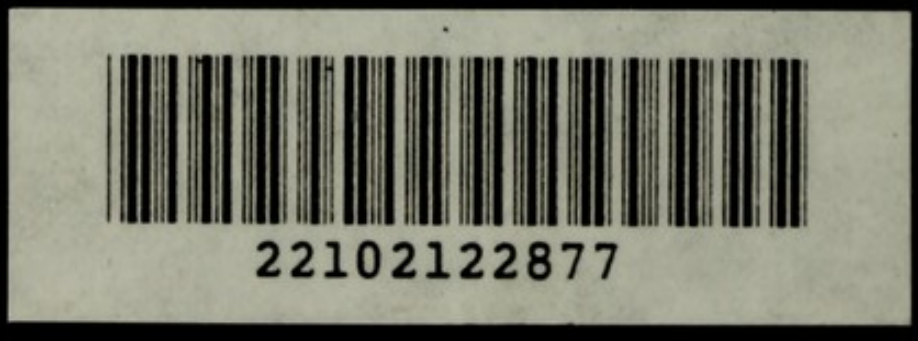
The uric acid diathesis : gout sand and gravel / by F. Levison.

The Uric Acid Diathesis

Gout, Sand and Gravel



THE URIC ACID DIATHESIS.

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GOUT.

SAND AND GRAVEL.

BY

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Kreisarzt in Copenhagen.

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CASSELL AND COMPANY, LIMITED:

LONDON, PARIS & MELBOURNE.

1894.

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AUTHOR'S PREFACE.

During the last fifteen years medical research has been directed particularly towards the study of surgery and infectious diseases, and great results have been attained in these departments.

The success, however, in these subjects has been accompanied by a disadvantage. They have absorbed almost the entire working power, so that other sections of pathology, which had equal need of renewed scientific investigation, have, in comparison, had to lie fallow.

This is particularly true as regards the anomalies of metabolism, and especially so in those morbid changes in metabolism usually designated "the uric acid diathesis." Researches have only recently been published, which appear to make an accurate insight into the nature of these morbid changes possible.

It is my intention to collect together, in the following pages, these new and important researches. In certain points I have sought to corroborate them, or to advance the ideas contained in them; and I have also endeavoured to accentuate various symptoms and morbid states, which, in my opinion, have not hitherto been sufficiently held in estimation. Finally, I have sketched out a treatment in keeping with the new conception of the uric acid diathesis.

The chemical analyses, to be found in various parts of this investigation, have all been conducted by Herr Beyer. To him, and also to Professor Stein, who placed his laboratory at my disposal, I accord my hearty thanks for their kindly assistance.

F. Levison.

Copenhagen.

TRANSLATOR'S PREFACE.

THE favourable reception generally given to Dr. Levison's work in this country led me to believe it would not be unwelcome in an English form.

It may be regarded as a logical summary of the more recent researches on the pathology of uric acid, and on the action of various remedies recommended in the treatment of this diathesis.

My thanks are due to Dr. Levison for kind permission to translate and publish his work in English.

LINDLEY SCOTT.

Sloane Street, S.W., June, 1894.

THE URIC ACID DIATHESIS.

INTRODUCTION.

UNDER the common designation "uratic diathesis," or perhaps more correctly "uric acid diathesis," many authors have described together groups of very different symptoms, although they have but one thing in common: *i.e.*, in the course of the disease pathological products may form in the body, which consist chiefly of uric acid, or uric acid compounds. The two most important representatives of the uric acid diathesis—gout and uric acid gravel—agree so little in their symptoms that they might not be considered closely related, were it not established that the predisposition to these diseases may be transmitted in certain families, sometimes as gout and sometimes as gravel. The two affections must therefore rest on a common basis, in spite of the evident differences in their symptoms and course.

After Garrod* found in 1848 that uric acid could be shown to exist in the blood of gouty subjects, and invented the so-called "thread experiment," by means of which uric acid can be detected even in a small quantity of blood, the fact was corroborated by all later investigators, and will never again be called in question.

* "Natur und Behandlung der Gicht." Deutsch von Eisenmann. 1861.

On the other hand, later researchers have not succeeded in finding uric acid in the blood of healthy men, although it certainly must be present there. Uric acid is one of the normal constituents of the urine, and nothing justifies the supposition that it is formed only in the kidneys. The reason why we are not able to find uric acid in the blood of healthy subjects is certainly because our methods of analysis are not sufficiently sensitive to detect uric acid in the small quantity of blood which the analytical chemist has at his disposal in these apprehensive and blood-sparing times.

More than forty years have passed since Garrod's first publications, without our coming to an accurate understanding as to the nature of the uric acid diathesis. There has been no want of theories, but a lack of their proof; and no one has even succeeded in establishing a theory which afforded a plausible explanation of all the symptoms, or of their peculiar course, etc. Researches have been published only recently which have brought us nearer the solution of this difficult question, although it has occupied the ingenuity of physicians for hundreds of years, and has had produced in its cause many hundreds of books.

THE QUANTITATIVE ESTIMATION OF URIC ACID IN THE URINE.

It has already been stated that chemistry leaves us in the lurch when we come to demonstrate uric acid in healthy blood, and that a quantitative estimation of

uric acid in the blood of gouty subjects is possible only when several hundred centigrammes of blood are at our disposal, which is indeed very seldom the case. The estimation of the amount of uric acid excreted in the urine in twenty-four hours is also difficult. Heintze's method, which as a rule was formerly employed, and which Garrod* also used, consists in adding to the urine an excess of strong hydrochloric acid (1 in 20), letting it stand for forty-eight hours, removing the precipitate by filtration, washing with water and then with alcohol, and weighing.

This method is easy, but is very inaccurate, as a portion of the uric acid remains in solution, and as it is not even known what proportion of the uric acid contained in the urine is precipitated.

All earlier investigations with Heintze's method are not, therefore, of great value; and this also holds good for the conclusions arrived at with respect to metabolism in health and disease, and the medicinal and dietetic treatment of the uric acid diathesis, conducted by this method of examination.

Reliable methods have been brought forward by Ludwig and Salkowski,† and also by Fokker,‡ but these are so difficult to pursue, and require so much time, that only analytical chemists can perform them in a satisfactory manner. There are, therefore, only a small number of examinations based upon them.

All quantitative estimations, which will be mentioned later, have been conducted according to the method suggested by Fokker, and modified by Salkowski,

* "Natur und Behandlung der Gicht," p. 400.

† Vogel und Neubauer, Harnanalyse, 9 Aufl., p. 545.

‡ Vogel und Neubauer, Harnanalyse, 9 Aufl., p. 547.

when no other method is particularly stated. The urine for twenty-four hours is collected, and from this an average sample of 200 cc. is taken, and rendered alkaline by 20 cc. of a solution of bicarbonate of soda (1 in 10). In the course of an hour 10 cc. of a saturated solution of ammonium chloride are added, and the mixture left standing for forty-eight hours. The deposit is then removed on a dried weighed filter, and washed two or three times. A clean glass is next placed under it, and a mixture of hydrochloric acid and water (1 in 10) poured on the filter, till all the urate of ammonium is decomposed. The uric acid, which after six hours has deposited in the filtrate, is thrown upon the filter, washed twice with water, and then with alcohol, till the acid reaction is lost. Finally, the filter is dried and weighed, and the amount of uric acid deposited on the filter estimated; to this amount 0·030 grm. has to be added to compensate for the loss which ensues from some uric acid remaining in solution.

This method is rather quicker and more convenient than the Salkowski-Ludwig method, and has been tried and approved of by experienced chemists. It occupies, however, three times twenty-four hours, and must be very conscientiously done to give a good result.

Gowland-Hopkins* has recently suggested a new method, which is comparatively simple, and which appears to give trustworthy results. It will, therefore, perhaps, furnish the much-desired clinical method. For the estimation of uric acid by it, the following reagents are necessary:—

1. Pure powdered ammonium chloride, which should

* Guy's Hospital Reports, 1891, p. 299.

contain no organic matter, and should therefore not blacken on heating.

2. A saturated solution of ammonium sulphate.

3. A twentieth-normal solution of permanganate of potash, prepared by dissolving 1·578 grms. of the salt in one litre of distilled water.

4. Pure strong sulphuric acid.

Method.—From the urine of the twenty-four hours an average sample of 100 cc. is taken, and saturated with ammonium chloride, from 30 to 35 grms. being necessary; the mixture is left standing for a few hours; the specific gravity being very high it is necessary to shake or stir it up occasionally, so that the ammonium urate precipitate may subside and not float at the top. It is next passed through thin filter paper, and the precipitate washed with the saturated solution of ammonium sulphate to remove the remains of the ammonium chloride. As the sulphate of ammonium passes slowly through the filter, the filter pump may with advantage be used to accelerate the washing.

After two—or, at most, three—washings with the ammonium sulphate solution, the precipitate, which now consists of pure ammonium urate, is washed into a beaker by means of a jet of hot distilled water, and is dissolved in the water by heating and the addition of a few drops of carbonate of soda solution. The solution is then cooled, and made up to 100 cc. with distilled water. It is then poured into a large flask, and 20 cc. of strong sulphuric acid added, by means of which the temperature rises above 60° C. Titration with the permanganate solution is then immediately commenced, and as the latter is run in from a burette—at first quickly and then drop by drop—the red colour disappears

immediately it comes in contact with the urate solution. Titration is finished whenever the red colour remains unchanged for a few seconds, and is disseminated throughout the solution on shaking. One must not be misled by the colour again disappearing in the course of a few seconds; the uric acid itself is quite oxydised by the permanganate, but the newly-formed compounds may be further oxydised, and so take up a large quantity of the titration fluid. The amount of uric acid is then calculated from the quantity of permanganate solution used, 1 cc. of which is equal to 0·0037 grm. of uric acid.

As this method appeared to promise good results, I conducted—with my assistant, Herr Beyer—six examinations by the Fokker-Salkowski and the Gowland-Hopkins methods, simultaneously. Of these six experiments, five gave excellent results, as the following table shows :—

	Fokker.	Hopkins.
1.	0·450 grm. uric acid.	0·487 grm.
2.	0·725 ,, ,,	0·731 ,,
3.	0·9947 ,, ,,	0·9918 ,,
4.	0·787 ,, ,,	0·834 ,,
5.	0·734 ,, ,,	0·734 ,,

In the last experiment there was a great difference, namely—

6.	0·702 grm.	0·616 grm.

It was found difficult in the last case to conclude when titration was just finished, so that this discrepancy cannot be counted altogether against the method.

In view of these satisfactory results, and taking into account that they are obtained with greater expedition

than by other reliable methods, and do not require large apparatus, it may be concluded that the Gowland-Hopkins method is the most advantageous for clinical purposes.

THE FORMATION AND PHYSIOLOGICAL SIGNIFICATION OF URIC ACID.

In order thoroughly to understand the uric acid diathesis, it is necessary to have an accurate knowledge of the genesis and physiological signification of uric acid. This knowledge we have lacked till now, and even in the most recent handbooks of physiology we find only defective and doubtful information on the subject.

It is evident that a satisfactory theory of the pathological alterations in the production and excretion of uric acid cannot be given, so long as we have only an imperfect knowledge of the relations of this substance to the healthy organism. It is for this reason that authors who have devoted their attention to this question, have constructed theories diametrically opposed to each other. Thus Ebstein* is of opinion that, in the subjects of gout, uric acid is formed in abnormal situations—in muscles, bone, marrow, etc.—or that it may be produced in these parts of the body only in abnormal amount. The proportion of uric acid circulating in the

* "Beiträge zur Lehre von der harnsauren Diathese," p. 23. 1890.

lymph and blood being thus increased; and when, from any unknown cause, stasis occur in the lymph vessels in some locality, it gives rise to irritation and morbid changes in the organs, according to its degree, from the uric acid acting as a chemical poison. When the stasis is very severe, acute gout and the deposition of uric acid salts supervenes.

This theory is just as hypothetical as Pfeiffer's,* according to which the uric acid diathesis depends on the fact that uric acid is formed in the system in a modified form, not easily soluble, which becomes deposited in healthy portions of the body, or crystallises in necrosed parts. In his view an acute attack of gout sets in when the alkalinity of the blood is temporarily increased, so that the deposited uric acid is again dissolved, and acts as a chemical poison.

Our knowledge of the subject has extended only in recent years as contributions have been made in various quarters upon the origin of uric acid in the healthy body, and the conditions which increase or diminish its amount. An endeavour will be made in the following pages to give an account of these recent investigations, and also to show from them how various items in the pathology of the uric acid diathesis, which formerly were unexplained phenomena, can find a simple explanation.

Of the less recent contributors, Mach† may be mentioned. He was able to produce a considerable increase in the excretion of uric acid in birds by feeding them on hypoxanthin; he concluded from this that hypoxanthin

* "Verhandlungen des Congresses für innere Medicin," p. 166. 1889. *Berlin klin. Wochenschr.* 1892. No. 16 ff.

† *Archiv f. exper. Pathol. u. Pharm.*, 1887, p. 148.

must be an intermediate stage in the disintegration which albumen undergoes while being transformed into uric acid. This may, perhaps, be the case in birds, where the solid, nitrogenous constituents of the urine consist almost of uric acid alone, but it cannot hold good in mammals, as they normally form only a small quantity of uric acid, while urea is the normal final produce of the disintegration of the albumen introduced into the system as food.

The same author* has also shown that the generally accepted theory, according to which uric acid is said to be formed chiefly in the liver, is untenable. This he seeks to prove by the fact that the formation and excretion of uric acid remains unaltered in birds when the liver is deprived of its circulation by ligaturing its vessels.

Maress† has found that every individual excretes after the thirteenth hour of fasting an almost constant amount of uric acid; after a large meal the excretion of uric acid rises very rapidly, and sinks again after several hours. The quantity of urea does not begin to rise till later; it reaches the maximum nine hours after the meal, and then falls again.

From these investigations Maress concludes that urea is formed from the albuminous substances introduced in the form of food, but that the uric acid is formed from the tissues of the body, and that the increased uric acid production immediately after a meal does not arise from the albumens of the food, the digestion of which has

* *Archiv f. exper. Pathol. u. Pharm.*, 1888, p. 389.

† *Archives slaves de Biologie.* *See* Hirsch-Virchow's *Jahresb.*, 1889, i. p. 145.

scarcely commenced, but from the increased cellular activity during digestion.

The most important and complete researches into the question have been made by Horbaczewski* and his pupils, he having already shown that uric acid, as well as xanthin and hypoxanthin, could be prepared from spleen pulp.

When fresh splenic pulp is rubbed down with eight to ten times the amount of distilled water, and the mixture left standing at a temperature of 50° C. for eight hours, bacteria gradually develop; numerous gases are produced, and towards the end of the experiment a slight foul odour becomes apparent. The experiment must then be interrupted, otherwise further products of decomposition occur.

By digesting in this way, the greater portion of the spleen tissue is dissolved, and on separating the undissolved portion, and precipitating with acetate of lead, the albuminous bodies are removed and the fluid sterilised. Nitrogenous substances are now found in the solution, and appear to be forerunners of uric acid, as well as of xanthin and hypoxanthin, but their chemical condition has not yet been accurately ascertained, and they have not so far been isolated. When the fluid is heated, and again filtered, and the filtrate condensed by evaporation to a small volume, xanthin and hypoxanthin, but no uric acid, are found in it. Guanin and adenin, which former investigators have prepared from spleen pulp, were not found in the solution, because, by the decomposition, adenin is transformed into hypoxanthin, and

* "Beiträge zur Kentnisse der Bildung der Harnsäure und der Xanthin basen." "Sitzungsbericht d.k. Acad. d. Wiss. in Wien." Math-naturw Classe Bd. C. (Tome 100). Abth. iii. April, 1891.

guanin in toxanthin. If the fluid obtained by precipitation with acetate of lead is heated at 40 to 50° C., with an equal volume of arterial blood, or a dilute solution of peroxide of hydrogen, uric acid forms in it after several hours. The same result can be obtained with an abundant supply of atmospheric air. About 2·5 milligrms. of uric acid can be formed from 1 grm. of spleen pulp.

Horbaczewski treated 100 grms. of spleen tissue in the manner described above. 250 cc. of the fluid obtained in this way were used for the preparation of uric acid, and from this 0·0607 grm. uric acid, representing 0·0201 grm. nitrogen, resulted. A second portion of 250 cc. was used for preparing xanthin and hypoxanthin (xanthin bases), and the nitrogen in them was estimated at 0·01995 grm., being almost equal to the amount of nitrogen of the uric acid experiment.

It follows from these experiments that substances exist in the spleen which are easily decomposed, and that by this decomposition nitrogenous compounds are formed, which can further be transformed either into xanthin and hypoxanthin, or into uric acid; but when the xanthin bases are once formed, they cannot be further oxydised into uric acid. The question next arises: what constituents of the spleen can become decomposed into xanthin bases or uric acid? It had formerly been supposed that this mother substance was the nuclein of the lymphatic constituents of the spleen, and Horbaczewski has now brought forward proof of this. Fresh spleen pulp was digested with a strong acid solution of pepsin, for about twenty-four hours, at 37° to 40° C. The fluid, in which most of the nuclein

was suspended, was shaken up with ether. The nuclein settled on the top of the watery fluid, below the ether, as a dense grey layer.

It was then removed from the fluid, again shaken up with water and ether, and with alcohol as long as it coloured it, digested at 40° C., and extracted with ether. It then appeared as a grey powder, which on microscopic examination was found to consist of pure nuclein. Horbaczewski was able to prepare uric acid, by dissolving this nuclein in a very weak lye, and treating it with blood at 40° C. As the nuclein, when treated in this way, decomposes very slowly, the task is more readily accomplished when the solution is heated with water and a weighed quantity of spleen pulp. It is then easy to calculate the amount of uric acid arising from the nuclein, by comparing it with the quantity of uric acid obtained from the same quantity of spleen pulp alone.

