy which was conducted by Herr Orth revealed bronchial catarrh, and emphysema; hypertrophy of the left ventricle, and malignant hæmorrhagic left-sided pleurisy; commencing suppurative pericarditis; abscesses in the left lung, suppurative prostatitis; hypertrophy of prostate and bladder; gastric catarrh; old interstitial uratic nephritis; gout in the joints of both great toes.

I seek the causes of such severe diseases which, for the most part, induce death, in the greater facility of disposition, and lesser resisting power of the organs, the nutrition of which has become impaired under the influence of the gouty diathesis. The more the individual is exhausted by the gouty or other complicating affection, or unfavourable external conditions, so much the more is he threatened in this respect.

In relatively powerful gouty subjects, and those living under favourable external conditions, very serious complications of the kind may be recovered from in gout. In the year 1879 I attended along with Herr Koppen Kreisphysikus of Heiligenstadt, an elderly gentleman who,

from the year 1855, had suffered every year or two, and often twice a year, from attacks of gout, occasionally lasting six weeks. These first appeared in the right great toe, but they had gradually drawn into participation very many joints, and had led to extensive gouty nodules. Gouty deposits were also present in the cartilage of the right ear. I was consulted respecting a grave, acutely commencing inflammatory attack in the left lung, which advanced to expectoration of quantities of putrid stinking sputa, and afterwards to the formation of an evident cavity, but the patient in the course of about four months completely recovered. Since then about three attacks of gout have recurred, but not very violent. Besides this the patient now labours again, as for many years past, under arthritic ulcers arising from the bursting through of arthritic tophi on the heel, from which uric acid compounds have been evacuated in great quantity. In closing the description of the grave septic inflammations that occasionally complicate primary articular gout I will yet mention two pathological processes, of which the first is complicated with gout with especial frequency, whilst the second may occasionally render its diagnosis difficult, and particularly in earlier times, was actually confounded with it. These are calculus and rheumatism.

First as regards calculous disease and its relation to gout, the statement of A. Hirsch is very interesting and worthy of further study. He found that the geographical spread of both, notwithstanding their genetic connection, was not identical. In my opinion the matter stands thus, that gout can only be the cause of the formation of calculi in those cases in which uric acid or its compounds are deposited in the urinary tubules and afterwards in the exit passages, which, notwithstanding the assertions of a number of authors, is not by any means constantly the case (p. 24). On the other hand, it is

certain that even in people who do not suffer from gout, uratic deposits in a crystalline form are occasionally met with in the urinary tubules and passages, so that in this manner uric acid calculi may form in them. Buhl found calculi in 7 per cent. of his cases of granular degeneration of the kidneys, the stones either lying in the pelves of the kidney, or driven forward into the ureters where they were the cause of either hydro- or pyo-nephrosis.

As regards the complication of gout with rheumatism, Garrod has already remarked that in people who have previously suffered from rheumatism, on the occurrence of gout, the joints that have been before affected are mostly the ones attacked. The increased disposition to gout of joints, after previous attacks of acute rheumatism of which Garrod speaks, consist, in my opinion, in this: that the permeability of the vascular structures to the fluids impregnated with uric acid compounds is diminished by the articular disease. The predisposition of the first metatarso-phalangeal articulation to gout may be explained in part by the frequent disease of this joint due to other causes as has already been mentioned. (p. 127). No other causal relationship exists either between the so-called rheumatic, or between inflammations of joints due to other ætiological conditions on the one side and gout on the other. Acute rheumatism is plainly an acute infectious disease, the foundation of which is probably a micro-organism, in which, as in some other infectious diseases, such as tuberculosis, and syphilis, the joints are indisputably favourite parts for local manifestation. If these affections attack an individual disposed to gout, they may be the occasion of an outbreak of gouty articular disease. For the rest each of these articular diseases has its own specific cause just as uric acid is in the case of gout.

In my view, as has been already stated, uric acid is formed in the muscles or also in the medulla of bones in those suffering from articular gout. As I have also already stated, as, according to the present state of our knowledge, it is not known that uric acid is formed under normal conditions in human muscles, I would assume that in primary articular gout uric acid is formed in abnormal localities. That such formation of uric acid does take place in muscle under pathological conditions is determined beyond doubt by the researches of so careful an inquirer as Neukomm. But why, might be asked, does not gout come on as a consequence of typhus, in which Neukomm demonstrated uric acid in the muscles? For this reason: because in typhus the anomaly of tissue change is transitory, whilst I hold the formation of uric acid in the muscles and in the bones or in their medulla, in persons with a disposition to articular gout, to be in the majority of cases a congenital and lifelong anomaly of tissue metamorphosis that is always present if not always in an equally well-marked degree. This may remain latent for the life-time of the individual, but often under the influence of certain causes it gives rise to gouty symptoms. Nothing shows this in a more striking manner than the observations of Charcot cited on page 123, where in a case of hemiplegia advanced gouty changes had taken place, but only in the joints of the paralysed side. The idea of such a congenital anomaly of tissue metamorphosis finds its analogies in pathology; for that there are congenital anomalies of tissue metamorphosis there can scarcely be any reasonable doubt. This is shown with great probability by a case of pyrocatechinuria observed by Julius Müller and myself in 1874, and which is still in existence. The characteristic

peculiarities were observed in the first weeks of life. Had not the striking Burgundy-red spots on the soiled napkins of the infant drawn attention to it, this apparently rare anomaly of tissue metamorphosis would certainly have escaped notice. Our knowledge of cystinuria proves that heredity and predisposition in certain families may be of striking importance in such anomalous tissue metamorphoses. Whether this is to be always looked upon as a congenital anomaly cannot up to the present be determined with certainty. It has been often observed in little children. Ultzmann reports a case in which a cystin calculus was successfully removed by lithotomy from a child, æt. 2 years and 10 months. Such anomalies pass away unnoticed when they do not interfere with the well-being of the patient; or they are discovered accidentally. In one of my five cystine cases, which I have observed since the year 1874, the commencement of the concrement formation is referred to the 6th or 7th year of life, and in the urine of his brother, æt. 29, I found rather numerous crystals of cystine. The cystinuria in this case had remained undiscovered up to this date, as no morbid symptoms were induced by it. Such facts throw bright beams of light, and explain why the fathoming of questions so long escapes the observation of physicians, the solution of which is of the greatest importance for the pathogenesis of abnormalities of tissue metamorphosis. If we linger for a moment on the subject of cystinuria, it is observed that under certain circumstances, in some cases at least, these anomalies of tissue change may be influenced by certain changes in the mode of living, &c. We know, that under certain conditions, at present not more closely definable, the quantity of cystine excreted varies. I have seen with one of my patients that a diet of lentils increases the excretion of cystin nearly threefold, with an increased excretion of sulphuric acid, but not

to the same extent, and an increased excretion of urea and uric acid. It was further observed in the same patient that in the course of treatment by inunction on account of constitutional syphilis the excretion of cystine disappeared completely, or to mere traces. Neither did it again increase on a diet of lentils, whilst the inunction was being carried on, whilst in consequence of the leguminous diet an increase of the excretion of sulphuric acid and urea was noted. For the rest the former did not increase during the period of diminished or arrested excretion of cystine induced by the inunction course. I have again seen the patient in whom the facts now communicated were observed in 1880, in 1882, and there was again a very copious deposit of cystine in his urine. It, however, sets up no disturbance; the urine shows at most a few mucous shreds, but nothing else abnormal.