Further experiments showed how far uric acid could be obtained from other organs and tissues. Horbaczewski's assistants, Sadowenj and Formanck, treated a large number of organs of men and calves, in the same way as described in the case of the spleen, and found that uric acid was present in almost all tissues of the body—in the mucous membrane of the bowels, in the bone-marrow, thymus, liver, muscles, lungs, brains, kidneys, and skin. It was shown at the same time that these tissues, and the blood used in the experiments, did not normally contain uric acid, and if so only in traces. As all these tissues corresponded to the spleen in the preparation of uric acid, and as either the xanthin bases, or uric acid, could be at will prepared from them, it can no longer be doubted that, in the case

of these organs also, the nuclein contained in the cells is the mother substance. This author leaves it undecided whether there is only one or several nucleins. At any rate, they must closely resemble each other chemically, as their products of decomposition are identical.

Accordingly, Horbaczewski and his pupils having shown that outside the system uric acid can be prepared from the nuclein present in all tissues of the body, the only question now was whether a similar decomposition also took place in living human beings. In order to settle this, Horbaczewski first investigated how nuclein acted when it was introduced into the body. The investigation showed that the excretion of uric acid can be increased, both when nuclein is taken with the food and when a solution of it is injected subcutaneously. A weak alkaline solution of 0·75 grm. was injected subcutaneously into a rabbit, and, in place of the normal 7 to 8 milligrammes, it excreted 25·8 milligrammes of uric acid in twenty-four hours.

A man was fed during the experiment for five days on a regulated diet consisting of flesh, bread, butter, etc., and the production of uric acid reached 0·689 to 0·861 grm. per diem. Ten grammes of nuclein were then given to him daily in addition to his food, and the uric acid rose to 1 grm. The day after taking the nuclein it was 0·957 grm., and again gradually diminished. In this case there was not a very considerable increase; it is more striking when the nuclein is administered during fasting. As Maress has shown, during fasting the excretion of uric acid falls during the first twelve hours, and the minimum so reached remains

unchanged from about the fourteenth hour; if, during this period of equal production, nuclein is administered and the fasting continued, the secretion of uric acid is thereby considerably affected.

A man fasted eighteen hours, and took then 5·5 grms. nuclein suspended in water. The amount of uric acid and the total amount of nitrogen were estimated every two hours. The result will be seen from the following table:—

	Hours.	Amount of urine.	Nitrogen.	Uric acid.
Nuclein was given at 11.	9—11	81 cc.	1·065 grm.	46·8 mgrm.
	11—1	670 „	1·040 „	46·9 „
	1—5	335 „	1·013 „	64·7 „
	3—5	148 „	1·096 „	93·6 „

A second experiment gave similar, although not so evident, results. Therefore, on the administration of nuclein by the mouth, the uric acid excretion is increased. Nuclein is not very quickly digested, and takes several hours to show its action.

It is most probable, from these experiments, that uric acid is formed in health by the disintegration of the nuclein, which exists in different quantities in all tissues of the body. All the constituents of the tissues cannot be so rapidly disintegrated that a sudden variation in the uric acid production can be explained in this way. This can be true only of the leucocytes, which are present in the blood, lymph, connective tissue, glands—in short, everywhere in the body. If a large meal is able to cause a considerable increase in the number of leucocytes in the blood, and this increase after a few hours disappears, it is reasonable to suppose that the cells have become broken up, and the nuclein contained in them

converted into xanthin bases or uric acid, within the system. This hypothesis is also supported by the fact, demonstrated by many observers, that a temporary or permanent leucocytosis is always accompanied by a corresponding increase in the amount of uric acid (or xanthin bases) formed in the body.

In childhood the blood is richer in leucocytes, and the production of uric acid is also greater than later in life. The nitrogen of the uric acid reaches in the first day of life 7 to 8 per cent. of the total nitrogen eliminated, while in adults it is only 1 to 2 per cent.

Martin and Ruge* found that the daily excretion of urea in new-born children was 0·1923 grm., and the amount of uric acid 0·0214 grm., the proportion being 1 to 9 or 11 per cent.

According to Pfeiffer† the excretion of uric acid in healthy subjects is almost constant in amount, and varies only with age. During the first ten years it is 1·280 grms. daily per 100 klgrms. body weight; during the second ten it is 1·113 grms.; in the third, 1·024; the fourth, 0·965; the fifth, 0·882; the seventh, 0·752; and the ninth, 0·577 grm.

As already stated, the excretion of uric acid in adults is diminished during fasting, and rises after taking food, especially flesh food. The behaviour of the white blood corpuscles corresponds to this, their number sinking to a minimum after eighteen hours' fasting—where they remain if fasting is continued—and then again rising considerably two hours after a meal.

* *Zeitschrift f. Geburtskunde*, 1875. (*See* Schmidt's *Jahrb.* 1876, Bd. 169, p. 304.

† "Vorhandlungen des Congresses für innere Medicin, 1889," p. 166. *Berl. klin. Wochensch.*, 1892. No. 16 ff.

According to the researches of Maress,* the excretion of uric acid remains unchanged from the thirteenth to the twenty-fourth and twenty-seventh hours of fasting, while the absolute amount varies according to the individual. After a meal abounding largely in flesh food, the amount of uric acid excreted immediately rises, and reaches the maximum in five hours; after this it sinks, and twelve hours later is again at the level from which it started. The production of urea rises more slowly, reaches the maximum nine hours after food, and sinks again more slowly.

Roberts † examined the urine of a healthy man who, during twenty-four hours, partook of two good meals; the urine was collected every two hours and examined. He found that after six hours' sleep and sixteen hours' fasting, the urine was strongly acid, yet did not contain much uric acid; three to four hours after food the urine was less acid, sometimes alkaline, but contained a much larger quantity of uric acid.

More recent experimental researches have been conducted by Horbaczewski.‡ Five healthy young medical men fasted for eighteen hours on end. The urine from the seventeenth to the eighteenth hours and the amount of leucocytes in the blood were then examined (Zeiss-Thoma). They then partook of a meal consisting of meat, bread, butter, beer, etc.; three to four hours after the meal the urine collected during two hours and the blood were again examined.

* *Archives slaves de Biologie.* (*See* Hirsch-Virchow's *Jahresbericht für*, 1887, i. p. 145.)

† *Edin. Med. Journal*, 1860, pp. 817 and 900.

‡ "Beiträge zur Kentniss der Bildung der Harnsäure und der Xanthin basen."

The following table gives the result of this experiment:—

Individual examined.	During Fasting.				After taking Flesh Food.			
	Number of leucocytes after 18 hours' fasting.	Urine from 17th to 18th hour of fasting, in cubic centimetres.	Amount of uric acid, in milligrams.	Total nitrogen in milligrams.	Number of leucocytes 5 hours after taking food.	Urine of the 4th and 5th hours after taking food, in cubic centimetres.	Amount of uric acid, in milligrams.	Total nitrogen, in milligrams.
1	4,500	170	39·9	1,034	7,250 = + 61·1%	340	148·1 = + 271%	1,445
2	4,750	50	42·5	642	7,500 = + 57·9%	85	117·3 = + 176%	1,014
3	5,002	120	49·6	1,056	7,744 = + 54·8%	330	143·2 = + 188%	1,838
4	9,950	50	57·2	756	14,900 = + 49·5%	260	106·0 = + 86%	1,445
5	5,700	160	33·3	463	7,700 = + 35·1%	85	102·0 = + 206%	925

The increase in the number of leucocytes in the blood after a meal, demonstrated by Horbaczewski, is to be explained only by leucocytes being formed in large numbers in other parts of the body, and passing with the lymph stream into the blood.

Hofmeister* proved by experiments on animals that the number of lymph cells in the adenoid tissue of the intestines was increased during digestion; the same thing took place in the adenoid tissue of the stomach. The cells appear to be the product of an autochthonic

* *Archives f. exper. Path. u. Pham.*, Bd. 22, p. 306.

new formation, and he was also able to detect extensive mitosis in Peyer's patches.

Some authorities assert that the increase of uric acid makes its appearance after animal food only, and not after vegetable food; accordingly the experiment was repeated, and a meal, consisting entirely of vegetable food, given after eighteen hours' fasting.

	During Fasting.				After taking Vegetable Food.			
Individual examined.	Number of leucocytes after 18 hours' fasting.	Urine from 17th to 18th hour of fasting, in cubic centimetres.	Amount of uric acid in milligrams.	Total nitrogen, in milligrams.	Number of leucocytes 5 hours after taking food.	Urine of the 4th and the 5th hours after taking food, in cubic centimtrs.	Amount of uric acid in milligrams.	Total nitrogen, in milligrams.
1	4,500	170	39·9	1,034	5,900 = + 23·1%	95	77·4 = + 94%	869
2	4,750	50	42·5	642	4,900 = + 3·1%	55	52·9 = + 24·5%	793
3	5,002	120	49·6	1,056	5,050 = + 0·95%	280	59·3 = + 19·5%	1,159
5	5,700	160	33·3	463	5,850 = + 2·5%	290	42·3 = + 27%	1,086

The above tables show that there exists a certain proportion between the number of leucocytes in the blood and the quantity of uric acid excreted; further, that both factors are considerably increased when the individual under examination takes a meal consisting largely of animal food, after eighteen hours' fasting. Finally, that only in one of the individuals there was a

considerable increase in the excretion of uric acid after a meal of vegetables, and that this increase was accompanied by an increase in the number of white blood corpuscles. On the other hand, the difference in the total amount of nitrogen eliminated after both meals was much more limited, which strongly points to the probability that the increased excretion of uric acid is due to leucocytosis, and not to the disintegration of the albumen introduced as food.

In patients in whom no digestive leucocytosis takes place, or does not make its appearance till very late, there is no increased excretion of uric acid, or it only appears much later after the meal than usual; as Horbaczewski has shown by repeating the above feeding experiments in three persons suffering from carcinoma ventriculi.

These experiments show that the excretion of uric acid is of unequal amount in different individuals, and in them is affected in different degrees by influences, which diminish it—as fasting, or increase it—as flesh food.

In Horbaczewski's experiments the urine passed only during the fourth and fifth hours after food was examined; and there remained a deficiency in the fact that one did not know how the urine passed during the whole twenty-four hours was influenced by the different foods. This blank was filled up by Bleibtreu and Schultze.* These authors conducted the experiments upon themselves, taking for a few days in succession almost entirely animal food, and then for another few days entirely vegetable food. The urine passed during a space of twenty-four hours was then examined.

* *Pflüger's Archiv*, Bd. 45, p. 401.

Bleibtreu examined his urine after three days' flesh diet and three days' vegetable diet. His examination gave the following results:

	After Flesh Food.	After Vegetable Food.
Total nitrogen eliminated	24·4465 grms.	10·9217 grms.
Urea	47·3882 „	19·8082 „
Nitrogen in urea...	22·113 „	9·2432 „
Uric acid	0·859 „	0·791 „
Nitrogen in uric acid	0·2863 „	0·2637 „
Proportion between uric acid and urea	1 to 55·16	1 to 25·04
Nitrogen in uric acid: nitrogen in urea	1 to 73·6	1 to 35·05

From a series of very carefully conducted experiments Schultze found that his excretion of urea, on the usual mixed diet, varied between 31·647 and 33·8549 grms. in twenty-four hours; on a purely flesh diet it was raised to 58·89—67·23—73·65 grms., successively, while at the same time the amount of uric acid reached 1·3886 — 1·270 — 1·473 grms. in the twenty-four hours, his normal excretion of uric acid being 0·836 — 0·844 grm. per diem. If the excretion of uric acid was raised by means of animal food, the urine collected during the twenty-four hours deposited numerous crystals of uric acid; if at the same time Schultze took a considerable quantity of a solution of bicarbonate of soda, and also abstained from tobacco and alcohol, the uric acid remained in solution, although the percentage was not influenced in this way.

During the course of the experiments fever and malaise, accompanied by headache, appeared one day; the diet on this day was mixed, but not very abundant. In twenty-four hours 37·08 grms. urea and 1·2687 grms. uric acid were excreted; consequently, while the excretion of urea was nearly normal, the excretion of uric acid was almost as much increased as by a large quantity of animal food.

Hirschfeld * also found that the daily excretion of uric acid was comparatively independent of the food. On a diet very poor in nitrogen he excreted daily 0·417 grm. uric acid; on one rich in albumen 0·386 grm., and on a highly albuminous diet 0·492 grm.

On the other hand, the urea was proved to be entirely dependent upon the amount of albumen consumed, rising and falling in proportion to the quantity of nitrogenous food digested.

These investigations strongly indicate that uric acid is formed by the destruction and disintegration of the constituents of the body—processes which are decidedly influenced by the food, but not in proportion to the amount of albuminous substances consumed. On the other hand, the urea excreted can be doubled or increased even in a higher degree, if a large quantity of easily-digestible albuminous food is taken.

Pathologists have for a long time endeavoured to find out whether the urea and uric acid excreted with the urine stand in constant proportion to each other.

So long as the generally accepted opinion was that the uric acid arose from oxydation of albuminous substances, and could be changed by further oxydation within the body into urea, it followed that of the total amount of nitrogen excreted with the urine a certain portion was thrown out as uric acid, the rest as urea. Many writers accepted the existence of such a constant proportion, and endeavoured to estimate the normal relation. Haig † is one of the last that has arrived at such an estimate. According to him, the normal ratio

* *Virchow's Archiv*, Bd. 117, p. 301.

† S. Schmidt's *Jahrbücher*, f. 1888, u. St. Bartholomew's Hospital Report, 1890.

is 1 of uric acid to 33 of urea, and every departure from this is pathological.

This theory is overthrown both by the investigations of Horbaczewski,* which show that the proportion can vary from hour to hour, and by the experiments of Bleibtren† and Schultze,‡ whereby it was established that the proportion can readily be changed by means of the diet without the general health being influenced. Entirely similar conclusions appear to follow from Stadthagen's§ experiments on patients suffering from leucocythæmia, who were fed in different ways. These experiments will be given later in detail.

Hirschfeld‖ and several other German researchers found, as already stated, that by taking an increased quantity of albumen in the diet the excretion of urea could be markedly raised, whilst the uric acid was affected in a less degree. In conclusion may be mentioned the reliable reports of Busquet¶ on the case of a stout chemist, who, in order to get rid of his corpulency, lived upon a very limited diet, and estimated daily during the whole hunger cure the amount of urea and uric acid excreted. In a year and a half he lost in weight 32·5 kilogrammes (his weight falling from 107 to 74·5 kilos.), and at the same time the daily excretion of urea fell from 28 grms. to 10, while the uric acid remained stationary at about 0·6 grm. per diem. It never was less than 0·4 grm., and on the last examination reached even 1·02 grms. per diem. In this investigation the excretion of uric acid was just as little increased

* "Beiträge zur Kentniss der Bildung der Harnsäure und der Xanthin basen."

† *Pflüger's Archiv*, Bd. 45. ‡ Ibid.

§ *Virchow's Archives*, Bd. 109, p. 390.

‖ *Virchow's Archives*, Bd. 114, p. 301.

¶ *Revue de médecine*, 1892, p. 572.

by an abundance of food, as it was diminished by a long-continued scarcity of it, while the urea showed itself directly proportional to the quantity of albumen consumed.

Haig's conclusions upon the disturbances in the circulation, in the arterial tension, etc., which are said to result from every departure from the normal proportion, 1 to 33, have therefore no *point d'appui*. We must regard the excretion of uric acid, in each individual, as a fairly constant quantity, changes in which indicate variations in the metabolism of the body; and in order to establish their degree and importance, we should not compare the daily excretion of uric acid with that of urea.

The fact that the production of uric acid is increased in a whole series of diseases, characterised by the formation and destruction of a large number of leucocytes, corresponds with the rule laid down by Horbaczewski: that there exists a constant proportion between the number of white corpuscles in the blood, and the amount of uric acid secreted.

Foremost among such diseases is leucocythæmia. Very many observations have been made upon the condition of uric acid in this disease, only some of which will be introduced here. Laache* affirms that the amount of uric acid can rise to 4 grms. in the twenty-four hours, and has himself observed in a person suffering from this complaint a daily excretion of 3·7 grms. Bartels† observed in a case of splenic leucocythæmia, a daily excretion of 4 grms. uric acid; and in another case of leucocythæmia, accompanied by enormous enlargement

* "Klinische Urinanalyse," 1892, p. 31.

† *Deutsches Archiv f. klin. Med.* Bd. i., p. 13.

of the spleen, concretions from the size of a hemp seed to that of a pea were passed.

Bohland and Scherz,* by means of carefully conducted examinations according to Fokker's method, found a decidedly increased uric acid excretion in patients suffering from leucocythæmia. In one case it was 1·227 grms. per diem; and on later examinations as much as 1·4223. In another case the increase was less pronounced.

Stadthagen† made a comparative estimation of the urine of a healthy person, of a leucocythæmic, and of pseudo-leucocythæmic. The healthy person gave off in twenty-four hours 33·0 grms. urea and 0·577 grm. uric acid (1 in 59); the pseudo-leucocythæmic 32·65 grms. urea and 0·490 uric acid (1 in 66·6); the leucocythæmic 30·66 grms. urea and 2 grms. uric acid (1 in 15·33). Now the increased excretion of uric acid could not be due to the weakening nature of the disease, as in the pseudo-leucocythæmic there was no increase. Nor was the food the important consideration, as it was the same for the three individuals. Moreover, Stadthagen brought the excretion of urea down to 22·72 grms. by means of a vegetarian diet, while the uric acid remained unchanged—1·91 grms. On a purely albuminous diet the urea rose considerably, but the uric acid was not appreciably increased. On 2·5 grms. urate of soda being mixed with the food of a leucocythæmic patient, various symptoms were set up, such as malaise, palpitation, etc., but there was no increased excretion of uric acid.

Eichorst‡ gives reliable examinations of the urine in

* *Pflüger's Archiv*, Bd. 47, p. 13.

† *Virchow's Archiv*, Bd. 109, p. 390.

‡ *Handbuch der Therapie u. Pathologie.* 3 Aufl. 1887. Bd. 14, p. 20.

two patients affected with splenic pseudo-leucocythæmia. In them the amount of uric acid was not abnormally large; on some days it amounted to 1 grm. or still more, but on most occasions the quantity was very low—0·3 to 0·2 grm.—or so small that the amount could not be estimated.

Certain poisons appear to increase the production of uric acid. Bartels * observed this in a case of carbon monoxide poisoning, the amount of uric acid excreted being abnormally large during the first three days of the poisoning, but sinking again on the appearance of convalescence.

Other poisons also show a similar power. Fränkel and Röhmann † induced an increased excretion of uric acid in hens, by depriving them of food, and giving them phosphorus in toxic doses; but it has not yet been proved that the same thing takes place in mammalia and human beings.

Horbaczewski, moreover, gives examples of different febrile diseases, especially pneumonia, accompanied by leucocytosis and increased secretion of uric acid. Similar conditions prevail in the early stage of carcinoma, especially when the development is rapid, and more particularly in carcinoma of the liver. In one case reported the uric acid varied between 0·9 and 1·5 grms. per diem, and a like proportion is said to be found in commencing cirrhosis of the liver.

In cases of severe burns also an abundant secretion of uric acid takes place. A boy of fifteen, who had more than a third of his body covered with burns, gave off on the third day after the accident 0·97 grm. uric acid;

* *Deutsches Archiv für klin. Med.* Bd. i. p. 13.

† "S. Horbaczewski." Loc. cit., p. 36.

on the fifth 1·22, and on the seventh 1·87, while the total amount of nitrogen in the urine was not unusually large—as, for example, 15·57 grms. on the seventh day. The temperature was not high, remaining about 38° C., so that the increase of uric acid could not be attributed to fever.

Just as those morbid states, which are accompanied by an abundant formation and disintegration of leucocytes, cause an excessive excretion of uric acid, so Horbaczewski has found that those drugs and poisons, which increase the number of leucocytes in the blood, also increase the excretion of uric acid, and that various drugs of an opposite class, which prove of service in leucocythæmia, also diminish the uric acid excretion.

Pilocarpine very quickly brings about a considerable leucocytosis. Experiments on four healthy people showed that in one hour after the administration by the mouth of 10 milligrammes of pilocarpine, the white blood corpuscles were increased 25 to 34·5 per cent.; in the course of a few hours they were sometimes increased 48 per cent., and at the same time, or very soon after this marked rise, the uric acid excretion was decidedly greater, and in one case rose from 33 milligrammes to 56 milligrammes per two hours.

Alcohol is one of those poisons which increase the formation of uric acid. Chittenden* gave to big dogs 2·5 cc. of alcohol for every kilogramme of their body weight, and found that the total amount of nitrogen remained unchanged—in one case it was even diminished—while the uric acid was almost doubled, and remained in this proportion for several days after the administration of the alcohol.

* *Schmidt's Jahrbücher*, 1892, p. 61.

Camerer* found that after partaking largely of alcohol he excreted much more uric acid than usual, namely, in the proportion 3 of uric acid to 100 of urea.

By means of experiments which I made on myself I found that a moderate amount of alcohol (half a bottle of light claret and about 70 to 80 grms. of port wine) caused a decided increase of uric acid. While on a diet excluding alcohol the average daily excretion of uric acid was about 0·6 grm., on one containing alcohol it was 0·9918 grm. by Gowland-Hopkins' method of estimation, or 0·9947 grm. by the Fokker-Salkowski method.

Bodily exercise must be mentioned among those factors which increase the excretion of uric acid. After rather active muscular exercise in the saddle my excretion of uric acid was on each occasion considerably increased. Two experiments were made, eight days elapsing between them ; and the excretion rose, by this means, from about 0·6 grm. to 0·981 to 0·985, and in the second experiment to 1·089 grms.

Quinine and atropine have quite an opposite effect, and diminish the number of leucocytes in the blood, as well as the uric acid excreted.

Antipyrine and antifebrine appear, according to Horbaczewski's researches, to behave in a paradoxical manner; the number of leucocytes in the blood being always increased by these drugs, but the excretion of uric acid diminished. The explanation of these phenomena is still wanting. Horbaczewski supposes that the leucocytosis set up by pilocarpine is due to excessive new formation of leucocytes, and is followed by their rapid disintegration. Accordingly, one finds that the spleen is at the same time enlarged, and caryocinetic changes can be

* *Deutsche med. Wochensch.*, 1891, No. 10 u. 11.

made out in its lymphatic tissue. On the other hand, the leucocytosis of antipyrine and antifebrine is said to be brought about by a preservation of the leucocytes. If the corpuscles are formed in normal quantity, but have an abnormally long existence, leucocytosis, without an increase of uric acid formation, can be explained.

It has already been mentioned that the administration of nuclein can increase the uric acid excretion in a healthy person, also that after a plentiful meal, consisting largely of flesh, both the number of leucocytes in the blood and the excretion of uric acid quickly rise. Horbaczewski showed that decided leucocytosis was brought about by nuclein. Five grammes suspended in water increased the number of leucocytes from 6800 to 12450 per cc. in one experiment, from 4080 to 7350 in a second, and from 4800 to 7700 in a third. The individuals experimented upon had fasted for eighteen hours before the nuclein was administered, and took their first meal two and a half to three hours later, the blood cells having been previously counted.

From the investigations here enumerated we draw the following conclusions :—

1. Uric acid is formed in the body by the disintegration of the albuminous substances of its tissues, especially of the nuclein or nucleins.

2. The excretion of uric acid becomes increased or diminished by all factors (diseases, medicines, poisons, etc.) which give rise to a more rapid or slower disintegration of the cellular elements of the body, and especially of the leucocytes.

3. The taking of food, especially flesh food, causes a temporary leucocytosis (digestive), this leucocytosis probably arising from the nuclein of the food.

4. The amount of uric acid excreted in twenty-four

hours is not influenced to a great extent by food. There is, however, this distinction noticeable: the easily digestible animal albumens set up digestive leucocytosis and formation of uric acid much quicker than the vegetable albumens, which are difficult to digest.

THE URIC ACID CONTAINED IN THE BLOOD.

Garrod* showed in 1848 that a small quantity of uric acid can be found in the blood of healthy persons, and that the quantity in the blood of a person suffering from a gouty inflammation of a joint is much increased. This can be readily demonstrated both by the murexid test and the thread experiment. The latter is conducted by placing a fine cotton thread in serum derived from the blood itself, or the fluid raised by a blister, and acidulating well with strong acetic acid; if the serum contains a considerable quantity of uric acid it will form numerous crystals along the thread in the course of 24 to 48 hours, so that it looks like the thread in candy sugar when seen with the naked eye, or by means of a magnifying glass.

The soundness of this experiment has often been called in question. Pfeiffer† has affirmed, in accordance with his theory, that this experiment only proved that the uric acid existed in the blood in a difficultly soluble modified form, but not that it was increased in quantity. He also was of opinion that serum could hold in solution only a very small amount of uric acid, and that the

* Medico-Chirurg. Transactions, 1848, p. 83.

† "Verh. des Congresses für innere Medicin," 1889, p. 166.

large quantity of uric acid found by Garrod can by no means be dissolved in serum. The results of several experiments have convinced me that, within certain limits, a very considerable amount of uric acid can be dissolved in serum.

This has now also been demonstrated by Roberts,* who shows that the deposition of uric acid crystals upon the thread is more marked, as the solution of uric acid is the more concentrated.

On the 9th of March, 1892, I dissolved some uric acid in pure ascitic fluid, obtained from the body of a man who had died of aneurism of the aorta. The thread experiment gave

Pure ascitic fluid	No crystals.
1 Part uric acid to 4,000 ascitic fluid ...	No crystals.
1 „ „ 2,000 „ „ ...	A few crystals.
1 „ „ 1,000 „ „ ...	Very many crystals.

On the 5th April ascitic fluid, obtained by tapping a patient, was examined—

1 of uric acid to 2,000 ascitic fluid ...	Very many crystals.
1 „ „ 3,000 „ „ ...	Ditto.
1 „ „ 5,000 „ „ ...	Somewhat less.

On the 11th April ascitic fluid, freshly taken from the body of a man eighty years of age, was mixed with an alkaline solution of uric acid in the following proportions—

1 of uric acid to 2,000 of fluid.
1 „ „ 3,000 „
1 „ „ 5,000 „

All three mixtures showed, after forty-eight hours, abundant crystallisation, which agrees with the observation

* "Uric Acid, Gravel, and Gout." Lond., 1892.

of Garrod* that serum, containing per thousand parts 0·2 or more of uric acid, shows abundant deposition of uric acid crystals.

Only a few estimations of the amount of uric acid in the blood have been made. Salomon† found uric acid in the blood of four patients suffering from pneumonia and gouty arthritis. In diabetes mellitus, nephritis, and acute rheumatism the result was negative.

Abeles‡ was able to demonstrate uric acid in the blood of a man, who had died by hanging, four hours after his death. We can, however, draw accurate conclusions from blood taken from the living only, as the possibility is not excluded either that uric acid can be formed by commencing putrefaction (*vide* Horbaczewski's researches), or that it may escape detection by undergoing further oxydation after death.

v. Jaksch§ has taken up these investigations with abundant material, and all the precautions necessary for such intricate experiments; 100 to 300 grms. of absolutely pure blood were received in a cupping glass. The amount of uric acid was estimated by the Ludwig-Salkowski method after the albuminous substances had been precipitated by heating, the blood being diluted with three to four parts of water, and slightly acidulated with acetic acid. The albumens were removed from the fluid by filtration, some phosphate of soda added, and the estimation of uric acid could then be continued in the same way as in the examination of urine.

* "Natur u. Behandlung der Gicht," p. 56.

† "Charite Annalen," 1878, p. 139.

‡ *Wien. med. Jahrb.*, f. 1887; S. Hirsch-Virchow's *Jahresbericht für*, 1887, i. p. 130.

§ *Uber die klin. Bedentung.* "Von Harnsäure und Xanthinbasen im Blut." 1890.

Moreover, the results of the examination were controlled by means of experiments with a solution of uric acid in the blood of animals, and it was shown by these that almost the entire amount of uric acid dissolved in the blood could be estimated.

v. Jaksch did not find uric acid in the blood of healthy persons, which he attributed to the fact that he had not such a large quantity of blood at his disposal as Garrod, and had to be satisfied with 100 to 200 grms.; 300 grms. were available in one case only.

In his work v. Jaksch gave the results of the examination of the blood in ninety-four patients, whom he arranged, rather dogmatically, in different groups. Of such he mentions diseases of nervous system, typhoid and other acute fevers, diseases of the liver, the spleen, the stomach, and the peritoneum; diseases of the heart, of the pericardium and blood-vessels, of the lungs and pleuræ; acute rheumatism, diseases of the kidney, and anæmia.

In twenty-two cases examined of diseases of the nervous system uric acid was found in the blood only in one case, and this patient was affected with pachymeningitis, jaundice, and septicæmia, and could not be exactly characterised a nervous case. In the examination of ten patients who suffered from typhoid fever no uric acid was found during the fever. In one case, in which the blood was taken while the patient had already commenced the non-febrile stage, a small quantity only of uric acid was found.

In diseases of the abdominal organs the results varied. In one case of splenic tumour (sarcoma?) a considerable amount of uric acid was found in the blood. The same condition prevailed in hypertrophic cirrhosis of the liver and in carcinoma ventriculi. On the other hand, in a

series of other diseases of these organs no uric acid or only a trace of it was found.

In ten cases of disease of the heart or large blood-vessels the result was negative, or there were only traces of uric acid. In one case of pericarditis and double pleurisy a very considerable quantity was found, namely, 0·0117 grm. of uric acid in 122 grms. of blood.

A considerable proportion of uric acid was present in the blood of six patients afflicted with pneumonia.

The blood was examined in eleven patients with kidney disease, and contained uric acid in nine cases, in many, indeed, in considerable amount; moreover, the two negative cases should be excluded, as the amount of blood examined was only 7·7 grms., and a positive result was not to be expected from so small a quantity. The proportion of uric acid was particularly large in the cases of granular kidney and uræmia.

Finally, uric acid was found in the blood in cases of advanced anæmia, especially when the decrease in the number of red blood cells was accompanied by an increase in the leucocytes, as for example, in a case of pernicious anæmia, in which the number of red blood corpuscles was 1,060,000 per c.c., while the white numbered 9,186.

v. Jaksch concluded from his researches that anæmia specially favoured the occurrence of uric acid in the blood, and sought the explanation of this phenomenon in the fact that, according to his conception, most of the uric acid formed in the body became further oxydised in the blood by the activity of the red blood corpuscles. If the number and activity of these were diminished, in his opinion the uric acid remained unchanged, and was stored up in the blood as such.

It is very possible that the red blood cells have such

an action, but we must not forget that in all cases of anæmia, in which a considerable proportion of uric acid has been demonstrated in the blood, a decided increase in the number of leucocytes was also present, and, according to the experiments of Horbaczewski, the formation of uric acid will be directly increased by the leucocytes. The condition of affairs in pneumonia is more likely to be due to an excessive production of uric acid, arising from the abundant formation and disintegration of cells, which takes place in this disease. v. Jaksch believes that the normal amount of uric acid is formed, but that the blood having only an imperfect supply of oxygen the uric acid cannot undergo further oxydation.

On the whole, we are convinced, on an examination of v. Jaksch's table, that there are undoubted signs of an unusual abundant formation and an active disintegration of the cells of the body in almost all the cases in which a distinct reaction of uric acid was found in the blood. We also find occasional exceptions, as, for instance, the presence of uric acid in emphysema with cyanosis, but the diagnosis was only briefly stated, and perhaps the explanation of this phenomenon might be found by sufficient investigation into the history of the patient.

v. Jaksch was unable to show an increase in the quantity of uric acid in the blood of febrile patients, due, probably, either to the uric acid becoming quickly oxydised in the febrile state, or to its rapid elimination by the kidneys.

In diseases of the kidney he almost always got uric acid in the blood, which can only be explained, as v. Jaksch himself believes, by the excretion of uric acid being imperfect and slow in these diseases.

When v. Jaksch published his work in 1890 he could not have been acquainted with the researches of Horbaczewski; although his explanation of the facts discovered differs widely from the conception of Horbaczewski, it is evident from an analysis of his results that almost in all respects they are in favour of uric acid being a product of the tissues of the body, and derived from the disintegration of the nuclein.

THE CHEMICAL COMPOUNDS OF URIC ACID IN THE BLOOD AND URINE.

We have as yet discussed only the percentage of uric acid in the blood and urine without taking into consideration the chemical compounds which it forms with them. It is usual, in the text-books of physiology and chemistry, to describe uric acid as a dibasic salt, which can form neutral and acid salts with the alkalies.*

The neutral compound can only be prepared by dissolving pure uric acid in a solution of caustic soda or potash, and evaporating to dryness, without the entrance of air. This compound is readily soluble in water (1 in 44), but so unstable that it is rapidly decomposed by carbonic acid, and forms then the acid salt. As uric acid circulates in the blood before it is excreted in the urine, and as the blood always contains carbonic acid, this compound can never be formed in the body, and we need not refer to it again.

* *Vide*, for example, "Lehrbuch der Chemie für Mediciner," 1891, by Weyl.

The acid compounds of uric acid with the alkalies, and especially the acid urate of soda—the biurate, as it is shortly called—constitute the chief components of gouty tophi. This has often been demonstrated, and was verified by the latest researches of Ebstein and Sprague.*

Sprague found on analysis of these tophi that they consist of 72·112 per cent. of uric acid salts, and 27·85 per cent. of organic material. 57·2 per cent. of the whole mass was urate of soda, and 12·93 per cent. urate of potash. It is, moreover, usually supposed that uric acid occurs in the blood and urine as an acid compound—the biurate—and that this salt under circumstances is precipitated as lateritious deposit.

Roberts † has called this old view in question. He examined this sediment, after it had been purified, as far as possible, by filtration, washing with rectified spirit, and drying. On microscopic examination it is seen to consist of the well-known amorphous deposit, mixed with a few crystals of uric acid. On the addition of a few drops of distilled water to the deposit, it is evident that the amorphous urate of soda is an unstable compound; it rapidly forms a large amount of uric acid crystals, while the amorphous mass melts down and disappears. If this decomposition is maintained for thirty to fifty minutes, by continuing to add drops of water, the whole visual field becomes covered with large uric acid crystals, while the amorphous deposit entirely vanishes.

This simple experiment is very easily conducted, and always gives the same result. It shows that the

* *Virchow's Archiv*, Bd. 125, p. 208.

† *Lancet*, June 18th, 1892.

amorphous urate of soda is an unstable compound, which, on the addition of water, decomposes into uric acid and a soluble compound. This decomposition also takes place in the urine, though somewhat more slowly; and that is the reason why crystals of uric acid are always found in the amorphous sediment of urine which has stood for twenty-four hours or more.

An English chemist, Bence-Jones,* showed, before Roberts, that by dissolving uric acid in a pure solution of caustic potash or soda, and adding acetic acid till an acid reaction was given, a compound was formed consisting of four equivalents of uric acid with one equivalent of soda. This formed an amorphous deposit very like the sediment of urine, and was shown to be a quadriurate by Bence-Jones.