I have thought I might linger a little longer on these observations, as they afford the undoubtedly important result that anomalies of tissue change show exceedingly striking oscillations in the symptoms by which they manifest themselves, the causes of which are still in part hidden, whilst in other cases they are more clear. Amongst the anomalies of tissue change must be reckoned that of gout. It is the most important and the best known, because it is apparently the most frequent, and because, on account of the poisonous action of uric acid and its compounds, it gives rise to the most manifold disturbances. When Landois attributes the uric acid dyscrasia simply to long-continued free nitrogenous diet, immoderate use of spirituous liquors, and inactivity, especially when respiration is disordered, his statement is not covered by clinical experiences. Cohnheim properly emphasises the fact that people who, it is known, have never in their lives exceeded in any direction, are still

visited with the severest attacks of gout. I have observed this myself in a case the observation of which was the more instructive to me as it concerned a colleague with whom I was well acquainted, and who, moreover, himself observed very accurately and objectively. It was a case of very sharp gout in the right great toe of a colleague, then 28 years of age. The attack completely subsided in about ten days. Since then no fresh attack has recurred. This was more than five years ago. The patient had always led an orderly and active life, and had lived very moderately; his constitution is very powerful, his muscles are well developed, and the panniculus adiposus in correspondence. He was previously thoroughly healthy, and had never suffered from dyspeptic symptoms, neither have they come on since. There has been no sediment of urates in his urine, either before, at the time of the attack or since. The urine was always perfectly clear. The parents of the patient never suffered either from gout or stone, but the maternal grandfather had had gout. That the actual factor here was heredity is shown by the fact that a brother six years older than himself, a landed proprietor, living in a distant province, under quite different conditions of life, was attacked a year later by gout in the left great toe, and without any demonstrable ætiological cause. Such cases are no curiosities; every physician meets with them who has any opportunity at all of treating gout. That luxurious living, like many other things, is only a contributing factor, in individuals disposed to gout, is amply shown by those cases in which true articular gout occurs in individuals struggling with want and privations. Virchow has rightly remarked that individuals of the lower classes suffer from gout not so rarely as is generally thought. In the early part of the seventies, whilst I was conducting the hospital division of the municipal poorhouse in

Breslau I had for a long time a gouty tailor under observation. The man had struggled his life long with necessity and misery, and was just as moderate or immoderate—he thought the former, and gave one the impression of sobriety—as thousands of others of his calling, who have no gout. The diagnosis of gout with him was very easy. He had very considerable gouty nodules in the soft parts, which in part, and especially on the right arm, had broken out. On these indolent, completely painless ulcers white chalk-like masses appeared, which gave the most splendid murexide reaction. The patient died of dropsy, and the autopsy, made during my holiday tour, by Karl Weigert, revealed a perfect paradigm of the most advanced gout of the joints and kidneys independently of the gout nodules in the cutaneous covering of which mention has just been made.

On the other side we see occasionally individuals passing their lives in luxury, comfort, and refined good living laughing with impunity at gout, and that the use of beer only plays the part of a favouring factor in individuals predisposed to gout the following table which I have drawn up *ad hoc* affords at least a certain support.

In J. Bauer's report on the Medical Klinik of Munich for the years 1874-76 we find 11 cases of gout in a total of 4,670 patients (7 men and 4 women), in which number a little over 200 more women than men were treated.

In the indoor department of the St. George's Hospital, London, there were treated—

In the year	1869,	amongst	1,654	cases, 35	of gout.
„	1870	„	1,397	34	„
„	1871	„	1,644	28	„
	Total ..	..	4,695	97	„

Only the patients of the year 1869 are accurately classified according to sex and occupation in the London report

Of the 35 cases of gout 1-7th were women (cooks, washer-women, nurses); the men were by occupation publicans, labourers, coachmen, waiters, painters. Now the beer of Munich differs from English porter, and in several ways, one of which is by the lesser proportion of alcohol I have, moreover, no figures to hand by which the consumption of beer in England in litres per head and year can be determined. But when I make the statement that in Bavaria 219 litres of beer per head are drunk annually, it will be confessed that it is at least striking if in spite of this eleven times more cases of gout were treated in the London than in the Munich hospital. If we assume, *cæteris paribus*, that English beer is as rich again in alcohol as Bavarian—which, by-the-by, is not the case—it would have to be assumed, in order to account for the number of cases of gout in England by the consumption of beer, that not less than about 1,100 litres per annum are consumed per head. This statistical representation is indeed defective in many ways; one thing, however, it explains without any doubt: that the use of beer alone does not account for the frequency of gout in England. Roth explains the frequency of gout and calculus, and also that of aneurysm in England by the fact that in England sixty-eight kilos of flesh meat are consumed per head annually, whilst in France and other countries only twenty kilos are consumed. As regards the influence of alcohol on the production of gout, we know, moreover, that in countries where brandy is almost the sole alcoholic drink, and where alcoholism is at home, there is no mention of gout. That the undeniable predisposition to gout is not only congenital, but also inherited, is strengthened by so many facts and is so generally accepted, that there can be no doubt about it. As we have just remarked as regards cystinuria, there is also in the case of gout an hereditary tendency

of a most exquisite kind. We can say as little, however, as to what it consists in as in the cases of cystinuria and pyro-catechinuria. For all diseases towards which an inherited or congenital tendency exists, we can simply assume that in the anatomical construction of the tissues and organs certain abnormalities are present, which result in defective function, and which sooner or later become active. As regards primary articular gout, in my opinion the individual disposition, mostly congenital, in many cases inherited, consist in this: that the individuals in question form uric acid in perverse localities—in muscles and bones. This individual predisposition to a perverted formation of uric acid may (as in the case of cystinuria, so long as it is not discovered by accident, or gives origin to the formation of concretions) remain latent the whole life through and run its course without symptoms, so long as opportune causes do not give rise to manifestations—*i.e.*, produce gout.