Bence-Jones did not carry the investigation farther. Roberts then took up the question, and endeavoured to prove that the artificially-produced quadriurate was identical with the urine sediment. It is impossible to obtain a large quantity of the latter sufficiently pure for quantitative analysis. A sufficient quantity can only be got by letting the urine stand for twenty-four hours, and by that time decomposition and the formation of uric acid crystals has already commenced. Roberts obtained the sediment by dissolving bicarbonate of soda in urine till it became alkaline, heating the mixture in a flask to 100° C., and shaking up for a minute with pure uric acid. By this means a large amount of the uric acid was dissolved. The solution, while still warm, was filtered, and cooled rapidly under running water. It then gave an abundant deposit, which was removed by filtration, washed with alcohol, and dried at the temperature of the

* *Journal of The Chemical Society*, 1862, p. 212.

body. A still better result is obtained by dissolving 3 parts of acetate of soda in 100 parts of urine, instead of the bicarbonate of soda. On quickly cooling a deposit is got, as stated above, which in all respects corresponds to the urine sediment, and is also decomposed into uric acid and a soluble salt on the addition of water. On cooling slowly a crystalline substance separates, which exhibits the same form of crystals as found in the urine of birds and reptiles.

When a portion of the deposit formed in this way was weighed, mixed with 1000 times the amount of distilled water, heated till dissolved, and left standing for forty-eight hours, a large quantity of uric acid crystals was precipitated. These were removed by filtration, washed with alcohol, dried, and weighed. In like manner the uric acid remaining in solution was deposited by the addition of hydrochloric acid, washed, dried, and weighed. It was then found that the amount of uric acid which separated of its own accord from the solution of amorphous sediment was almost exactly equal to the quantity remaining in solution, which was precipitated by the hydrochloric acid.

An exactly similar result was reached on examining the urine of birds; but in reptiles the excretion of urine takes place at so long intervals, that it undergoes decomposition while still in the urinary passages.

By this experiment it was also shown that in all probability the compound of uric acid and soda, which constitutes the amorphous sediment, contains exactly twice as much uric acid as the salt which is soluble in water.

The artificially prepared deposit was subjected to quantitative analysis with the following result. In 1·328 grms. of the dried sediment were found :—

Uric acid	...	...	1·113 grm.
Potash	...	...	0·065 ,,
Soda ...	...	...	0·027 ,,
Ammonia	...	...	0·008 ,,
Water ...	...	...	0·115 ,,

The amount of uric acid reckoned necessary to form a quadriurate is 1·102 grm.

According to these researches, it is evident that the urine sediment, which exactly resembles the artificial quadriurate in appearance, chemical reactions, etc., has also the same chemical composition; and that this is also true of the compounds of uric acid in solution in the urine.

The quadriurate is decomposed, not only by distilled water, but also by almost all other fluids except the urine. There it likewise undergoes decomposition, but more slowly than in water; in hot alkaline urine a large quantity of the quadriurate can be dissolved, but falls down again on cooling.

The decomposition of the urine sediment takes place in the following way:—The sediment splits up into uric acid, which separates in the usual crystalline form, and biurate, which remains in solution in the urine, and again forms quadriurate with the acid phosphates of the alkalies. The newly-formed quadriurate next decomposes, and this goes on till all the sediment has formed crystals of uric acid; or, as usually happens, alkaline fermentation sets in and causes quite another decomposition. If most of the crystalline constituents of the urine are separated by dialysis, the decomposition of the quadriurates takes place much quicker. These, however, are not at all equally able to keep the quadriurate in solution: according to Roberts, the urea is of minor importance in this respect, the chlorides and

sulphates have more influence, and the neutral phosphatic salts are specially important. A two per cent. solution of neutral phosphate of potash can hold the quadriurate in solution as long as urine can. The pigment appears to be of some importance. If the urine is passed through a carbon filter, and so decolorised, the quadriurate is quickly precipitated and very rapidly decomposed. Roberts also calls attention to the fact that the reaction of the urine has great influence on the quadriurates: in very acid urine the decomposition takes place rapidly, even when it does not contain a very large amount of uric acid; in neutral, and still more so in alkaline urine, the quadriurate is held in solution for a long time.

Rüdel * has brought forward another explanation of the compounds of uric acid in the urine. It follows from what has been already mentioned, that uric acid is precipitated in an alkaline solution by acidulating with hydrochloric acid, but that a large quantity of hydrochloric acid is necessary for this purpose; and indeed so much has to be used, that a portion of the uric acid is again dissolved. Since he considered that uric acid existed as a biurate in the urine, he looked for a substance which, when combined with it, offered more resistance to acids than to alkalies, and believed that he had discovered this substance to be urea.

His experiments showed, that by adding to an alkaline solution of uric acid two per cent. of urea (about the normal proportion in urine), the uric acid formed a more stable compound, and was precipitated only by a considerable excess of hydrochloric acid.

When to an alkaline solution of uric acid, 6 per cent. of urea and then sulphuric acid are added, a flocculent

* *Archiv f. experim. Pathol. und Pharmac.* Bd. 30, p. 469.

precipitate falls down: these flakes and fragments gather into a mass, 70 to 80 per cent. of which is again dissolved by heating. Rüdel obtained a sufficient amount of this deposit for quantitative analysis, by which he found that urea and uric acid existed in it in such proportions that he considered it an acid urate of urea. Rüdel believes that he discovered also a neutral urate of urea; while the acid salt is precipitated by a 6 per cent. solution of urea, the neutral compound requires 10 per cent. for its formation.

Rüdel concluded from his researches that uric acid exists, in the urine of man, in combination with urea, as an easily soluble compound, and that this is decomposed only by the addition of a larger quantity of acid than is necessary to obtain an acid reaction.

Rüdel, not being apparently acquainted with the researches of Roberts, made his experiments only with artificially-prepared solutions of uric acid: the constitution of these solutions differs so widely from that of urine, that it is impossible to form any conclusions on the condition of uric acid in the urine from the results of his experiments.

Roberts endeavoured to solve the question of the composition of the uric acid circulating in the blood. Gouty tophi consist of biurate, but this salt is almost insoluble in serum, even at the body temperature only in the proportion of 1 in 10,000. When most of the salts are removed from the serum by dialysis, the biurate is much more soluble, and almost the same amount will dissolve as in water, *i.e.* 1 in 1,000. If 5 grms. chloride of soda and 20 grms. bicarbonate of soda are dissolved in 100 grms. of water, which is about the proportion of these salts contained in blood serum, the ability of the water to dissolve the biurate is so diminished that only

traces of it can be taken up. All salts of soda, but especially the chloride, decrease the solubility of the biurate in water; this, however, is not the case with the salts of potash. Compounds of lime, magnesia, and ammonia have a similar action to the soda-salts upon the solubility of the biurate in water, but their effect is not so marked.

In the above-mentioned solution of chloride and bicarbonate of soda, pure uric acid was dissolved in the proportion of 1 in 500. After a few days a deposit, consisting of acid urate of soda (biurate) formed. Uric acid behaves in an identical manner in blood serum. In both cases the formation of this deposit depends on the circumstance that uric acid becomes soluble as the quadriurate, but in a short time breaks up into the biurate, which is very insoluble, and so is deposited.

If uric acid, in the proportion already referred to (1 in 500), is dissolved in serum, the deposition of the biurate begins in twelve hours, and is finished in four days; by that time no traces of uric acid can be found in the fluid. Synovia resembles serum in this respect, but the deposition of the biurate takes place more rapidly.

The uric acid salts are met with in two forms—an amorphous, non-crystalline form, and a crystalline form. The non-crystalline form of the biurate is prepared by heating a saturated solution of urate of soda or ammonia with an equal quantity of alkaline chloride or phosphate, and then cooling. The biurate falls down as a structureless mass, which is gradually transformed into crystals.

Biurate, being more easily and more quickly soluble in hot than in cold water, is probably explained by the fact that it takes the non-crystalline form after

solution in hot water. This is shown by the following experiment:—A saturated solution of crystalline biurate of soda is made, and, after filtration, mixed with an equal quantity of a 20 per cent. solution of sodium chloride; in this mixture there forms an abundant amorphous sediment, which is removed by filtration, and purified by washing with cold water. It is readily soluble in blood serum at 37° C.

An amorphous modified form of the quadriurate also can be obtained, by heating a 5 per cent. solution of phosphate of soda with an excess of uric acid, filtering while still hot, and cooling the filtrate. There then falls down a gelatinous precipitate which can be dried between two sheets of blotting-paper, and on the addition of distilled water, is converted into the biurate and uric acid. In Roberts' opinion the amorphous form of the uric salts is a hydrate, and the crystalline form an anhydrate.

The researches of Roberts establish that, normally, uric acid exists in the blood as a quadriurate, and as such is excreted in the urine; under special circumstances the quadriurate is split up within the body into biurate and uric acid, and the latter is then eliminated by the kidneys; or the quadriurate may be transformed in the blood into biurate, which gives rise to the deposition of this difficult soluble compound in different parts of the body.

The special conditions of this pathological form of the quadriurate will be considered in the following chapters.

GOUT—ARTHRITIS URATICA—ETIOLOGY AND PATHOGENESIS.

The most recently published researches on the nature and origin of uric acid have been reviewed in the preceding pages. It was shown that its excretion varied according to age, diet, and physiological states, and was influenced by certain medicines and poisons and various diseases. Its chemical compounds in the blood and urine were then discussed, and mention was made of the various conditions, which so alter the constitution of these fluids that the uric acid salts are readily decomposed or deposited. The theories of those authors who have investigated the subjects of gout and gravel will now be shortly given; and it will be seen how far these theories correspond with the results of observation, and can give a satisfactory explanation of the clinical symptoms and pathological conditions of these diseases.

Since Garrod* called attention to the fact that uric acid could be demonstrated in the blood of the subjects of gout, but not in the blood of the healthy, or those suffering from other diseases, almost all authors who have made a study of gout have admitted that this fact may be considered a constant occurrence. On the other hand, the opinions as to what causes this increased amount of uric acid in the blood, and the relation of this abnormal state of the blood to the pathology of gout, differ widely from each other.

According to Garrod,† the following is the origin of gout:—The disease appears to depend upon a temporary

* Medico-chirurgical Transactions, 1848.

† *Natur und Behandlung der Gicht*, 1861, p. 206.

or continuous decrease in the ability of the kidneys to excrete uric acid, and all the symptoms, both of the acute attack and the more chronic conditions, are caused by overcharging of the blood with uric acid. Naturally, the course of the disease will be accelerated when an increased quantity of uric acid is formed in the body. In order, however, to explain the origin of the disease, a hyperproduction of uric acid is not necessary, but only a retention.

Garrod has endeavoured to support this opinion by analyses, both of the blood and the urine. He found in the blood, as already often stated, an excess of uric acid, and in the urine a distinct decrease of uric acid in chronic gout, and also in acute cases, except during the attack proper. The state of affairs was rather different during the gouty paroxysm. At the commencement the proportion of uric acid was considerably diminished; towards the end of the attack it largely increased, and could rise even above the normal. After the attack it was again small, but only reached the minimum shortly before the next attack.

It is to be regretted that Garrod made use of such unreliable methods in all his analyses that his results cannot be put forward as demonstrations of fact. The examination of the blood, in a few cases, was made by a somewhat modified form of Heintz's method; in the most of them he used only the thread-experiment, by means of which one can certainly show the presence of uric acid in the blood, but can form only an approximate estimation of its quantity All the examinations of urine were conducted after Heintz's method, and cannot therefore be considered trustworthy.

Only a few researches for the purpose of estimating the quantity of uric acid in the blood of gouty subjects

have been made by recent writers. Salomon* alone worked with a reliable method of examination; he found a small quantity of uric acid in the blood of three patients during the attack, but could find none except at that time.

v. Jaksch,† it is true, made a long series of estimates of uric acid in blood, but he did not take up the study of gout.

A trustworthy method of estimating uric acid in the urine had not then been often employed. Even those authors who, like Ebstein‡ and Pfeiffer,§ have specially studied the uric acid diathesis, were contented with Heintz's method. Only during the last few years do we possess chemical analyses performed by an unimpeachable method.

Camerer‖ found in the urine passed in twenty-four hours the following proportion of urea and uric acid:—

	Urea. Grm.	Uric Acid. Grm.		Urea.	:	Uric Acid.
1. Man, 36 years of age; ½ a year after last attack of gout ...	36·0	0·92	=	100	:	2·5
2. Man, 36 years of age; ¼ year after last attack of gout ...	27·1	0·75	=	100	:	2·8
3. Man, 56 years of age; 3 weeks after last attack of gout ..	23·7	0·73	=	100	:	3·1
4. Man, 54 years of age; 6 to 7 days after last attack of gout ...	18·4	0·55	=	100	:	3
5. Man, 54 years of age; ¾ year after last attack of gout ...	23·8	0·72	=	100	:	3
Second estimation	25·5	0 76	=	100	:	3·1

* "Charité, Annalen," 1878, p. 137.

† "Ueber die klin, Bedentung der Harusaüre," etc., 1890.

‡ "Verhandlungen des Congresses für innere Medicin," Wiesbaden, 1889.

§ Ibid.

‖ *Deutsche med. Wochenschrift*, 1892, p. 413 ff.

His investigations indicate that the excretion of uric acid in gouty patients does not distinctly differ from the normal proportion, or, at any rate, is not increased.

Pfeiffer* has given in his last work a series of examinations, conducted after Ludwig's or Salkowski's method. The quantities found by him were calculated per 100 kilogrammes of the body weight, in order that they might be directly compared with each other. He found that in health the excretion of uric acid decreased in proportion to the age. In the first ten years it is 1·250 to 1·311 grms.; then it gradually shows a further decrease, and reaches the minimum in old age. A man 65 years of age showed 0·616 grm. excretion of uric acid per 100 kilogrammes of body weight, one 86 years of age only 0·577 grm.

Pfeiffer compares, then, the analyses of the urine in gouty patients in whom the complaint had not yet become chronic with that of the healthy, and gives his results in the following table:—

Age.	Gouty Subject.	Healthy Subject.
30 to 40 ...	0·885 grm.	0·965 grm.
40 to 50 ...	0·818 ,, ...	0·882 ,,
50 to 60 ...	0·701 ,, ...	—
60 to 70 ...	0·661 ,, ...	0·752 ,,

All were reckoned per 100 kilogr. body weight. The excretion of uric acid was always rather less in the gouty subjects than in the healthy persons of the same age.

The proportion is rather different in gouty patients who have already shown chronic changes, such as abundant tophi, thickened arteries, albuminuria, and such like. Pfeiffer considers that he found in the urine of these patients an increased proportion of uric acid, but

* *Berliner klin. Wochensch.*, 1892, p. 413 ff.

only a slight one. While the average excretion in healthy people of thirty-five to sixty-five years of age reached 0·860 grm. per kilogr. of body weight, it was 0·973 grm. in eleven patients, aged thirty-six to sixty-nine years, the subjects of chronic gout.

In his most recent work Ebstein * has also given a few estimations of uric acid by Fokker's method. One of the patients examined, a man forty-eight years old, with marked gouty affection of the joints, with tophi in his ears, etc., eliminated on one occasion, at the end of an attack, 0·5736 grm. in twenty-four hours; on another day 0·8258 grm. At the close of a second attack the same individual excreted 0·3458 grm. of uric acid in one day.

On the whole, so few estimations of the urine of gouty subjects have been made by a good method of analysis, that I am justified in giving a small number of examinations conducted for me after the Fokker-Salkowski method by my assistant, Herr Beyer.

The patient, who was about sixty years of age, had his first attack of gout in 1873, and then a fresh attack each spring. At first only the metatarso-phalangeal joint of the great toe was affected, at a later period also the ankle and knee joints. In 1879 he had a very violent and prolonged attack, with pains in both knee and ankle joints. After this the attacks were of short duration, but during the intervals of attack there was some irritability and stiffness of the affected joints. In February, 1892, he suffered again from a slight attack, with swelling and pain in both knee joints. The urine passed every twenty-four hours was collected, and the uric acid estimated.

* "Beiträge zur Lehre von der Harnsauren Diathese," 1891.

The urine contained—

On	3rd	February	... ...	0·532	grm. uric acid.
	4th	,,	... ...	0·430	,, ,,
	5th	,,	... ...	0·480	,, ,,
	7th	,,	... ...	0·682	,, ,,
	8th	,,	... ...	0·831	,, ,,
	9th	,,	... ...	0·499	,, ,,
	15th	,,	... ...	0·593	,, ,,

During the last eight days, from the 8th to the 15th of February, 1 grm. of piperazine was given daily. The average amount of uric acid eliminated was ·578 grm. per diem, or 0·720 per 100 kilogr. body weight, since the patient weighed 80 kilogr. This almost corresponds with Pfeiffer's data of the average excretion of uric acid in gouty subjects from fifty to sixty years of age, but is rather less than his figures for healthy persons of the same age. It follows also from my investigations, as well as from those of Camerer, Pfeiffer, and Ebstein, already referred to, that the excretion of uric acid in the gouty is of variable amount. It can without hesitation be asserted that it is not greater than in healthy persons of the same age, but it cannot be determined in what degree it is always diminished from the few estimations put forward. In the first place, it is easy to understand that the excretion of uric acid, which is so quickly and easily influenced by various extraneous circumstances in the healthy, as shown by Horbaczewski, will probably be subject to greater variations in the gouty.

The retention in the blood of a large quantity of uric acid is by no means to be expected. If there is reason to suppose that the kidneys excrete less than the normal quantity of uric acid in many cases of gout, the daily quantum must either be very small, or the uric acid decomposes in the blood into more soluble compounds

If it were not so the gouty tophi would assume much larger dimensions than are met with. It may here be mentioned that Salomon* was able to find uric acid only in fresh blood of the gouty. When it was kept for twenty-four hours at 37° C. the uric acid disappeared.

Ebstein is also of Garrod's opinion, that the deposition of biurate of soda in the cartilages, joints, subcutaneous tissues, etc., of gouty subjects is caused by an increased proportion of uric acid in the blood; but he does not think that this arises from an affection of the kidneys. Pathological changes in the kidneys have decidedly been observed in gout, and in these cases they very early become extremely atrophied, with irregular, uneven surfaces, thickened capsules, and the deposition of uric acid in the tubuli uriniferi or the interstitial tissue. This form of gout—primarily an affection of the kidneys—is comparatively rare. More frequently, according to Ebstein, the kidneys remain for a long time healthy, and there may be found at the autopsy extensive changes in the articulations, etc., without any naked-eye or microscopic signs of disease in the kidneys.

Ebstein's theory is that the excess of uric acid in the blood is caused by a very plentiful formation of this substance in the body; he believes, moreover, that in gout the formation of uric acid takes place in parts of the body which normally do not produce uric acid—as, for example, the bone-marrow, cartilages, etc.

The lymph, as at a later date the blood, contains a larger quantity of uric acid than normal, but the normal proportion is again reached by an increased excretion of uric acid by the kidneys, or, perhaps, by its decomposition in the blood. When, however, from any cause the lymph charged with uric acid moves more slowly, or

* Loc. cit.

cannot proceed farther, the so-called premonitory symptoms—such as feeling of tiredness, vague pains, and so on—make their appearance, and if an actual stasis of the lymph stream supervenes, the typical attack of gout is suddenly developed. The uric acid in a concentrated solution acts like a chemical poison, causes morbid processes in the tissues, and can give rise to necrobiotic changes.

The uric acid is deposited in the tissues only when the process of necrosis has reached a certain degree; when it has not advanced to this degree all local symptoms can again disappear, and the joint may return to a comparatively normal condition.

According to Ebstein, this theory is supported by various experiments. He found on dissolving the uric acid salts deposited in the cartilages of gouty subjects, that the cartilage did not appear normal, but showed destructive changes as far as the layer of uric acid had reached. Occasionally the destruction extended even farther, and he found in the gouty joints portions of cartilage in which destructive processes were developing, but which contained no uric acid salts. The uric acid in solution, consequently, does not act as a chemical poison till the reaction of the tissues has been changed from alkaline to acid by their necrosis, and the uric acid is then deposited as the biurate of soda.

Ebstein has experimented on birds and reptiles, the urine of which consists almost exclusively of uric acid salts. When both ureters were ligatured in hens, and the blood thereby saturated with uric acid, there occurred processes of necrosis in the liver and muscular substance of the heart, which became infiltrated with uric acid salts, and caused inflammatory changes in the surrounding tissues. Necrotic processes did not occur in the kidneys,

although uric acid salts were deposited in the tubuli uriniferi. By the injection of a solution of chromate of potash under the skin of hens, necrotic changes were set up in the kidneys, and deposition of uric acid salts took place in the necrosed parts.

Ebstein's theory explains in an ingenious way the origin of the acute attack of gout, as well as the chronic symptoms; but the theory can hardly hold its ground, and his method of proof presents many assailable points.

The experiments performed upon birds can have no weight in the consideration of what takes place in mammals and human beings, without further investigation. The urine of birds contains almost uric acid salts alone, and ligature of the ureters will therefore cause an extreme overcharging of the blood with uric acid. Such a thing cannot take place in mammals, as in them uric acid constitutes only a small fraction of the nitrogenous substances eliminated in the urine.

Moreover, by ligature of the ureters a condition is established which corresponds to uræmia, and not to gout. Ebstein's theory is based on the supposition that uric acid forms in parts of the body which normally take no part in the formation of uric acid, or, at any rate, do so to a very slight extent. But it is shown by the investigations of Horbaczewski that all tissues of the body, and especially those which abound largely in cellular elements, take part in the production of uric acid; and for this reason Ebstein's theory falls to the ground.

Pfeiffer has shown, by means of subcutaneous injection of uric acid salts, that a solution of them can set up decided pain and irritation, but cannot cause necrosis, especially in the degree of concentration in which they

can be said to occur in the body. This might take place with a solution of uric acid which, under such circumstances, acts as a powerful irritant, but uric acid occurs in the body only in combination with alkalies. In opposition to Ebstein's theory, Pfeiffer brings forward the fact that, with the exception of during the acute paroxysm, gouty subjects excrete less uric acid than those who are in health. (*Vide* page 57.) According to Ebstein's theory they should give off a larger quantity than healthy subjects, as they form a larger quantity of uric acid, and the kidneys perform their functions normally.

In Pfeiffer's opinion both gout and gravel are due to the fact that in these affections (*i.e.* in the uric acid diathesis) uric acid is produced and excreted in a difficultly soluble modified form. As these patients excrete on an average less uric acid than those in health, the blood becomes overcharged with it, and the uric acid salts are deposited in different parts of the body unnoticed, and without symptoms of irritation. According to Pfeiffer, the attacks of gout occur when, from any cause, the alkalinity of the blood becomes so great that it dissolves the already deposited urates. These then give rise to irritation and inflammation, as was the case in the experiments made by him with subcutaneous injections of a uric acid solution.

This opinion Pfeiffer thinks is supported by his observation that acids, especially salicylic acid in large doses, quickly alleviate pain in attacks of gout, while it is increased by the administration of alkalies.

Although this observation may be quite correct, it is not easy to follow the working out of the result. That is to say, it is by no means so easy to change the alkalinity of the blood by the administration of acids. Pfeiffer

prescribed 5 to 8 grm. hydrochloric or phosphoric acid daily, and believed to have so changed the reaction of the blood that subcutaneous injections of uric acid solutions were painless.

Other observers, as, for example, Freudberg,* have made very careful investigations into the effect of various acids and alkalies upon the reaction of the blood and urine. Freudberg found that 4 to 8 grm. per diem of the official hydrochloric acid did not at all change the reaction of the blood; 10 to 30 grm. of lactic acid diminished its alkalinity by $\frac{1}{5}$th to $\frac{1}{4}$th; 5 to 10 grm. of tartaric acid by $\frac{1}{6}$th. Doses of 5 to 15 grm. of bicarbonate of soda, in some cases, increased its alkalinity by $\frac{1}{4}$th; in other cases the reaction was the same as before the experiment. As Pfeiffer used in his experiments chiefly hydrochloric acid, it is probable that the blood of the individuals experimented upon had the same reaction after the administration of the acid as it had before.

In another respect also Pfeiffer's theory rests on a feeble foundation. According to his view, uric acid is produced and excreted in a difficultly soluble form in this diathesis, so that the urine ought also to show unusual chemical conditions. In Heintz's method for the precipitation of uric acid in the urine by hydrochloric acid, usually only part of the uric acid is separated, and a considerable quantity can still be found by the Ludwig-Salkowski silver precipitation method. According to Pfeiffer's examinations of the urine, that portion precipitated by the addition of hydrochloric acid appears to decrease as age advances. Moreover Pfeiffer believes to have found that when the urine of a gouty subject is passed through a uric acid filter of

* *Virchow's Archives*, Bd. 125, p. 566.

0·5 grm. uric acid, not only does it not dissolve uric acid from the filter, but so much is deposited on the filter that no precipitation of uric acid takes place on the addition of hydrochloric acid to the filtrate.

Although he admits that sometimes this experiment fails, without palpable cause, yet he believes, on the whole, it is so trustworthy that it can be used as a test for the uric acid diathesis, equally applicable whether this appears as gout or gravel. Healthy urine will also give up its uric acid in the same way, but in Pfeiffer's opinion it is necessary to pass it through a much larger quantity of uric acid, say 2 to 3 grms. From all his investigations Pfeiffer concludes that uric acid occurs in healthy urine, in an easily soluble form, while in gouty subjects (except during the acute attacks), and in those who suffer from gravel, it appears as a difficultly soluble modification, and is therefore deposited more easily. In his opinion the uric acid changes from the difficultly soluble to the easily soluble form, during the attack of gout.

Pfeiffer's observations have been confirmed by Schetelig * and Camerer †; but have been strongly attacked by Ebstein,‡ Feliziani,§ and Roberts.‖ These writers have shown by many experiments that filtration with the uric acid filter gives very variable results. Feliziani examined the urine in 13 cases of gout, and found that the uric acid was separated in 6 of them by this means, while in 8 other cases a considerable quantity of uric acid remained in solution. On the other hand,

* *Verhandlungen des Congres. für innere Med.* Wiesbaden, 1889.
† *Deutsche med. Wochensch.* 1891, 10 u. 11.
‡ Ibid.
§ *Revista gener. di Clinic—S. Revue des Sciences Med.* 1890, p. 460.
‖ *Lancet*, 1890, i. p. 9.

numerous experiments with healthy urine gave evidence of those conditions which were considered by Pfeiffer characteristic of the uric acid diathesis.

Roberts has pointed out that almost the whole proportion of uric acid can be removed by passing the urine again and again through the same uric acid filter; the same result is reached, whether the urine is that of a healthy or of a gouty person.

In any case, there is no reason to suppose that in this diathesis uric acid is formed as a difficultly soluble modification. As already explained on page 51, Roberts has shown that the decomposition of the quadriurates in the urine depends upon its composition, and is accelerated by its concentration, by a strongly acid reaction, by the absence of neutral phosphate of soda, chloride of soda, and pigment. It is therefore probable that similar conditions give rise to the deposition of uric acid, and the uric acid crystals on the filter act only by favouring the collection of the uric acid.

Among the theories of gout we may also mention Haig's.* He believes that the excess of uric acid in the blood, whether it be due to hyperproduction or retention, shows itself first of all as an irritation of the vasa-motor nerves, by means of which the blood pressure is raised in the arteries and particularly in the smaller vessels. According to Haig, the increased blood pressure can give rise to a whole series of nervous and secretory disturbances, as a result of which he details numerous conditions (such, for example, as migraine and epilepsy), as signs of the uric acid diathesis. Haig's view has not received confirmation, and is not borne out by the data which he brings forward in its support.

Although the earlier hypotheses of the nature of

* *Lancet*, 1890, ii. p. 281, and St. Barth. Hospital Report, 1890.

gout hardly establish themselves, material for a tenable theory appears to be afforded by the researches of Roberts and Horbaczewski.

It may at once be admitted that an abnormal quantity of uric acid is found in the blood in gout. Upon this point all pathologists are agreed, and all observations indicate that the symptoms in gout can arise only from this chemical constitution of the blood.

In order to discover the conditions under which the biurate is deposited from the blood, Roberts endeavoured to imitate artificially the chemical composition of the blood serum of gouty people. He dissolved various amounts of pure uric acid in serum, and found that the appearance of the fluid changed after longer or shorter time; it became turbid, and deposited crystals of biurate at first only in microscopic quantities, but later also in amount quite perceptible to the naked eye. If the fluid was kept at the usual room temperature, and a few drops of chloroform added to keep it aseptic, all the uric acid was thrown down after a few days.

The more uric acid dissolved, the more quickly occurred the formation and deposition of the biurates.

Uric Acid dissolved in Serum.	Deposition of Biurate Crystals.	
1 in 1,000 after	6 hours a few crystals.	After 14 hours many.
1 in 2,000 „	33 „ „	„ 3 days „
1 in 3,000 „	3 days „	„ 12 „ fairly abundant.
1 in 4,000 „	6 „ „	„ 12 „ „ „
1 in 5,000 „	13 „ „	„ 30 „ „ „
1 in 6,000 „	14 „ no crystals.	„ 40 „ a few.
1 in 8,000 „	14 „ „	„ 40 „ no crystals.

It follows from this experiment that an excess of uric acid in serum cannot remain long in solution. If the uric acid is not eliminated by the kidneys, the

increased quantity will tend to its deposition in the body as biurate.

Roberts does not say how the retention of uric acid in the blood takes place, although he explains the origin and all the symptoms of gout by such a retention.

Only two explanations of the overcharging of the blood with uric acid appear possible. It must either be formed so abundantly that some is stored up in the blood, although the normal quantity is still excreted; or the production of uric acid being normal, or even diminished, an abnormal quantity is retained in the blood—in other words, the disease must be caused by a functional irregularity of the kidneys. There is still another explanation conceivable, namely, that under normal conditions uric acid is oxydised in the blood into a more soluble substance, while in gout this oxydation is not performed, or only imperfectly so.

The last theory, which used to be generally accepted, must now be entirely abandoned. The more recent researches have clearly shown that uric acid, being formed in the body by increased activity of the cellular elements, is very rapidly excreted with the urine. Moreover, v. Jacksch has shown by analysis of the blood that the diseases which were suspected of delaying the oxydation of the uric acid—as, for example, diseases of the heart and lungs—do not lead to an increased proportion of uric acid in the blood.

There remains, therefore, only the first two hypotheses: there must either be an increased production of uric acid, or it is with difficulty excreted by the kidneys.

We shall now endeavour to show that increased production alone of uric acid never leads to gout, but that it is more likely that changes in the action of the kidneys are its cause.

This theory has already been given by Garrod, but the analyses of the blood and urine, by which he sought to establish it, were performed by unreliable methods, and cannot be put forward as proofs. Later investigations, however, have shown that in all probability Garrod was right. There has already been given (page 56) a series of accurate examinations of the urine, all of which show that the excretion of uric acid is not greater in gout than in health, but that it is much more common to have a slight decrease in the daily excretion.

On the other hand, there is abundant experience to decide that an increased production of uric acid does not lead to gout, as long as the kidneys retain their normal functions; while the same unfavourable circumstances, which predispose to kidney diseases, are also known to give rise to gout.

Leucocythæmia may be named as a typical example of a disease, accompanied by a constant excessive production of uric acid, without usually being associated with gout. Very many writers—Bartels, Camerer, Laache, Bohland and Schurz, Stadthagen, etc.—found 3 to 4 grms. of uric acid per diem in the urine of leukæmic patients, and as this hyper-excretion lasted for a considerable time, it can have been caused only by an increased formation of uric acid, which must exist in the blood also, in a larger quantity than is normal.

The fact that gout is a disease of middle age may be brought forward in support of the view that it cannot arise from an excessive production of uric acid, as long as the kidneys act normally. Garrod, it is true, has seen a few cases of gout in children; older works (Scudamore) relate a similar experience, which the most recent writings confirm. Maboux* has seen an undoubted attack

* *Mercredi Medical*, Bd. 23, 1892.

of gout in a girl of eleven, and Dyce-Duckworth* tells of a patient, eighteen years of age, who had suffered from gout for nine years.

These are, however, exceptions: gout is extremely seldom met with in childhood and in youth. Nevertheless, the formation of uric acid is greatest in childhood, and appears to diminish in proportion to the advance of age (page 25).

A great many facts support the contention of Garrod and Roberts, that gout is caused by a retention of uric acid in the blood, and makes it most probable that this retention is occasioned by an affection of the kidneys.

It has already been shown that various diseases of the kidneys can give rise to retention of uric acid. v. Jacksch found on examination of the blood of twelve patients suffering from kidney disease of different kinds, that uric acid was present in nine cases—namely, in four cases of acute nephritis, two of chronic nephritis, one of waxy degeneration, and two of granular kidney. One of the two negative cases must be left out of count, as the quantity of blood (7·7 grms.) subjected to analysis was not sufficient. The quantity of uric acid in the blood was largest in atrophy of the kidneys and in uræmia.

Moreover, it must be remembered that several causes are common to gout and the chronic kidney affections usually designated Bright's disease.

Abuse of alcohol is mentioned by all observers as a harmful agent, which very often gives rise to gout. Garrod names several old writers who have observed it, and is himself of the opinion that continuous and extensive taking of spirits is a frequent cause of gout, although all alcoholic beverages are not equally injurious.

* *Lancet*, 1893, i. p. 144.

Later writers—as, for example, Camerer and Rendu*—have emphasised this fact.

Rendu points out, however, that the number of alcoholics greatly exceeds the number of gouty people. It must be remembered that alcohol belongs to the poisons, and their action varies greatly in different individuals. It is just possible that, when the hereditary predisposition exists, alcohol so affects the kidneys that it gives rise to the excretory changes characteristic of gout.

Garrod quotes a statement, recorded by William Budd, that certain workmen, who make a living by removing ballast from the bottom of the Thames, which can be done only when the tide is ebbing, and who must work very rapidly in any weather and at any hour, are very often attacked by gout. These men consume a great quantity of alcoholic drinks, but live like English workmen in other respects. They get into a state of violent perspiration with their heavy work, and are often wet through by rain or snow, without being able to leave off work. It cannot be denied that the same harmful agents, which give rise to gout in these cases, are also common causes of chronic kidney disease.

Lead poisoning resembles alcohol, in giving rise both to gout and to chronic kidney affections. In all writings upon the pathological anatomy of lead poisoning, the kidneys are always found altered. There is set up an interstitial nephritis, which shows itself as an atrophy of the organ, roughening of the surface, adherent capsule, and the formation of small cysts in the kidney substance. Writers do not agree as to the manner in which

* "Diction. Encycloped. des Sciences Med.," 1884, Article "Goutte."

this affection develops; but the statement, put forward by Charcot and Gombault,* appears to rest on the best foundation. These investigators found, on feeding guineapigs with white-lead, that in acute poisoning no disease of the kidneys resulted; but in the chronic poisoning a pronounced granular atrophy, with excessive formation of interstitial tissue always developed. The urinary tubules were first attacked with proliferation of their epithelia, the formation of casts, etc.; and then the disease spread to the interstitial tissue, involving almost equally the cortical and medullary portions of the kidney. They noticed, moreover, that the kidney substance was not uniformly affected, healthy and unhealthy portions alternating with each other. Corresponding to this there formed, in the later stages of the disease, a regular granulation of the surface of the kidney.