That certain affinities exist between the individual anomalies of tissue change is clear from medical practice. That there are certain connecting links between gout and *diabetes mellitus* is also known. Do these consist in both cases in disturbance of tissue change in the muscles? Pavy quotes an observation of Prout according to which there is a kind of diabetes that occurs in connection with gout and rheumatism, and from the statement of Charcot, Rayer has repeatedly drawn the attention of his pupils to the connection between uric acid sand, gout and diabetes. Moreover, Cl. Bernard considers the modification a principal form of the so-called *diabetes alternans*, in which the diabetes is associated with attacks of gout or rheumatism. "One sees occasionally (says Bernard) diabetic symptoms suddenly supervene, in gouty people whose urine contains much uric acid." The frequency of this complication between gout and diabetes

is at any rate one that has been observed with various degrees of frequency in the various circles of observation. Cantani, of Naples, expressly remarks that he has scarcely ever seen diabetes complicated with gout. I observed it in one case.

Griesinger mentions that of 225 cases collected by him, two had declared gout before the diabetes; once the diabetes commenced in an attack of gout. It appears to me that as gout attacks principally the better-situated minority, this complication of diabetes with gout principally affects the classes better off, and therefore it may well be that the anatomical changes in such are less studied on account of the difficulty in obtaining autopsies. Cornillon, a consulting physician of Vichy, saw in a total of diabetics only one-fifth of the number collected by Griesinger, four gouty individuals.

In the complication of gout and diabetes both do not usually come on together, but as Rayer and Garrod have already noted, the symptoms of gout cease when the diabetes appears. Charcot has, moreover, already pointed out, and has illustrated the point by very instructive examples, that in the various members and generations of a family an alternating relationship may be seen, and I have observed a case of diabetes with hypertrophic cirrhosis of the liver and guanin deposits in it which in this respect presented most interesting features. A brother of the diabetic patient was epileptic and died at the age of 54 during an attack of epilepsy, and of the three sons of the patient the eldest when not yet 30 years of age had already had a considerable number of attacks of *arthritis uritica*.

The gouty disposition first becomes active usually in the later years of life as a rule between the 30th and 40th years. But cases do occur in which true gout manifests itself in the tenderest childhood by distinct typical

attacks. I do not allude to the observations of the older observers, as they permit the objection that they may have been cases in which gout had been confounded with rheumatism. Gairdner, however, mentions an attack of gout in a girl, æt. 11, and Trousseau one in a boy, æt. 6. It is a matter in which mistakes may frequently be made in children. A colleague the subject of gout whose history in regard to another point was very interesting (p. 123), and who had the goodness to write it out for me, expressly states that in his 9th year he had what was then supposed to be rheumatism in the "ball of the left great toe." It soon left him, to return, however, every two or three years, sometimes in the right and sometimes in the left great toe.

Independent of this inheritance of the gouty predisposition, which is, perhaps, along with the psychopathic predisposition the most frequent, there can be no doubt that it is favoured in the strongest manner, not only in the case of the individual, but also in whole peoples by excesses in eating and drinking, by an effeminate mode of life, a labourless, agreeable existence. Very many gouty diseases come into existence under the influence of those agencies that injure tissue change, which but for this possibly, in spite of the predisposition, would not have become developed. It must be principally ascribed to this circumstance that the male sex, which is more disposed to dietetic excesses than the female, is far more frequently attacked with gout than the latter. Seneca in his time drew attention to the fact that in the degenerate times of the Roman Empire when the women gave themselves up to every kind of licentiousness they were as much subject to gout as men, whilst gout during the time of the Republic in older Rome was, generally speaking, but little known. As regards the style and manner of the *ratio et modus vivendi*, the principal

part bears reference to what has been said in regard to the relations of certain localities and climates to the frequency of occurrence of gout. At the time of the Roman Empire, as compared with the time of the Republic, less change had certainly taken place in these than in the mode of life of the steadily degenerating population. In more recent times less importance has rightly been attached to the influence of climate in regard to the frequency of gout than was formerly the case. G. B. Wood notes that in a part of the United States of North America in later years gout has diminished. He is of opinion that this fact may be simply placed to the account of greater temperance. Charcot also attributes the general decrease in gout which has become very noticeable in recent times to similar causes. The distribution of gout over the earth is extremely variable. The causes therefor are nothing less than transparent and clear. As regards North Germany in particular, the statement that it is in general very widespread would not be in correspondence to the actual conditions. For Bartels, who had for many years a sphere of great activity in Kiel, states that he had only very rare opportunities of observing true gout.

In the careful reports of the Medical Department of the Krankenhaus in Hamburgh from the year 1858 to 1863, which were published by Tüngel, I have not found a single case of gout noted. On the other hand, in my circle I have found gout, especially amongst the better classes, a relatively not rare disease. My colleague König informs me that he has observed a comparatively large amount of gout in the country districts of Mecklenburg. In the Harz also it appears to be not rare. Dr. Jacob, of Sautenthal, told me that he observed eight cases of true gout within four years, and in people who had not by any means lived luxuriously.

Unfortunately our knowledge of the geographical distribution of gout is defective. The little that is reliable on the subject has been collected by A. Hirsch, to whom I refer my readers.

Course, Prognosis, and Diagnosis of Primary Articular Gout.

As regards the course of primary articular gout, an acute and a chronic, a typical or regular and an atypical or irregular form are distinguished.

Gout as a whole is in any case an "exquisit" chronic disease. The disposition thereto—whether congenital or acquired—is present in a greater or lesser degree the whole life through. Any opportune cause may again determine an outburst of gouty symptoms often after a long interval. It is the typical gout only that usually appears in an acute form, which coming on usually in the night with the well-known symptoms, very often indeed at the selfsame period of the year, in the spring or autumn, sometimes twice in the year, frequently returning after a longer interval, makes its appearance in robust men, in the character of a so-called sthenic disease. Under the influence of the above-named causes the attacks are repeated decidedly more frequently, *cæteris paribus*, than without them. The more frequently the attacks now recur, the more new joints are attacked, the more does the general health suffer, and the shorter is the period between them free from intervallary symptoms. These intervallary symptoms consist in the onset of gouty inflammations, or localisations in the various tissues and organs which I have shortly glanced over above. The course of gout then loses more and more the character of an acute attack with free intervals, and gains more the character of a chronic disease in which the character of the separate attacks, becoming more

and more asthenic, induces no special change. Still more joints are attacked, the attacks are more prolonged, last for weeks and even months, attack in irregular order one joint after the other, and later, take on a vague and atonic character. The less resisting and more decrepit the organism becomes, or is from the first so much the more does this character display itself. In this case the order in which the gouty symptoms appear is neither the same in all individuals nor do they all appear in the same individual. The organs especially which from any individual cause are usually the *locus minoris resistentiæ* for the disease are not seriously endangered. This explains why individual observers differ so much as to the frequency of diseases of individual organs in gout. Whilst some declare gouty diseases of the stomach to be exceedingly frequent, Brinton, for example, almost absolutely denies the existence of gout of the stomach, and maintains only a certain irritability of the stomach in gouty subjects; everything beyond this he holds to be an accidental coincidence. Graves is certainly right when he says that not unfrequently in hereditary arthritis the paroxysms come on suddenly before the slightest perturbation of the digestive organs has been noticed.