Chronic lead poisoning always leads to a chronic disease of the kidneys; at the same time it also tends to give rise to gout. This fact was mentioned by a few older writers, but attracted attention only after Garrod had made the statement that one-fourth of the gouty patients whom he treated at University College Hospital were painters or other artisans who had contracted chronic lead poisoning; and that in his private practice also he had often observed the combination of gout and chronic lead poisoning.

More recently many writers, especially English and French, have related similar experiences, among them Charcot, Bucquoy, Jaccoud, Ollivier.†

* *Archives de Physiologie, Norm. et Path.*, 1881. *S. Hirsch-Virchow's Jahresb.*, Bd. i., p. 123.

† "Dictionnaire Encycloped. des Sciences Med.," 1884, Article "Goutte."

Lancereaux * has collected twenty-four cases of nephritis due to lead-poisoning, one-third of which showed signs of gout, such as tophi, etc. Dyce-Duckworth † found among 136 gouty patients, twenty-five who exhibited symptoms of chronic lead poisoning, and one-fourth who suffered from chronic nephritis.

With regard to experiments on animals, it may be mentioned that Prevost and Binet ‡ have produced chronic and interstitial nephritis by feeding animals on salts of lead. Most of the lead taken into the body was eliminated by the kidneys. Ellenberger and Hofmeister § have seen a corresponding action of lead salts in experiments on sheep.

Garrod found uric acid in the blood of patients affected with chronic lead poisoning, even when they showed no symptoms of gout; and he believed he could prove that the quantity of uric acid excreted in the urine could be diminished by the administration of lead salts in the usual medicinal doses.

Moreover, if one takes into consideration that the description of the early stages of gouty kidney, which is without exception given in every work on the pathological anatomy of gout, entirely corresponds to the description of the kidney of lead poisoning, it appears almost certain that both these kidney affections, which so closely resemble each other, act in the same way upon the body and upon metabolism. Lead poisoning then, in which the kidneys are very early affected, gives rise to gout, and it is also probable that the primary cause of

* *Hirsch-Virchow's Jahresb.*, 1882, Bd. ii., p. 234.

† *Union Médicale*, 24, 11, 92.

‡ *Revue Suisse. Hirsch-Virchow's Jahresb.*, 1891, p. 384.

§ *Bericht über das Veterinärwesen im Konigreich Sachsen Hirsch-Virchow's Jahresb.*, 1885, Bd. i., p. 406.

gout, even when lead-poisoning does not enter into consideration, is an affection of the kidneys, by means of which their ability to excrete uric acid is diminished.

Garrod * found pathological changes in the kidneys of patients who had had only one or two attacks of gout; although Ebstein † asserts that the kidneys of gouty patients may be found perfectly healthy at the autopsy. It is, on the other hand, to be noted that the kidney disorder at its commencement need give rise to very few anatomical changes, as the primary cause is a decrease in the secretory power of the kidney, whereby uric acid, alone or in combination with other constituents of the urine, is less easily eliminated. Charcot ‡ has drawn attention to the fact that, in commencing interstitial nephritis, in which the excretion of the very soluble urea is not at all affected, various other substances—as, for example, certain odoriferous bodies—cannot pass off in the urine. He also refers to the circumstance, often met with in gout, that the administration of turpentine does not give to the urine the characteristic odour of violets, which is never absent when this drug is medicinally employed in other instances.

Against the supposition that retention of uric acid is the origin of gout, the reply has been made that the disease would progress quickly and uniformly if this were the case. Nevertheless, it has been overlooked that the production of uric acid is not always of the same amount, but may increase from time to time, through various influences and diseased processes, and return again to the normal. Further, that the entire extent of the kidneys is not simultaneously attacked. Even in

* "Natur und Behandlung der Gicht."

† *Beiträge zur Lehre von der Harnsauren Diathesen*, 1891.

‡ *Leçons sur les Maladies du Foie et de Reins*, 1877, p. 320.

lead poisoning, where the kidney affection most rapidly develops, portions of the organ remain healthy for a long time, by means of which a certain amount of uric acid can be eliminated, and it is known that in other affections of the kidney, the one kidney can take on the function of the other, the healthy portions doing the work of the unhealthy within certain limits. It is, therefore, conceivable that, in the early stages of gout, the biurate is deposited in the tissues when from any cause the production of uric acid becomes exceptionally great. At a later period, when the kidney disease has extended, the deposition of the biurate occurs more frequently, and then the true attacks of gout and larger tophi make their appearance.

The above conception of the pathogenesis of gout requires further proof. It has, however, the advantage over the other theories that it brings into one category all the etiological and pathogenetic factors with which we are acquainted, and gives a plausible explanation of gout both in poor and badly-nourished subjects and in the rich and *bon-vivants*. By it the enigmatical gout of lead poisoning is intelligible in the same way as the other forms of gout.

It may also enable us to establish a rational form of treatment, instead of the old empirical methods of therapeutics, which often enough were directly opposed to each other.

If the possibility of a retention of uric acid is once admitted, then every circumstance which causes a temporary increased formation of uric acid will naturally take effect, so that the blood can no longer hold in solution the quantity of uric acid with which it is charged; the uric acid is then deposited as biurate, and the blood by this means rendered pure for some time. If the

deposition goes on slowly without hindering the circulation in the small lymph channels, then new tophi are formed, or old ones increased in size, without the patient experiencing further suffering. When the deposition of biurate suddenly obstructs the lymph channels, pain and inflammatory symptoms set in, and the typical attack of gout is established.

In this manner, the extensive use of alcohol, and also excessive bodily or mental work, may give rise to an attack of gout, as often related. The proportion of uric acid in the blood can, in another way, also affect the occurrence of gout. Roberts found that in a solution of 1 part of uric acid in 5,000 of serum, crystals of biurate separated equal in length to a blood corpuscle, or at most two or three times as long; while, in a more concentrated solution, the biurate crystals which deposited were both longer and broader. The larger and more voluminous the crystals the more easily do they obstruct the lymph channels, or give rise to the formation of thrombi.

In serum rich in soda salts the biurate crystals are more easily separated than usual. In a solution of 1 of uric acid in 1,000 of serum the deposition of microscopic crystals commenced in six hours, and they were most plentiful in fourteen hours; but when Roberts added to this solution 2 per mille of sodium chloride, crystallisation began in five hours, and was very abundant in twelve hours.

In a solution of 1 of uric acid in 2,000 of serum, crystallisation commenced in thirty hours, and was copious in ninety-six. When, however, 2 per mille of phosphate of soda was added, it commenced in twenty hours, and was abundant in forty.

All salts of potash, irrespective of the acid with which they are combined, delay the deposition of crystals

of biurate. Bromide and iodide of potash act in this respect like the carbonates and phosphates; the reaction also of the potash salts was a matter of indifference, the neutral iodide having the same effect as the alkaline carbonate of potash.

Salts of lime and magnesia show no decided action, although they appear to slightly delay deposition. Lithia salts and piperazine, in the proportion of 0·1 to 0·2 per cent., do not really affect the rapidity and the degree of deposition.

The biurate crystals become deposited chiefly in the different kinds of cartilage, ligaments, tendons, skin, and subcutaneous tissues; especially tissues bathed in synovia become infiltrated.

According to Roberts, the explanation of this circumstance is to be found in their chemical composition; the tissues rich in soda being earlier attached than those which contain less salts of soda.

Roberts gives the proportion of sodium salts in different tissues as follows:—

Serum	contains	0·70	per cent.	sodium salts.
Lymph	,,	0·70	,,	,,
Synovia	,,	0·80	,,	,,
Cartilage	,,	0·90	,,	,,
Fibrous tissues	,,	0·70	,,	,,
Blood corpuscles	,,	0·20	,,	,,
Brain	,,	0·20	,,	,,
Muscles	,,	0·08	,,	,,
Spleen	,,	0·04	,,	,,
Liver	,,	0·02	,,	,,

From this table it is easy to explain why synovia is so intimately concerned in the development of gouty phenomena. In the first place, synovia contains more salts of soda than serum or lymph; and secondly, it is

enclosed in a cavity, where it has little opportunity for movement or renovation. Blood and lymph, being subject to more continuous and rapid movement, cannot deposit many crystals in every situation; but when synovia is saturated with uric acid, it can rid itself of the excess by depositing biurate crystals in the joint-cavity. In the slighter forms of gout the disease is limited to single joints, and to the surfaces of the cartilages and the tendons with which the synovia comes in contact. The cartilage appears to become impregnated by the synovia in a purely mechanical manner.

Roberts suspended the metatarsal bone of a young pig in a flask of warm concentrated solution of sodium biurate; and after adding a few drops of chloroform, to keep the solution aseptic, left it standing at the ordinary room temperature. As soon as the solution cooled, the biurate gradually fell down, and after some time Roberts found that the cartilage of the bone suspended in the fluid was infiltrated with crystals, which, just as in gout, were chiefly laid on the surface of the cartilage, and became less frequent towards the depth.

Although we can understand that the joints should particularly become affected, it has still to be made clear why a few joints, such as the metatarso-phalangeal joint of the great toe and the knee joint, are more apt to be attacked in gout. Roberts was inclined to think that the state of the temperature might be of importance, and that the joint which was subject to frequent exposure might be specially liable to attack, but found nothing to support this view on experimenting with solutions of uric acid in serum. The rapidity of crystallisation was influenced neither by rise nor fall

of the temperature, but was always the same at blood heat.

The explanation must rather be sought for in the experience that wounds, blows, and continuous pressure appear to dispose to gouty affections.

Garrod * has observed, as already stated, that the joints mentioned above are chiefly affected in gout, and that any exception to this rule is usually due to a contusion or trauma of another joint. In one case a patient who had injured his knee joint did not at first experience any inconvenience, but in a few days the pain became unbearable, and a typical attack of gout developed, complicated a little later by a similar attack of the great toe.

Pfeiffer † likewise mentions that he had noticed gouty concretions, particularly upon those parts of the body which had been subject to injuries or lesions of various kinds.

It is now sufficiently well known that the metatarso-phalangeal joint of the great toe is more exposed to injury than any other. In walking, it bears the weight of the rest of the body in the position of hyper-extension, it suffers very frequently from contusion and strain, and is often subjected to pressure from badly-fitting boots in all directions and positions.

Apart from the question of gout, this joint is subject to painful and irritable states caused by strain alone, or by any kind of contusion.

For several weeks I saw a patient who was suffering from pain in this joint, so severe that it caused him great distress on walking. It was treated by massage without success, and only disappeared on the discovery that the

* "Natur und Behandlung der Gicht."

† "Verhandlungen des Congresses für innere Medicin," 1889, p. 166.

patient was in the habit of holding his bed-clothes in position during his sleep by pressing the great toe of one foot against the end of his bed. In another case a young mother had developed a similar condition of this joint by dancing her child on her knee with her foot resting on the great toe alone. In both cases the trouble rapidly disappeared when the cause was discovered.

In other cases any hindrance to the circulation will favour the onset of a gouty disturbance. Charcot reports the occurrence of gout in a hemiplegic in whom the joints on the paralysed side only were attacked.

A very sedentary life without bodily exercise is said by many authors to predispose to gout. Roberts remarks that this may perhaps be explained by the synovial fluid in joints which are very little used becoming more watery and more plentiful than in the normal state, and at the same time containing less albumen and more soda salts than normal synovia. This circumstance has been corroborated by Frerichs * by a comparison of the joints of stall-fed animals and those used in field work.

Although the well-known and often-described pathological changes in cartilages, ligaments, tendons, etc., are usually found at the autopsy of gouty patients, in some cases no such changes are found. This must be due either to the concretion again becoming dissolved, or to the deposition of biurate crystals, without giving rise to painful disturbance in any joint, taking place in some part of the body not subjected to examination at the autopsy. Roberts mentions that Dyce-Duckworth had made an autopsy on one patient who had suffered from

* *Wagner's Hand-wb der Physiologie*, 1884, Bd. iii. Abth. i. p. 466.

a typical gouty attack of the great toe, etc., without finding any pathological changes in the joints. Small tophi can appear and again disappear in the upper part of the ear; and Dyce-Duckworth has found gouty changes in joints in which neither pain nor signs of inflammation had been observed by the patients, and where the deposition must have gone on without producing any symptoms.

If serum or synovia contains uric acid in the proportion of 1 in 6,000 or more, crystals of biurate are deposited; on the other hand, the blood can again take up uric acid if it contains a less quantity than 1 in 6,000. The re-dissolving of the crystals can take place most readily in fibrous tissues, in the skin, and subcutaneous tissues, as here the circulation of lymph is more active; while in cartilage it is more difficult, as the lymph moves more slowly.

Uric acid dissolved in the blood does not appear to act as a poison. A gouty individual may feel in perfect health up to the onset of an attack, and yet directly before this the blood must contain a large amount of uric acid. According to Roberts' showing, the inflammatory phenomena and the pain are brought about quite mechanically, the biurate crystals acting as a foreign body, obstructing the lymph canaliculi, and giving rise to thrombosis. In this respect the size of the crystals is important, but there appears to be a greater disposition to inflammation, etc., by obstruction of the lymph canaliculi in firm cartilage, than when these pathological conditions make their appearance in loose subcutaneous tissues or in the skin.

SYMPTOMATOLOGY, COURSE, AND PATHOLOGICAL ANATOMY.

These are so well known and so fully described in every monograph and in every text-book of pathology that I have no inclination to go over ground so familiar, especially as the more recent writers have given us nothing really new on these points. It must, however, be mentioned that Roberts has endeavoured to explain the attacks of irregular gout by the deposition of biurate crystals in unusual situations; as, for instance, in the meninges, neurolemma of nerves, etc., and thus giving rise to the so-called visceral symptoms. In the literature of the subject the existence of such a condition has several times been mentioned.

Watson, Gairdner, and Dufour report the finding of biurate deposits upon the meninges; Cornil found microscopic crystals of biurate in cerebro-spinal fluid; Albert has seen uratic concretions on the spinal meninges; Ollivier found at the autopsy of a gouty subject who had been troubled with a feeling of constriction in the throat, chest, and abdomen, as well as lancinating pain in the extremities, deposits of biurate on the spinal dura mater, from the third cervical vertebræ to the sacrum, extending for some distance along and compressing the roots of the spinal nerves. Further, Schroeder van der Kolk* has seen aggregations of biurate crystals in the neurolemma of peripheral nerves.

These observations, however, are very limited in number, and we must suppose that the irregular gouty concretions in most cases again become dissolved, or perhaps are overlooked in the post-mortem room.

* *See* Le Gendre: "Traité de Médicine," Paris, 1891, tome i., p. 492.

PROPHYLAXIS, AND TREATMENT.

In most cases of gout hereditary predisposition plays an important part. Against this hereditary tendency itself nothing can be attempted. It appears not to be transmitted in equal degree to all members of a family; the women especially escaping, or being attacked much later in life. This may perhaps be explained by the more regular mode of life and greater abstinence of women from alcoholic beverages, which may partly neutralise the hereditary predisposition.

On the whole, all forms of alcohol must be classed among the most important agents in the production of gout; and the use of alcoholic drinks is fraught with danger to every person suffering from gout, and to those who have a predisposition to it. Alcohol is injurious both by increasing the production of uric acid and by diminishing the excretory power of the kidneys by its continued use.

As the kidneys are so largely concerned in the origin of gout, every form of prophylactic treatment which diminishes the risk of kidney disease is specially indicated. It is, therefore, advisable to stimulate the skin, and harden it against changes of temperature; and for this purpose cold friction or sponging the whole body may be successfully employed: it should be commenced in childhood, and continued throughout life; also dry friction of the skin, continuance in the open air, suitable—and especially woollen—clothing, gymnastics, and other forms of bodily exercise. It is specially to be noted that every over-exertion must be avoided.

Excessive exercise is a source of danger, because it can suddenly increase the production of uric acid to

such an extent that the kidneys cannot excrete the amount produced. Several older writers, like Scudamore and others, mention that they have seen attacks of gout set in immediately after excessive bodily or mental exertion.

Particular attention has always been given to the question of diet in the treatment of gout. Putting aside abstinence from alcohol—upon the injurious effects of which almost all authors agree—the opinions as to the suitable diet differ widely from each other, as they have been founded upon the various theories of the nature of gout.

As uric acid was considered by many a product of the disintegration of the albumen of the food, it followed that flesh and other albuminous foods were forbidden, and stress was laid upon the great importance of an almost vegetarian diet. Other writers (Cantani), on the other hand, believed in a kind of Banting cure, with a diet preponderating in flesh food, and particularly forbade carbohydrates. Roberts also is of opinion that nitrogenous articles of food must be considerably diminished, while he allows an unlimited quantity of sugar and starch. All these recommendations aim at limiting the excessive production of uric acid. As long as the kidneys retain their normal functions—that is, in all individuals with an hereditary predisposition, but still without any symptoms of gout, whose urine for three or four consecutive days, on the usual mixed diet, shows no abnormal decrease in the proportion of uric acid—there is no reason to order a fixed diet: such patients can be left to their own discretion within certain limits. When a little more uric acid than usual is formed, it can be eliminated in the urine, without being stored up in the blood.

One must also take into consideration, as shown by the researches of Horbaczewski, that the excretion of uric acid becomes rapidly and considerably increased after a meal consisting largely of flesh food, and that a similar, though rather less, increase takes place after a vegetarian meal. Moreover, the investigations of Bleibtreu and Schultze show (*vide* page 29) that the excretion of uric acid during twenty-four hours is almost as large on a purely vegetarian diet as on a mixed diet, or even as on one in which flesh food preponderates.

Even in the pronounced form of gout also, there appears no reason to forbid certain articles of food. A rational mixed diet, in which the usual nutritive elements are uniformly distributed, is much more to be recommended.