In the individual case *the prognosis* in view of the manifold course of primary articular gout is various and difficult. Whilst it has its termination in many patients with some typical attacks, or the gouty manifestations are limited to the joints, whereby the patient may reach old age, others die comparatively early with localisations of the gouty process in vital organs. The importance of the organs attacked plays naturally in the prognosis of gout a preponderating *rôle*. The earlier the kidneys and heart are affected *the graver cæteris paribus is the prognosis*. Therapeutic or dietetic means never succeed in *setting aside* the gouty predisposition; whether this may

disappear spontaneously has not been proved. It may *become latent*, or *remain restricted* in a great number of cases.

This is the only favourable prognostic that can be offered to anyone disposed to gout.

As regards the *diagnosis of primary articular gout*, we can only indicate with certainty those individuals as gouty who have either had typical attacks of gout—which many gouty people are in the habit of concealing—or in whom we can demonstrate gouty deposits, *i.e.*, crystalline urates in the tissues—thus in gouty ulcers of the skin (p. 152) or in the cartilage of the ear. The latter has often done me good service; the former is possible much more rarely. All other diagnostic means of assistance are more or less uncertain. The same is true of the proof of uric acid in the body fluids, in regard to which the so-called thread experiment of Garrod is most conveniently employed. We should not forget that according to Garrod's own statement 0,025 grm. per m. of uric acid must be present in the blood in order to give 2-3 crystals of uric acid on the thread. This thread demonstration essentially consists simply in this, that about 4 to 8 grm. of serum, taken from the blood direct or from a blister, are poured into a flat watch-glass, to which 6 to 12 drops of acetic acid, such as is in use among us (30 p.c.) are added, After a thread 2 to 3 cm. in length has now been placed in the fluid, and the glass with its contents has been exposed for 18 to 24 hours to a temperature at most of 16° to 20° C., so far as a sufficient quantity of uric acid was present in the fluid, it is found crystallised out on the thread and ready for examination.

That this method, neatly as it has been conceived, is only of limited practicability in practice Garrod has been one of the first to confess when he says: It is occasionally

a little difficult to demonstrate the presence of uric acid in the blood, as venesection is rarely necessary in gout, and one scruples to perform it when only a single ounce of blood is required. In such cases I have recourse to a blister plaister, which independently of this is often advisable as a therapeutical agent, and can never act disadvantageously. I must confess, however, that blister serum does not answer the purpose so completely as blood serum, although in cases where it does afford evident proof of the presence of uric acid the result is as reliable as that obtained in the experiment with blood.

As regards the practical value of examination of the serum of blood in gout for uric acid the following points are to be borne in mind in determining the question :—

1. Garrod discovered uric acid as well as urea in traces in healthy blood also by careful examination. The blood only contains uric acid in abnormal quantity in gout. In this respect Garrod considers both gouty and albuminuric subjects as equal.

2. The investigations of Salomon, at which a passing glance was given (p. 118) the only investigator who, like Garrod, and making use of a method of examination improved in the interval, has tested blood for uric acid in gout and also with special reference to the presence of uric acid in the blood in other conditions, have shown that uric acid in the blood is not specific—only a product peculiar to gout. He found it on and off in the blood in other diseases also, but he denies that it is a normal or ordinary constituent of blood.

"Last not least" heredity and family predisposition play an important *rôle* in determining the question whether a symptom or group of symptoms is to be regarded as "masked gout."

If these do not permit any exact diagnosis, they are still of inestimable value as regards treatment, and that

for us practitioners is a fact not to be valued lightly. I would, moreover, once more say emphatically that in determining whether any gouty affections of the joint have made their appearance before we cannot be sufficiently scrupulous where the diagnosis of masked gout is in question, for, as I have already remarked—(1) a number of gouty people intentionally conceal their attacks; or (2) they are overlooked or wrongly interpreted, from their being slight or vague in character (for instance, looked upon as articular rheumatism, or inflammations of sheaths of tendons), in short, they are not appraised at their true value.

I shall speak on the differential diagnosis between primary articular and primary renal gout when I come to the discussion of the latter.

Therapeutics of Primary Articular Gout.

Finally, in giving briefly my views on the treatment of primary articular gout, I shall first show beforehand that, notwithstanding the strife of opinions as to the nature of gout that has existed for so long on more than one point, which it is to be hoped will probably in no long time be smoothed over; the treatment has in so far judiciously developed as no essential differences exist as to the object to be attained in general, if they do as to the ways and means by which these objects are to be reached; but in individual cases in particular the views are not widely divergent.

This unanimity in the intentions of physicians in their endeavours to treat gout has its root in the general and undisputed conviction that a congenital disposition can only be overcome by keeping within bounds those exciting causes that render and keep such disposition active. But what these causes are is taught, not by the history

of individual cases only, it is taught also by the history of whole generations and peoples, and I have explained the fundamentals of our knowledge on the subject in the description of the ætiology of primary articular gout.

In the front rank stands a judicious regulation of the diet and of the whole mode of life of people who have any inherited disposition to gout, or at least after the existence of such a disposition has unmistakably declared itself by the appearance of an attack. As there are patients in whom the gout terminates in one, or a few and rare attacks, one must in every case seek to put a limit to the gouty disposition by regulating the habits. The absence of typical attacks of gout gives no certain guarantee that the gouty process as such is cured. On the contrary insidiously and gradually, serious diseases of vital organs may develope, at first without a symptom, and specially without any striking symptom. Such people whilst they bear within themselves the seeds of death are sometimes lauded by the laity as examples of health. In the meantime one symptom should always lead the physician to beware, and that is a steadily increasing obesity in individuals who are, from the first, disposed to gout. If an abnormal accumulation of fat is *per se* a condition that alters the normal relations of the individual, it is so much the greater a disadvantage as it plainly affords a very favourable soil for the gouty predisposition. It is for this reason that we see obesity and gout so frequently associated with one another. When we thus, in the case of a gouty individual with increasing accumulation of fat, already above the normal, reduce the corpulence, we do not by this cure the gouty disposition, perhaps it is not in our power to permanently relieve all the gouty symptoms, but we do remove one of the most active exciting causes of them. Those gouty people who have grown old with their gout are almost

all people who have known how to keep abnormal accumulations of fat at a distance.

The treatment of obesity frequently forms not only an integral, but a main part of the treatment of gout. My views on the treatment of obesity differ widely from those generally favoured in medical practice since the time of Harvey, Banting, and which Cantani has recently followed up with special ardour and rigour. I cannot treat this subject more thoroughly here. As I have given my views on the question of the treatment of obesity in another place, I refer my readers to that publication. I will only give the *facit* of the matter. Cantani teaches that we should forbid carbo-hydrates and fat to gouty subjects instead of meat. My rule is this: we may permit flesh and a corresponding amount of fat, but should limit to a minimum the carbo-hydrates. If, along with so much albuminous material, a relatively small quantity of carbo-hydrates is permitted a man he becomes fat. The carbo-hydrates protect the albumen from complete destruction, and a portion of the albumen taken in, which is not added as albumen, or used up in tissue changes is added as fat and must increase the layer of adipose tissue. Fats do indeed protect the albumen from decomposition, but far less than carbo-hydrates, and that part of the albumen that is decomposed with a corresponding use of fat is decomposed completely and does not remain in the body in an intermediate state as fat. Wherefore, fat lessens the need for nourishment by protecting the systemic albumen as Hippocrates was already aware. The food requirements, increasing with a pure or almost pure meat diet ceases, aud the corpulent individual notwithstanding the limitation of the quantity, especially of the too abundant albuminates which was at first called for, generally easily, and without any troublesome feelings of hunger, falls

back on the right quantity of food, so far as the corresponding amount of fat, which is not stored up or consumed, is added to his diet. I accordingly permit to corpulent people, along with the albuminates, a corresponding quantity of fat, either in the form of fat meat or of marrow, as an addition to the broth, and permit them butter, but require that they shall abstain from carbohydates. 80 to 100 grms. of bread are the utmost limits, within which they must keep, and sugar and pastry, as well as potatoes, are forbidden things. As vegetables, I permit legumes (without their hulls) spinage, cauliflowers, red cabbage, &c., but naturally in moderate quantities. Turnips, carrots, and beets I forbid almost altogether. I do not treat obesity with fat, but I add this important article to the diet of corpulent patients of which we so often seek to deprive them to their hurt.

It has been often thought that the use of fat, as well as that of malate of lime and asparagin, increases the disposition to gouty affections. This view is believed to have found support in a series of valuable physiological inquiries made by Meissner and R. Koch. These investigators determined (1) that by the use of the first-mentioned material succinic acid appeared in the urine; and (2) that under these circumstances large quantities of uric acid alkalies could be demonstrated in the urine. Now, if an increased formation of uric acid can be at once followed by a disposition to gout, for the development of which a stasis of uric acid in the tissues is necessary under all circumstances, the fear will disappear when it is seen by the experiments that Koch made upon himself that the succinic acid only appeared after the incorporation of a certain superfluity of fat. Koch found on exclusion of vegetable food which could cause the appearance of succinic acid in the urine, that it first appeared in the morning urine after he had, for

three successive days, eaten 250 grms. of butter in the afternoon. There is no such employment of fat in the dietary scale introduced by me. The workman who does and will consume a large amount of bacon is he least of all who falls a prey to corpulency or gout. Neither do I exclude fat from the food of candidates for gout, and for this reason, that fat is a necessary part of a judicious dietary, and also that there is certainly no ground for permitting a gouty-disposed individual to make use of a diet that is unsuitable, and that will weaken his constitution. That the intelligent use of fat in moderate quantity favours an outbreak of gout there are absolutely no facts to show. Moderation in every respect is naturally of the first importance to the gouty subject.

If we now understand (and it is not too difficult) how to find the proper limits in what is permitted, whereby every excess is to be avoided, and the correct proportions are to be accurately observed, then not only will the excessive accumulation of fat be reduced for the time, but permanent relations will be established whereby the patient will keep to the diet, which indeed will require very little sacrifice on his part. The introduction of a suitable quantity of fat into the diet is no difficulty to the gouty patient. The consequent carrying out of this form of diet is beneficial to him, as his capabilities for exertion are increased thereby, and are rendered more lasting. There is, however, scarcely any point of more importance in the treatment of gout than to take care that the organism does not suffer in its capacity for exertion and resistance.

As regards the use of alcoholic liquors in the gouty diathesis, beer should be altogether avoided, simply on account of the carbo-hydrates it contains, but I would not totally forbid the use of wine to the man accustomed

to good living, so far as he places a high value on it, and simply for the reason that experience shows that greater compliance on the part of the patient in other respects, and thus in keeping to the prescribed diet, is thus attained. If an attack of gout comes on, the patient is then easily induced to avoid the disagreeable guest by total abstention from wine. To people with a gouty disposition I thus permit one to two glasses of good light wine without any disadvantage. The communication of Mooren is interesting, and certainly worthy of bearing in mind, who found that the acids of the urine increased by far the least on Dortmund beer. This took place far more with Rhine wine, next to this still more with choice kinds of Moselle, and with good stored Bordeaux, and above all with the ordinary qualities of Moselle. Where there is a disposition to gout and there is no obesity nor any tendency thereto, certain small quantities of beer need terrify neither more nor less than wine.