On the other hand, it is right to condemn very large meals, especially taking part in banquets and such-like. Indulgence in an unreasonably large quantity of food is quite as severe a trial to the kidneys as it is to the stomach and liver; and at such big meals there is always a temptation to take large quantities of wine or other alcoholic drinks.

What has been said here of the diet holds good for all stages of gout. When repeated attacks of gout occur, or when the disease is already chronic, one must endeavour to maintain the strength of the patient by a sufficiency and variety in the food.

The treatment of the acute attack must consist in as little interference as possible. The treatment of the old writers consisted chiefly in patience and the application of flannel, or such-like, and the attempts made to cut short the attack by drugs were in the most fortunate cases without avail. There are, however, many observations which show that a too energetic

use of therapeutics has caused sudden death or very severe after-effects.

In accordance with the theory already referred to, alkalies, especially salts of soda, have been recommended in order to dissolve the urate of soda or to prevent its deposition; or when one dreads, like Pfeiffer, the solution of the uric acid salts in the blood, acids are prescribed to diminish the alkalinity of the blood.

Both recommendations are at the best decidedly useless. All writers who have specially studied the reaction of the blood—as, for instance, Rumpf,* Peiper,† and Freudberg ‡—found that its alkalinity is, on the whole, subject to very little variation; that the reaction is not in the least altered by the administration of mineral acids (as Pfeiffer recommends); while, by giving a fairly large quantity of organic acids, as 10 to 30 grms lactic acid, or 5 to 10 grms. tartaric acid daily, the alkalinity of the blood is decreased by one-sixth, one-fifth, or one-fourth; and that it is impossible to further diminish the alkalinity by the administration of acids. Jaquet§ injected a considerable quantity of acids directly into the veins of living animals, without thereby decreasing the alkalinity of the blood to an appreciable extent.

The soda salts have been the most commended of the alkalies, although several very observant authorities have freely expressed the opinion that they have seen only harm, and never good, from their use. Trousseau‖ likewise thinks that the administration of bicarbonate of soda merely changes the typical attack of gout into

* "Centralblatt für klin. Medicin," 1891, p. 756.
† *Virchow's Archiv*, Bd. 116, p. 337.
‡ *Virchow's Archiv*, Bd. 125, p. 556.
§ *Archiv für exper. Path. u. Pharm.*, 1892, p. 311.
‖ *Clin. Med.*, 1877.

a slow chronic malaise; and a similar opinion has been expressed by Golding-Bird and Owen-Rees.*

It is also known, from the experimental researches of Roberts, that an excess of soda salts always hastens the precipitation of biurate in serum; and all medication of an acute attack of gout by soda salts is absolutely to be set aside. The same thing applies to the lithia compounds and the most recent gout medicine, piperazin, which has been largely praised during the last few years as a solvent of uric acid. Both piperazin and lithia are unable to delay the deposition of biurate crystals in serum, and are consequently useless.

When piperazin was being recommended on all sides a year ago, I tried it in two cases of slight attacks of gout. One gramme was given daily, dissolved in ordinary soda-water. The result was absolutely negative; the attacks lasted even longer than usual, and the drug was most unpleasant to the patients. In one of them, the urine passed during twenty-four hours was collected, and the amount of uric acid estimated after the Fokker-Salkowski method, in order to find out if piperazin increased the daily excretion of uric acid, as this would most probably be the case if it exercised a solvent action on the biurate deposit. On the day before the piperazin was given the amount of uric acid was 0·532 grm., and on the following days, with 1 grm. of piperazin administered daily, it was:—

0·430 grm. per diem.
0·480 „ „
0·682 „ „
0·831 „ „
0·499 „ „

and on the day after stopping the piperazin,

0·593 grm. per diem.

* Rendu: "Dict. Encyclop." Article "Goutte."

Only on one day, therefore, was the amount of uric acid appreciably increased; and this may have been occasioned by the attack of gout, and the fever arising therefrom.

The employment of the potassium compounds appears much more reasonable, and various authorities —as, for instance, B. Bouchard*—have warmly recommended their use. Roberts found that the salts of potassium—the iodide and bromide, as well as the carbonate and acetate—delayed the precipitation of biurate in serum. Haig† also commends the administration of potash salts, although from quite a different motive.

The preparations of colchicum are among the drugs most frequently employed in the treatment of the acute attack of gout. It was at first employed by quacks, and subsequently found a certain amount of favour among medical men. Colchicum, given either as the extract or the wine, appears to alleviate the pain of the gouty attack—at least, this is the opinion of patients. On the other hand, it does not appear to have any effect on the constitution of the blood or the uratic deposits in the joints. Some physicians‡ believed that the attack could be cut short by large doses of colchicum: it is generally advised, however, to refrain from attempting this until the pain, of its own accord, begins to abate. When the attack takes a slow tedious course, an endeavour may be made to bring it to an end by means of colchicum. A fresh attack is then said to occur before long, which in some cases may be preferred to the long duration of a half chronic condition.

No explanation of the effect of colchicum has yet

* "Maladies par Relentissement de la Nutrition," 1882.

† St. Bartholomew's Hospital Reports, 1891.

‡ Le Gendre: "Traité de Medecine," 1891, tome i. p. 495.

been found; perhaps it is due to an action upon the peripheral nerves, by means of which the painful sensations become alleviated. One must take care that the dose is not so large as to give rise to vomiting and diarrhœa, as the health of the patient thereby suffers greatly.

Among the drugs used in gout, quinine and salicylate of soda may also be mentioned; the latter, owing to its success in acute rheumatism, has also been tried in gout, but has by no means proved of like service in this disease.

Most observers sound a note of warning against the use of opium preparations and morphia. It is difficult to refuse the patient the rest which can be obtained by a few drops of morphia solution, or, perhaps, better still, by an equal dose of chloral. Hypodermic injections of morphia are considered particularly dangerous, probably due to the existing affection of the kidneys, whereby the elimination of morphia is rendered difficult, in the same way as morphia is a dangerous remedy for the headache and neuralgia of commencing uræmia.

Of other forms of treatment, warmth, rest, elevation of the part, and wrapping in flannel have always been praised. More recently, the judicious inunction of a 10 to 20 per cent. ichthyol ointment has been recommended. Schwimmer* has spoken in favour of ichthyol. I have tried it in this way only in a few cases, and in these I have certainly experienced an analgesic action; the alleviation of pain commenced in a few hours (four to six), and was lasting.

When the attack and extreme pain have passed away, and only stiffness and sensitiveness of the affected joint remains, convalescence may be accelerated by

* *Wiener med. Wochenschr.*, 1892, No. 29 u. 30.

careful massage. It is also advisable not to keep the patient at rest longer than the pain renders necessary. Usually, both redness and painful sensations disappear more rapidly when the patient carefully uses the joint in walking, etc.—as soon as his strength will in any way permit of it—than when he is kept in bed till all inflammatory symptoms are gone.

The galvanic current was formerly recommended in the treatment of uratic deposits, just as it has been tried in almost every other disease; this treatment was almost forgotten, when Edison drew attention to it again by favourable comments, which made their appearance chiefly in the daily press. It is difficult to see how success can attend the use of the galvanic current. Something might rather be expected from the modified electrical treatment introduced by Foveau de Courmelles* under the name of "Bielectrolysis." This author made the following experiment:—Crystals of urate of soda or oxalate of lime were enclosed in an animal membrane, and the small packet so formed was immersed in a saturated solution of carbonate of lithia, and the galvanic current allowed to pass through the solution and the packet. He found that the outer surface of the membrane was rapidly covered with crystals, while those inside dissolved and disappeared. The treatment consists in conducting a galvanic current through the affected joint or the skin tophi by electrodes, moistened in a concentrated solution of carbonate of lithia (or, perhaps, iodide of potassium).

When the attack is once over, the next question is: What can be done for the patient so that the next attack may not set in at an early date, and that the tophi already formed may be made to disappear? For this

* *Universal Med. Journal*, Jan., 1893.

purpose, the administration for a long period of soda or lithia salts, as well as the drinking of the strong alkaline springs of Carlsbad, Vichy, Ems, etc., or common salts waters like Homburg, Kissingen, and Nauheim, are usually recommended.

Mordhorst* believed that he could prepare a water particularly adapted to gout by dissolving a considerable quantity of bicarbonate of soda in the Wiesbaden Kochbrunnen, which contains a large quantity of sodium chloride. It follows from what has already been said that the only way in which soda salts can be considered to have a curative effect upon a gouty tendency is by their action as diuretics. Beckmann† made some experiments on himself with carbonate and citrate of soda, and believed he found that they were of some influence in this respect; on the other hand, the quantity of uric acid excreted is not in the least increased by the taking of alkalies. According to the researches of Spilker,‡ the prolonged use of alkalies brought about even a slight diminution in the daily excretion of uric acid; but probably this must be explained by a decreased production of uric acid in the body, and not by its retention in the blood.

It is evident that there is no indication for the employment of mineral springs containing soda in gout if their use succeeds in increasing the proportion of soda salts in the blood in an appreciable degree; the only result is to increase the likelihood of the formation and deposition of biurate of soda.

* "Verh. des. X. Congres. für innere Med., 1891," Wiesbaden.

† "Experimentelle Untersuchungen über den Einfluss des Hohlen- und Citronensauren Natron," Diss. Dorpat, 1889. Hirsch-Virchow's *Jahres Vericht*, 1889, i. p. 155.

‡ *Virchow's Archiv*, Bd. 117, p. 570.

Physicians at the various health resorts frequently state that the first consequence of a course of treatment in many cases is the occurrence of a typical attack of gout. As the patients find themselves immediately well after it, the occurrence of the attack has been put forward as a result of the "treatment," and considered to have a "critical" signification. This assumption is quite an illusion. A mineral spring can be serviceable to a gouty subject in three ways:—(1) by adding to the blood those substances which can keep the quadriurate in solution and unchanged; (2) by increasing the secretion of urine and the amount of uric acid eliminated by the kidneys; or (3) by strengthening the patient.

In order to establish a plentiful excretion of urine, patients have been advised to drink large quantities of ordinary water; it is, however, doubtful that the elimination of uric acid can be increased in this way. Schönborn * found in his researches that this was not the case, not even by taking a large quantity, like six litres, of water daily.

It is very often advantageous to the patient to be removed from his habitual mode of living and usual diet; and on this account it is sometimes advisable to send him to a health resort. Of health resorts, the so-called "indifferent springs," the waters of which contain only a small quantity of inorganic compounds, are to be preferred. Among such are Wildbad, Pfaffers, Gastein, etc.

As the salts of lime and magnesia do not hasten the precipitation of biurate crystals in the blood, one can without hesitation send patients to Nenndorf, Contrexéville, and similar springs, whose waters contain chiefly compounds of lime and magnesia.

* *Pflüger's Archiv*, Bd. 44, p. 529.

The sulphur springs, which formerly enjoyed a reputation for gouty conditions among the older physicians, can also be recommended, particularly if the affections are chronic. The most preferable are those which contain a limited proportion of soda salts, like Nenndorf, Gurnigelbad in Switzerland, Aix-les-Bains, or St. Sauveur.

Patients who are unable to undertake the journey to a health resort can, perhaps, attain a similar effect by drinking daily a moderate quantity of warm water at home.

LITHIASIS. SAND AND GRAVEL.

Although gout is by no means a common affection in Denmark, and is met with very seldom in hospital and private practice there, the other manifestation of the uric acid diathesis—the tendency to the formation of uric acid concretions—is quite different in this respect. With us this affection is very common, and we are, therefore, in a better position to form an opinion about the pathology and theories of the disease, by comparing them with our own experience.

In the following pages we shall discuss only those uric acid concretions which are still small enough to pass down the ureters without causing the attacks of violent pain designated renal colic. The large concretions also which remain lying in the pelvis of the kidney, causing there extensive pathological changes which may make surgical interference necessary, as well as those concretions made up of other than uric acid and uric acid salts, will not be further referred to.

ETIOLOGY.

Of the etiological factors, hereditary predisposition is the most important. The disease is in many families transmitted both by the male and female members. Gout and gravel appear to alternate in certain families. Some members suffer from the one, others from the other affection. So general is the hereditary predisposition to gravel, that the physician may confidently expect in a family, the father or mother of which suffer from lithiasis, to find symptoms of this affection in one or several of the children.

As the proportion of uric acid in the urine of newly-born children is considerably larger than in the urine of adults (*vide* page 25), it is easy to understand that there is a great tendency to the deposition of uric acid in the kidneys during the first year of life. These deposits are, moreover, so frequently met with, that many authorities (Virchow and others) have considered them physiological: or at least so little removed from the normal condition that they could not be regarded pathological.

Salomonsen * in his treatise has collected the published cases of uric acid deposits, and tabulated them with those coming under his own care, with the following result:— Of 306 newly-born or very young children examined *post-mortem*, uric acid deposits were found in 140 cases, and none in 166. Ebstein † gives a similar account of 409 autopsies in 157, or 38·38 per cent., of which these deposits were found.

They are most frequent in children who have lived only a few days, and disappear in those who have lived

* "Urinsyreinfarcthos Nyfödte Diss.," Copenhagen, 1859, p. 58.

† "Natur und Behandlung der Harnsteine," p. 81.

a few weeks. There are also reliable instances of them in fœtus which died before or during birth, and they are met with in older children also. Henoch* found in the kidneys of children seven and eight weeks old remains of uric acid infractions, some in the lumen of the tubuli uriniferi, some firmly adherent to the papillæ; and Ebstein † mentions a pronounced case in a boy five years old who died of lymphadenoma of the anterior mediastinum, and whose urine contained a large deposit, which consisted chiefly of pure uric acid. At the autopsy, uratic deposits were found in the papillary portions of the pyramids of both kidneys.

True uric acid concretions are frequently met with in older children, and may be formed at a very early age. Salomonsen mentions four cases of true uric acid concretions in children one to four months old, in one of which—a child which had lived thirty-five days—uric acid stones, the size of a pin's head, and uric acid deposits, were found. Wöhler‡ also found a small uric acid stone in a stillborn immature fœtus. Hirschsprung§ records the death of a child, aged five months, from double hydronephrosis, arising from the blocking of both ureters by concretions of uric acid.

According to Prout, West‖ relates that of 1,256 patients suffering from stone admitted into the hospitals of Bristol, Leeds, and Norwich, quite 500—*i.e.* about 40 per cent.—were children. Lewschin¶ has likewise

* "Vorlesungen über Kinderkrankheiten," 1881, p. 539.

† "Natur und Behandlung der Harnsteine," p. 84.

‡ Ibid.

§ *Hospitals tidende*, 1873, p. 81.

‖ *Börnesygdomme*, 1855, p. 485.

¶ *Verhandlungen des X. inter. Congres.*, Berlin, 1891, Bd. iii. Abth. v. p. 157.

observed that in Russia stone and operations for stone are more common in children than in adults; and at the discussion upon the subject, Aretaios* stated that this was also the case in Greece.

Many writers make similar statements; and as the statistics are usually collected by surgeons, and only the cases subjected to operation counted, it is most probable that a much larger number of children suffer from the milder form of the disease, in which the concretions are still small enough to pass along the urinary passages and be washed out by the urine. This opinion appears to be shared also by Henoch,† Goodhart,‡ Sutherland,§ and da Costa.‖

During the last two years I have kept a record of all cases in which the presence of uric acid concretions could be verified by symptoms, examinations of urine, and results of treatment. I have treated altogether twenty-eight such patients — twenty-one adults and seven children—five of whom were boys and two girls. In six of the children hereditary predisposition could be established. My experience, however, does not appear to support the assertion that uric acid concretions are more common in children than in adults; but in such an important question no definite conclusions can be drawn from such a small number of cases.

Both the uric acid deposits in the kidney and the true concretions consist, according to Ebstein's examinations, of pure uric acid; at least, this is always true of

* *Verhandlungen des X. inter. Congres.*, Berlin, 1891, Bd. iii. Abth. v. p. 157.

† *Vorlesungen über Kinderkrankheiten*, 1881, p. 539.

‡ *British Med. Jour.*, 1891, ii. p. 251.

§ *British Med. Jour.*, 1892, i. p. 856.

‖ *Amer. Jour. of Med. Science*, January, 1893.

their nucleus. The frequent occurrence of concretions in children probably depends on the fact that the urine of children—even of the older children—is very rich in uric acid. This large proportion of uric acid is due to the active building-up and breaking-down of cells which takes place in the earlier part of life, and which is manifested by the abundance of leucocytes in the blood.

It follows from the cases already mentioned of uratic deposits in stillborn fœtus, that respiration is not necessary for the formation of deposits or concretions, as Virchow* originally believed.

It is often stated that men are particularly liable to stone; this is quite correct, if only those cases in which operation is necessary are taken into account. As all the statistics on this subject have been collected by surgeons, we can certainly suppose that the preponderance in males is due to anatomical conditions, which make it more difficult for a concretion of any size to be passed in a man than in a woman. If this predisposition of the male sex to the formation of uric acid concretions really exists, it can be explained only by men partaking more largely of alcohol than women, and thereby producing more uric acid.

Of my twenty-one adult patients, seven were males and fourteen females, and in four cases hereditary tendency could be established.

Mode of living and diet have always been considered among the most important etiological factors of this disease. On this point all authorities agree. Opinions on this subject are found to vary considerably when the question is asked: What diet may be considered injurious, and what beneficial?

Most authorities, especially the older ones, lay blame

* *Gesam. Abhandl. für Wissensch. Medicin.*, 1856, p. 833.

upon a diet too rich in nitrogenous constituents, particularly when combined with a plentiful use of alcohol and a very sedentary life. This opinion is founded, in a purely theoretical manner, upon the generally accepted hypothesis that uric acid is produced by imperfect oxydation of the albuminous constituents of the food. There are also some observers—as, for instance, Magendie*—who, although they do not hold the theory that a purely vegetarian diet, poor in nitrogenous matter, can equally give rise to the formation of uric acid concretions, declare that they have found it so in their experience.