The more rigidly this form of diet is adhered to, so much less need will there be to wash away the ejecta of tissue change by an extra copious supply of water. I therefore, in carrying out the above-named system of diet, do not need to recommend the copious use of water, at least two to three litres a day of spring water, soda water, or Vichy or Vals water, as Cantani does. I do not do this because I do not consider such a "flushing" out of the system with liquid for a lengthened period as advantageous or useful. The patient who is dieted after Cantani's method requires such an abundant supply of liquids, he desires it. With the diet of which I have spoken, it is not needful for the patient, and in this respect one must, to a certain extent, respect the requirements of the patient. I do indeed recommend to gouty-disposed patients a somewhat copious supply of water, for which purpose I recommend one that is

strongly impregnated with lime, generally natural seltzer water, but not more than one bottle per day. Neither do I recommend, as Cantani does, alkalies in large quantity, particularly lithia, potash, or iodide of potassium, and still less sulphate of potash, which Cantani orders only in the intervals, and in small doses for the cure of the gouty constitution, and the gouty diathesis. I generally avoid medicines so long as there are no special indications therefor in the individual case before me. Gairdner says quite correctly: "Whoever wishes to ward off an attack of gout, or to root out the disposition to the disease, must not take his remedies from the apothecaries' shop." As regards the employment of alkalies in the treatment of the gouty diathesis, and of gout itself, however, I stand upon the standpoint of Trousseau, who warns against the excessive use of alkaline mineral waters. He gives a picture of the cachexia induced by their use, a cachexia that is very destructive to gouty people. On the other hand, I lay a high value on suitable bodily movements, and particularly for the reason that, under their influence the movements of the fluids take place under the most favourable conditions, and because intelligent walking, or other exercises of the muscular apparatus which should be carried out in accordance with the individual inclination and requirements, but not to exhaustion, and which in any case are to be regulated methodically, such as rowing, gymnastic exercises, velocipede riding, hunting, bowling, &c., according to what I have seen have not unfrequently, under certain circumstances, averted a threatening attack. Far more difficult than in the case of the muscular activity that must be brought into play in gouty people, and on an extended scale, is the question of vigorous mental activity, which Cantani recommends in opposition to a series of other observers, who look

upon cerebral strain as a favouring cause of the appearance of gout. Under any circumstances it is not to be forced to such an extent as to lead to exhaustion, and in any case the necessary bodily movements should not suffer. For those who are with difficulty brought to practise these, I order daily rubbings, or hydropathy. Dry rubbings every morning are always borne, and after the patient is accustomed to them, I proceed to moist friction with water, usually from 84° to 72 Fahr., and not under 68° Fahr. The use of massage methodically carried out is very rational. The degree of resisting power of the individual determines the choice of the plans above sketched out.

If I limit myself to the measures given above, to which I add a summer tour amongst the Swiss or Tyrolese mountains, so long as I have to deal with so-called candidates for gout only, *i.e.*, with individuals who have been disposed to gout from the first, in order to avoid an outbreak of gouty symptoms, whereby satisfactory results have been obtained, the treatment becomes at once complicated when individuals seek our advice who suffer from typical, particularly severe and frequently recurring attacks of gout, or those in whom symptoms manifest themselves, which point to the fact that one or other vital organ is under the influence of the gouty process, or those in whom, it may be slight, but more or less obstinate, complications of the typical attack of articular gout develope; amongst these I count especially chronic gastric catarrh, also chronic bronchial catarrh, and the tedious neuralgias of gouty people.

In these cases, also, the ordering of a modifying diet according to the case and the condition of the patient, according to the principles just laid down, is the first duty that falls to the physician. The diet need not be on this account to pattern, in any case the avoidance of

fat, as carried out in a perfectly ridiculous manner in some health resorts, is wrong. In regard to this S. Wolff berg's remark is quite correct: "At present the use of fat is particularly forbidden, and I found a prejudice extended amongst the patients themselves that the use of fat was incompatible with mineral water treatment. I believe that the great importance of fat as regards nutrition, not only in health, but in chronic diseases, is at present undervalued to an extraordinary degree." In what respect this is true of gout I have just explained, and after this expression of Wolff berg's it is rather curious when, on the following page, he says he believes he has obtained good results in gout by following Cantani's directions. But along with the diet I place the drink and bath treatments in the first rank, and especially such as are carried out in the health resorts themselves: the latter for the reason that here may be most speedily and agreeably combined all those factors that are requisite for the successful carrying out of the treatment.

First, as regards drink treatment, this consists in rendering as harmless as possible the uric acid, of which we know that it injures the tissues and organs of the system under the circumstances described above, by the copious imbibition of suitable mineral waters.

In any case the use of water has an essential part in the action sought. Thermal water is usually employed, although the warmth does not play any preponderating *rôle*. The action only takes place more quickly than when the water is drunk cold. For the drink treatment of gout we do not require water chemically indifferent, but rather springs of a decided chemical constitution—thus especially:—1. Those of the alkaline mineral waters (*a*) the pure soda-water (natural alkaline aërated waters), and *b*. the alkaline saline (compound glauber salt) waters; and

2. The mild sodium chloride waters. As regards the alkaline waters, the stronger springs especially have great reputation. It was thought that the soda waters favoured the oxidation of uric acid to urea, and in this way removed the overloading of the system with uric acid. Although the correctness of this view has not been proved; and, also, proof that soda-waters in gout—or generally—facilitate the carrying off of uric acid or urea has not been adduced with any certainty; yet these waters, used with caution, are of great value, not only as material for "flushing," but also for combatting some—for example—gastric symptoms and other affections of the mucous membrane. The other gaseous alkaline waters—Vichy at the head—long played the leading part in the treatment of gout, and Durand Fardel, the celebrated physician of Vichy, placed them first amongst the remedies for gout, to which he added in the second rank those of Wiesbaden and Carlsbad. In the meantime, however, Carlsbad has quite outflanked Vichy. Carlsbad—the most celebrated of the alkaline saline springs—is especially recommended in those forms of gout that are associated with plethora. The treatment of gout by sodium chloride springs has been long and wrongly neglected, especially the milder sodium chloride springs, in the first rank of which I count Wiesbaden—which is, moreover, eminently suited for treatment by baths, and enjoys an exceedingly fortunate climate withal, combined with the most excellent general hygienic conditions. As the investigations of Pfeiffer show, the Wiesbaden water excites the urinary secretion and excretion of urea in considerably larger quantities than the water of the Carlsbader Mühlbrunnen. Quite recently, special importance has been attached to the lithia constituents of mineral water in the treatment of gout—an importance arising from the fact that carbonate of lithia

and, as Gescheidlen found, lithium chloride also is a valuable solvent for uric acid. Lithia was discovered in 1825 by Berzelius in small quantities, but with certainty in Eger, Carlsbad and Marienbad water, and we now know quite a number of springs in which lithia is present in quantities of more than 0·01 per litre, partly as lithium carbonate (Kronenquelle [Obersalzbrunn], Königsquelle [Elster], Assmanhausen, Bilin Sauerbrunnen, &c.); partly as lithium chloride (Salzschlirf, Baden Baden, Dürkheim, Homburg, Kissingen). Above all stands the Bonifaciusquelle of Salzschlirf with 0·22 grm. of lithium chloride to the litre. The trial regarding the importance of lithium in the treatment of gout is not yet completed. At any rate chloride of sodium is a principal constituent of water rich in lithium chloride, and in springs containing carbonate of lithium other constituents are present in greater or lesser quantity, with the action of which, together with the effect of the imbibition of large quantities of water, a reckoning must in the first place be made. For further exact experiments the artificial lithia waters of Ewich, and of Struve and Soltmann commend themselves. They allow of accuracy of dosage, and will the sooner permit an insight into the action of lithia. The warning of Binz is to be taken to heart, that carbonate of lithia is not unimportant as regards gastric digestion. One must, therefore, begin with small doses.

As regards baths in gout, the treatment of the gouty exudations, which form the main trouble of the poor sufferer from gout, is the first indication. For the reduction in part of large gouty articular exudations, even if they cannot be altogether dispersed, warm baths such as those afforded at Wiesbaden and Teplitz are required. Their action is, moreover, assisted in an extraordinary degree by the mildly saline water employed in Wiesbaden, and

which is well borne by many patients. The bads of Wildbad, as well as those luke-warm baths of Schlangenbad, Landeck, Johannisbad, are suitable for those requiring care, or for after-treatment after the use of baths at high temperatures. These indications must suffice, the details must be left over to special balneotherapy. A careful consideration of the individual, of the present state of his illness, of the locality of the bath and its arrangements, the time of the year in which use is made of it, and of many other allied circumstances, makes the choice of a health resort suitable in all respects for the case, a task frequently not altogether easy. In all cases a cautious commencement is advisable. Patients should not under any circumstances be weakened in their constitutions, or have their powers of resistance diminished by the treatment adopted. Too sanguine hopes should not be excited in them. Gouty people find themselves better when they are not attacked too sharply, nor treated by too heroic means, and especially hydro-therapeutic measures should only be made use of very cautiously when the constitution is strong and not shattered by serious general illness. Only such a cautious way of proceeding—the avoidance of all useless meddling with the gout in general, but especially in the acute attacks, and carefulness in avoiding all treatment that can render worse the general condition, and the serious organic lesions that complicate the gouty affection can and must be stringently prescribed. In this way the only thing that is attainable is advanced, namely, the longest possible retention of life in a disease in itself chronically constitutional. From this point of view the whole of the invigorating healing apparatus may come into use in the later stages of gout.

As regards the treatment of the typical attacks of gout we can easily decide what is to be done therapeutically

when we call to mind its pathogenesis, as I have explained above (p. 119).

I have related above that we can frequently ward off apparently threatening attacks of gout by judicious bodily movements. If the attack, which mostly comes on quite suddenly has already made its appearance movements of the affected limb are forbidden of themselves. The attack ceases the more quickly the earlier the retained uric acid is destroyed, or is expelled from the parts attacked. The former, *i.e.*, the destruction of the uric acid we cannot compass by our therapeutical means. For the purpose of expelling it from the affected member, *i.e.*, overcoming the stasis of uric acid, we have the means at hand which we employ in every stasis—we can raise the affected limb. Instructive use is made of this by the patient himself. The limb is further enveloped in wadding. Wadding and patience are the first requisites with which the gouty patient is to arm himself.

During the attack the regulation of tissue change is generally easy, The much-tormented creature has little inclination to indulge in the pleasures of the table; he satisfies himself with the mild diet allowed, and drinks harmless liquids such as natural seltzer water.

With regard to medicinal treatment of an attack of gout, along with colchicum, the salicin preparations—and especially the salicylate of lithia—are at present the order of the day. Quite recently we have become more cautious with colchicum; and properly so. For the purpose of promoting action of the bowels we do not use colchicum, and we attain a soothing action by means of other narcotics, especially the subcutaneous injection of morphine, more readily, more easily, and with less hesitation than with colchicum. In regard to the preparations of salicin I have seen the use of them cut short the attack, and for a long time. I have seen that under the use of salicylate

of soda the inflammation has quickly disappeared from one joint to reappear immediately—and in spite of the continued employment of the salicin preparation—in another.

The attack, says Cantani quite correctly, follows its natural process of development and passes away more or less quickly. The elderly subject of gout, as I know from manifold experience, holds himself aloof from all useless interference, and declines it.

The complications of gout require a treatment in accordance with their nature, whereby regard to the basic affection is always to be emphasised, and especially the dietetic side of it. The earlier we succeed in combatting the gouty tendency in the way emphasised above, and the greater the energy developed by the patient in carrying out a judicious regimen so much the better are the results. Even in more advanced cases it often has at least comparatively good results, so far as the view is resolutely kept in mind—and this conviction quickly finds its way into the mind of the thoughtful sufferer—that up to the present no sovereign and radical *remedy* has been discovered for his ill, and that his main reliance is on a judicious mode of life.

2. Primary Renal Gout.

Whilst in primary articular gout, as I have explained above (p. 109) the kidneys only become diseased secondarily, *i.e.*, in consequence of the joint affection, and sometimes not at all during the whole course of the disease, so that occasionally on section the kidneys are met with completely unchanged, concerning which I have brought forward some proofs in my description of primary articular gout (p. 110), there are cases n which *the autopsy reveals the most advanced gouty disease of*

the kidneys with more or less deposition of crystalline urates, in which, however, the joints are completely free from any gouty change. These cases I designate as *primary renal gout.* I have communicated such a case above (p. 20) from my own experience. It ran its course under the guise of a chronic nephritis, and never presented symptoms that allowed a suspicion of the presence of gout.

Senator declares that the only constant anatomical condition in the bodies of gouty subjects who have succumbed to the disease after a lengthened period, consists in changes in the joints. Now as Senator states, however, in regard to the kidneys, that these are only exceptionally affected at the commencement of the disease according to this the anatomical diagnosis of gout must be tolerably dubious in the early stages. My view of the matter differs from this. I assume that even when death has taken place in the earlier stages of articular gout residua must be found in the affected cartilages which point out the attacks of gout that have been passed through, whilst in primary renal gout the kidneys alone may be affected without any participation of the cartilage. I know of no case of articular gout where the diagnosis has been based on former typical attacks where it has not been confirmed by the autopsy. Thus in primary renal gout the kidney affection is the first symptom, all the other phenomena follow.

That *arthritis uritica* comes on as a consequence of nephritis has been often stated by observers, but without sufficient value being placed on the fact as regards the pathology of gout. In the cases of old atrophic nephritis Lancereaux points out the infiltrations of the articular cartilage with urate of soda and lime, as he has noted them as ordinary occurrences in the metatarso-phalangeal joint of the great toe, more rarely in the thumb and knee-joints, as analogous with the various inflamma-

tory affections of the serous membranes, the bronchi and lungs that are so often observed as resulting conditions in nephritis. He has expressly remarked that he never observed the deposition of urates in the joints in young subjects of lead-poisoning with renal sclerosis, in whom he is inclined to connect the kidney affection with narrowness of the aorta. Buhl, also, has directly pointed out the arthritis uritica as a not infrequent phenomenon of the longer continuing Bright's disease, and looks upon nephritis uritica as a complication of granular atrophy. The following case, whatever ætiological factor it may be that underlay the remarkable renal changes that were observed in it, shows that, independent of the ordinary nephritis, gout may be associated with the other grave anatomical lesions of the kidney. A man, 52 years of age, suffered for ten years from gout. He had swelling of most of the large joints and moderate albuminuria. Death took place suddenly from profuse epistaxis. Section showed deposition of urates in nearly all the joints. The kidneys were enlarged to one-fifth; their parenchyma was completely destroyed, and converted into numerous small cysts filled with a thickish fluid.

This was thus one of those rare cases in which, in an adult, complete cystic degeneration of both kidneys was observed. I have given a short history of this affection in my Nierenkrankheiten, from which it results that the pathogenesis of it is completely unknown. So much, however, is certain, that by reason of it the excretion of important urinary constituents is imperfectly performed, and that under certain conditions it may give occasion to retention of uric acid.

Whether the renal affection that gives origin to primary renal gout has its rise on a gouty basis, *i.e.*, whether there are cases in which the uric acid rises in the kidneys themselves—so far, we assume that the kidneys partici-

pate in the formation of uric acid as well as in the excretion of it, as do many other organs—cannot at present be decided. At any rate, it is not necessarily the case. We must say that every affection of the kidneys that hinders the normal excretion of uric acid may be the means of originating primary renal gout. The stasis of uric acid that occurs first damages the kidneys, and then extends itself over the whole body, and first of all over those parts of it in which symptoms of obstruction generally first manifest themselves. That in primary renal gout gouty changes in other organs frequently never take place at all is comprehensible. The kidney affection itself threatens the existence of the individual attacked, and sometimes puts a termination to life before any gouty affection of other organs is reached. When however, the life of the patient is prolonged in spite of the kidney affection, then, if in a lesser degree than in primary articular gout, gouty localisations in the joints take place. Frerichs has pointed out that in chronic nephritis the excretion of uric acid is materially diminished, although less so than that of urea. The figures given by him and Becquerel, however, never sink below 0·2 grm., *pro die.*, an amount that has often been met with by Neubauer in perfectly healthy people (p. 109).

We may especially expect gouty localisation in the joints of people afflicted with chronic nephritis when along with the primary kidney affection there is a gouty disposition in the sense employed by me above (p. 148). When describing primary articular gout I made the further statement that its progress received considerable impetus as soon as the kidneys became damaged by it as excretory organs. In the case described by me no decided cause for the kidney affection could be discovered, Lancereaux and Buhl also make no statement regarding the ætiology of the inflammatory affections of the kidney

that are complicated by gout. Only one form of renal affection has been frequently brought into connection with gout, viz., the so-called lead atrophy kidney (Bleischrumpfneire), and in this the kidney affection has been described as the primary. Dickinson says decidedly enough "that form of gout that is to be attributed to lead-poisoning especially affects the kidneys, and the patient succumbs to the disease before his joints are affected." E. Wagner, who collected 15 cases of lead atrophy kidney from among his own observation found gout in the joint of only a fractional part of them.

I have myself too little experience of lead poisoning, to found a judgment on it, but when one looks over the literature of the subject one finds a lively divergence of view, as to whether lead-poisoning leads to atrophy of the kidney at all. Inquirers such as Bouillaud, Jaccoud, and above all Tanquerel des Planches, whose experience is so great did not find changes of any kind in the kidneys in lead-poisoning, and Rosenstein, in common with these observers regards the albuminuria that comes on in lead poisoning, and granular kidney as complications of the lead poisoning, not as immediate consequences of the action of it. Experimentally also, Rosenstein succeeded in producing saturnine epilepsy in dogs, but no changes in the kidney. But Garrod himself, who first pointed out the connection between lead impregnation and gout in 1854, as many of his gouty patients were either lead workers or painters, who had suffered in some part of their lives from lead-poisoning, has not disguised the difficulty of exactly explaining the connection between lead-poisoning and gout. He says: a circumstance which appears to indicate that lead *per se* cannot dispose to gout, is this, that women who work in lead works often indeed suffer from lead colic, but rarely from gout. In the face of such objections I could not decide to assume

direct connection between lead-poisoning and atrophy of the kidney and along with this falls the assumption that lead stands in any decided causal relationship to primary renal gout. In regard to this, the observations that Dr. Jacob, medical officer to the workmen in Lautenthal, had the goodness to communicate to me confirmed me. I have already briefly mentioned above that Dr. Jacob observed eight cases of gout in four years, the whole of them men between thirty and fifty years of age, in whom the disease began with typical attacks of podagra; three of them were miners, who, however, had nothing to do with lead, three were individuals engaged in the lead huts, and two were merchants. Of about 150 hut workers observed by Dr. Jacob, only about one-half were engaged with lead. Since that time Dr. Jacob has observed an average of five cases of lead colic in each half year amongst his lead workers, in only two cases did encephalopathia saturnina appear as a further symptom. He found uric acid gravel only once in a lead-worker. As in the circle of Dr. Jacob's observation, of the three lead workers who suffered from gout none of them had symptoms of lead-poisoning, and his other five cases of gout were not engaged with lead, one would not be going astray in denying that the lead-poisoning was the connecting link in these cases in the production of gout.

As regards the differential diagnosis between primary articular and primary renal gout, the anatomical diagnosis is easy so far as in the first the kidneys, and in the second the joints, were found to be free from gouty change. In the case of advanced and extensive gouty changes in the joints with minor participation in the disease on the part of the kidneys, it will be considered exceedingly probable that it is one of primary articular gout, with which a kidney affection has become associated. Clinically, the diagnosis of primary renal gout will be decided upon

when later gouty symptoms in the joints are added to nephritic symptoms already pronounced. Many cases of primary renal gout remain unrecognised, and indeed those in which, and it appears to happen frequently, no characteristic articular symptoms develope.

The treatment of primary renal gout, and this is evident from what has been related, is necessarily much more thankless than that of primary articular gout. It is, however, based on the same principles, and must be equally active in opposing stasis of uric acid, according to the method stated above in the description of the treatment of primary articular gout.

In the treatment of renal affections already in existence in primary renal gout the mode of procedure must be in accordance with therapeutical principles adapted to them. The primary renal affection demands an exceedingly cautious mode of procedure, and excludes every kind of debilitating treatment. Invigorating treatment here comes to the front.

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