Believing from all the more recent experiments that the production of uric acid is not increased—or, at any rate, not in an appreciable degree—by taking a large quantity of albuminous food, the dietetic theory referred to above becomes untenable. The question has been answered by Roberts in a totally different way.

According to Roberts,† a diet which is poor in saline constituents is particularly apt to cause the deposition of uric acid crystals in the urinary passages. As proof of this assertion, he mentions that uric acid concretions frequently occur in poor, badly-fed children, and is very prevalent among the Hindoos, whose food consists almost exclusively of rice. Rice is a rather low food substance, and, according to his account, contains only 0·39 per cent. of saline constituents, while wheat-flour contains 0·51 per cent., oatmeal 2·50 per cent., milk 5·5 per cent., meat and fish 5 to 5·5 per cent., saline constituents of the total water-free solids.

These figures do not exactly agree with those given by Jürgensen, but in any case, a diet composed largely of rice is very poor in nitrogenous matter.

* "Les Causes, les Symptoms, etc., de la Gravelle," 2nd edition, p. 51.

† *Lancet*, 1892: "Croonian Lectures."

Roberts also mentions that the formation of concretions is much more common among English agricultural labourers, who live as a rule on vegetable and non-nitrogenous food, than among workers in the cities, accustomed to a stimulating, mixed diet. Roberts lays great stress upon the taking of a large quantity of common salt. He states that sailors, who eat large quantities of salt meat, rarely suffer from uratic calculi. This has been corroborated by Hutchinson,* who was able to find only one case of stone of the kidney among 34,000 English sailors, while this affection is by no means uncommon in naval officers, whose mode of living is not so different from that of most men on shore.

My own experience throws no light upon this question, as all my patients were of the middle class, comparatively well off, and accustomed to a nourishing mixed diet.

The frequency with which uratic calculi occur appears to vary in different countries and peoples. As already stated, the disease is very common among the Hindoos; English doctors say it is very frequently seen in England amongst agricultural labourers, especially in Norfolk; but one part of Norfolk—the marsh-lands—where the drinking water contains so much common salt that it must be called brackish, is, according to Plowright,† almost exempt from it. German writers also state that the disease occurs with unequal frequency in adjoining towns and districts, but give no satisfactory explanation of the circumstance. Neither has Lewchin‡

* *Vide* Le Gendre.

†*Med. Times and Gazette*, 1885, p. 491. *Vide* Hirsch-Virchow's *Jahresb.*, 1885, ii. p. 225.

‡ Verhand. des X. Intern. Congresses, Berlin, 1891.

endeavoured to find why calculus is so common in certain parts of Central Russia—as, for example, around Moscow; but it is seldom met with in the western provinces: so much so, that it never occurs in half-civilised races, like the Tartars who live in Western Russia.

Older writers mention contusions and wounds of the kidney as causes of stone, but if this is ever the case, it is assuredly a rare occurrence.

Certain diseases predispose in a high degree to uric acid gravel. Among such comes, first of all, gout, which is frequently accompanied by the deposition of uric acid in the tissues of the kidney, or the formation of true uric acid calculi. This combination is discussed by various writers. Garrod* quotes the opinion on this point of Morgagni, and of Sydenham, who himself suffered both from gout and stone of the kidney. Garrod has also seen both diseases in the same patient, but thinks that they seldom occur together. In Ebstein's† experience, most of the patients who in earlier life suffer from gravel are at a later period affected with gout. It will be shown below that the deposition of uric acid in the kidneys acts as an irritant, which may give rise to kidney disease. This appears to indicate the manner in which uric acid concretions may lead to gout. When the kidneys are diseased and perform their function imperfectly, the uric acid may be retained in the blood, and we have then the chief factor in the production of gout.

Charcot‡ mentions a case, observed by Ball, of a patient fifty years of age, who frequently passed, after

* "Natur und Behandlung der Gicht," p. 388.

† "Natur und Behandlung der Harnsteine," p. 142.

‡ "Leçons sur les Maladies du Foie," etc., p. 111.

attacks of severe colic, small stones of uric acid. The serum of a blister on the abdomen was shown, by Garrod's thread experiment, to contain a large proportion of uric acid, although the patient never exhibited any symptoms of gout. Charcot believes that in this patient the formation of concretions was caused by an excess of uric acid in the body. As indicated above, we cannot conclude from this experiment that an increase in the production of uric acid is the primary condition, as the excess of uric acid in the blood may be secondary to the disease of the kidney.

There are, however, diseases in which uric acid is formed in increased quantities, and so tend to the formation of calculi. Leucocythæmia is among the most noted of these; in it there is always a hyper-production of uric acid. Westphal* names quite a number of observers (Ranke, Salkowski, Hoffmann, Fleischer, etc.) who have demonstrated this; and uric acid concretions have been frequently observed in the kidneys. Bartels† mentions a leucocythæmic, with an enormous splenic tumour, who often passed concretions, varying from the size of a hemp-seed to that of a pea, reddish-brown in colour, and composed of uric acid. The patient died from persistent renal colic and suppression of urine, of three days' duration.

Eichorst‡ states that the urine of leucocythæmic patients frequently contains glittering crystals of uric acid, and often forms a sediment composed entirely of these crystals.

Other diseases can also increase the formation of uric acid, and thereby perhaps give rise to concretions.

* *Deutsches Archiv für klin. Medicin*, Bd. li., p. 100.

† *Deutsches Archiv für klin. Medicin*, Bd. i., p. 13.

‡ *Pathologie und Therapie*, Bd. iv. p. 8.

Among these, according to the investigations of Horbaczewski, all commencing cachexiæ must be classed, especially those which are accompanied by a rapid development of carcinomatous degeneration, certain cases of poisoning, particularly carbon-monoxide, and extensive scalds, pneumonia, etc.

A tendency to stone is said to occur in obesity;* and not unfrequently diabetes mellitus is accompanied by an unusual disposition to the deposition of uric acid. Two patients of my own, who suffered from a mild form of diabetes, frequently showed symptoms of gravel, in addition to the excretion of sugar; and in one of them blood from the kidney was likewise passed.

Lastly, a number of kidney diseases are often accompanied by the formation of calculi. In such cases it is not always easy to distinguish whether the deposition of uric acid or the changes in the kidney tissues is the primary condition. Among such kidney affections the kidney peculiar to gout has been already referred to; but other forms of chronic kidney disease are also often associated with uric acid gravel. Buhl† found this to be so in seven per cent. of the cases of granular kidney, examined *post-mortem* by him. In his opinion, the overgrowth and retraction of the interstitial connective tissue is associated with changes in the circulation of the kidney, and in the epithelia of the tubuli uriniferi, especially in the convoluted tubules and the loop of Henlé. The urine is said to be so altered by these changes that its watery constituents are increased, while the excretion of the solid components is rendered more difficult; this, indeed, may lead to the production of uric acid concretions, and, in the course of time, to gout also.

* Le Gendre: "Traité de Médecin," 1891, tome. i., p. 362.

† *Mittheilungen aus den pathologischen Institut. zu München*, 1878, p. 50.

If this view is correct, we must also mention among the causes of uric acid gravel all agents which favour the production of chronic granular nephritis, and again refer to over-indulgence in alcohol, lead-poisoning, wet and cold, etc.

PATHOLOGICAL ANATOMY.

Uric acid calculi found *post-mortem* in the kidney present different appearances. In the case of uratic precipitation, the deposits are so fine that the individual granules cannot be distinguished with the naked eye; in other cases small glistening golden dots or brownish sand may be seen in the kidney; or the concretions may be somewhat larger, and present an irregular mulberry-like appearance. While the larger concretions are found in the calices and pelvis, the smaller ones occur in the collecting tubes of the pyramids, and the fine sand, which constitutes the precipitation, may even be found in the cortical substance, and can be seen even through the capsule of Glisson. Further, large branching coral-shaped calculi may form in the pelvis when it is dilated. It is evident that when such concretions lie for some time, they may become the starting point of further pathological changes in the kidneys, calices, and pelvis; but it would lead too far from the point under discussion to enter into details. Here we are concerned only with the structure and composition of concretions, and especially of the smaller ones, which are found in the kidney tissue, and which are still sufficiently small to pass down the ureters.

It was formerly supposed that these stones were composed of urate of soda or ammonia. This opinion rested partly on the supposition that the urine had deposited the same salts as in the amorphous sediment, and that these were held together by some sort of cement; and partly on less reliable chemical examinations. More recent writers, like Ebstein and Roberts, are agreed that the concretions consist of pure uric acid, or, at least, that it always forms the basis of these stones; while the very large concretions, which have lain a long time in the pelvis of the kidney, and set up catarrh and inflammation therein, often show layers of other chemical compounds round the nucleus of uric acid.

Ebstein subjected the large and middle-sized uric acid stones to careful examination, and came to the conclusion that all of them, from the microscopic uric acid deposits to the larger stones, are formed in the same manner. By examining very thin sections of the uric acid concretions, he found that they were formed in two ways. In one type, which was seen chiefly in concretions up to the size of a cherry-stone, there was a nucleus composed of small rounded granules cemented together, and surrounding this a number of concentric layers, here and there intersected by radiating striæ. The other type occurred most frequently in the large calculi; the formation was quite irregular, the masses of crystals having no definite arrangement, and looking as if they had rolled together in a haphazard fashion. Still, it could be seen in the better sections that these stones also had one or several nuclei, composed of concentric layers, like the small concretions, and intersected by radiating striæ. These nuclei appear to have been deposits from the large

collecting tubes, which, being washed into the calices, or pelvis, laid the foundation of continued fresh deposits of uric acid.

All concretions, irrespective of their size, were not composed of uric acid alone, but had likewise a substratum of organic matter. If such a calculus (by preference one which has not lain for a long time) is treated with a weak alkaline solution—say, a solution of borax—the uric acid gradually dissolves, and there remains an organic substance: so that by degrees, as the dissolution proceeds, the firm hard mass appears to be surrounded by an ever-increasing border of soft floating substance, which at last is all that remains of the calculus.

This organic substance appeared to possess all the reactions of an albuminous body; it had everywhere a uniform consistence, and no cellular outlines, nuclei, or similar appearances of organisation could be found in it. Ebstein also examined the uric acid deposits of young children, and gives a detailed account of what he found at the *post-mortem* of a syphilitic child seven days old. In this child the deposits were not, as is usually the case, confined to the large collecting tubes of the pyramids, but occurred also in the cortex, where they appeared to be located chiefly in the convoluted tubes. The large collecting tubes were, in many cases, transformed into sinuous cavities of considerable size, filled up partly with granular masses, and partly with yellow, rounded, very refractile bodies, sometimes arranged in rows like a rosary, or packed closely together. In the collecting tubes Ebstein could easily see the epithelial cells round the deposits, but in the finer tubules the convoluted tubes and the loop of Henlé, in which the deposits consisted entirely of yellow round bodies, the epithelia

were in many cases completely or partially pushed off. Sometimes it was totally without order, so that the lumen of the tube was filled up with a mixture of uric acid spherules, cells, nuclei, and a fine granular structureless substance. On later examination of kidneys with deposits of uric acid, Ebstein did not, however, happen to find them in the cortex, so that they seem to be carried from it into the collecting tubes rather early.

From the above investigations and from experiments upon lower animals, Ebstein has formulated the theory that uric acid becomes deposited within the epithelia, so that they, either physiologically or from the deposits formed within them, must break up before the spheres of uric acid become free. It has been found, moreover, in snails and some other lower animals, that uric acid is formed in the epithelial cells of the kidney; and several observers have believed that they found this in birds. Ebstein now believes that this may also take place in mammalia and in human beings.

As the entire theory stands and falls with the observation that uric acid is deposited in the epithelial cells of the kidney tubes in birds, it can no longer be maintained in the face of the work of more recent investigators, particularly Manfred Bial* and Heidenhain,† who were unable to find any uric acid crystals in the kidney epithelia of birds. When birds are fed on flesh, or their ureters ligatured so that numerous depositions of uric acid take place, such deposits lie in the lumen of the tubuli uriniferi, and never in the epithelial cells.

* *Plüger's Archiv*, Bd. 47, p. 116.

† Hermann, "Handbuch der Physiologie," Bd. v., S. Bial.

PATHOGENESIS.

It is comparatively easy to be agreed upon the etiology of uric acid gravel, since statistics can be brought together as to how far the alleged causes of its production operate; but it is much more difficult to come to an understanding upon its pathology; and it is particularly difficult to elucidate the reasons why in some cases the deposition of uric acid in the urinary passages becomes the starting point of a true stone formation, while in other cases it may remain there for a longer or shorter period without occasioning any real danger. This difficulty is accentuated, since cases in which the formation of concretions is in its earliest stages rarely are obtained for *post-mortem* examination; perhaps, also, because this early development very readily escapes attention.

Many efforts have been made to theoretically account for the production of stone. One of the oldest theories was that the urine under certain conditions deposited an amorphous sediment while still in the kidneys, and that the concretions consisted of this deposit, which had become increased in size by additional layers, or by being cemented together with mucus or some other organic substance. When attention was drawn to the fact that in many cases the urine, after elimination, became gradually more acid, Scherer's explanation of this phenomenon—namely, the occurrence of acid fermentation—was adopted; and it was then believed that this acid fermentation could commence so abnormally early that uric acid was precipitated in the kidney. Again, others agreed with Ultzmann that the urine, under certain unknown conditions, deposited

uric acid crystals of a particular size and acciular in form, and that calculi were formed by these crystals being wedged together in the calices and pelvis of the kidney, and so becoming the nucleus of a calculus.

These explanations are constructed quite in a theoretical fashion, and in reality explain nothing. Equally unsatisfactory is the new theory that various micro-organisms play a part in the production of stone, and that the disease arises in the kidney epithelia, or that they are the primary cause of calculus by the uric acid becoming deposited round about them in the same way as Bilharz * has shown, that in Egypt the ova of distoma may become the starting-point of concretions in the bladder.

Ebstein and Nicolaier † have proved that calculus is quite independent of microbes, by experimentally producing stone of the kidney in dogs through feeding them on oxamide.

Tuffier,‡ who has come to a similar conclusion on this theory, examined the concretions for micro-organisms, but found them absolutely sterile.

It has already been stated that Roberts concluded, from his examinations and researches, that various conditions conduce to the deposition of free uric acid in the urine. As such he enumerates a large amount of uric acid, especially in proportion to the amount of urine; the reaction of the urine; its richness in salines, especially chloride and phosphate of soda; and, finally, the quantity of pigment. We shall now traverse the etiological factors which, in our experience, lead to uric acid

* *Vide* Ebstein, "Natur und Behand. der Harnsteine."

† *Centralblatt f. Chirurgie*, 1891, p. 675.

‡ *Mercédi Med.*, Dec. 28, 1892.

concretions, and examine how far we may believe them to arise from changes in the nature of the urine in one or several of the directions already referred to.

From the first predisposing cause—hereditary tendency—we are able to learn very little. So long as we do not know upon what peculiarity of metabolism the uric acid diathesis depends, we have no prospect of knowing that the predisposition operates through one of the peculiarities in the composition of the urine to which Roberts has referred.

On the other hand, the theory that age is an important cause is well supported. As already demonstrated, the urine of young children contains an extremely large proportion of uric acid, and this excessive production continues in later childhood, though in a rather less degree. According to Pfeiffer, uric acid appears to be produced for all ages in a gradually decreasing proportion (*vide* page 25), so that it reaches its minimum in old age.

It is also true that in leucocythæmia, where the production of uric acid rises to five to eight times the normal quantity, the formation of concretions is very common.

In the same way, other diseases may cause gravel when they are associated with an excessive uric acid production—as for example, pneumonia, which Hahn* mentions as a frequent cause.

Gout has frequently been classed among the diseases which give rise to calculus. It is true that these affections are often associated; but it is very questionable whether gout is the primary condition. In opposition to this,

* "Dictionnaire Encyclopédique des Sciences Medicales." Article "Gravelle.

among other things, is the experience that uric acid gravel frequently occurs in the earlier years of persons who show signs of gout later on. This rather supports the belief that uric acid gravel and the kidney affection resulting therefrom is the primary state, and is also indicated by other facts, which will be treated more in detail later on.

The relative or absolute quantity of uric acid in the urine is not, however, the sole factor in gravel, for it may occur both with a normal or an abnormally low excretion of uric acid. Roberts found this on examining the urine of four patients with a disposition to gravel, which immediately after elimination contained crystals and aggregations of uric acid, although the percentage varied greatly.

No. 1 contained 0·084 per cent. uric acid (above the average).
„ 2 „ 0·076 „ „ „ „ „
„ 3 „ 0·032 „ „ „ (rather below the average).
„ 4 „ 0·022 „ „ „ (much „ „).

I have endeavoured to elucidate this point by making a series of experiments with my own urine, having first settled that I had a pronounced and hereditary predisposition to uric acid gravel. As an introduction to the study of the effect of piperazin upon the excretion of uric acid, the urine was examined on four days, on which the usual mixed diet, without alcohol, was taken, and the general health normal. The amount of uric acid, estimated by the Fokker-Salkowski method, was as follows:—

Feb. 3rd. 0·603 to 0·609 grm. per diem (two estimations made at the same time).
Feb. 4th. 0·643 to 0·650 „ „ „ „
Feb. 5th. 0·714 grm. per diem.
Feb. 6th. 0·580 „ „

The average of these, 0·633 grm. daily, did not rise above the usual physiological average. At another examination :—

	Uric Acid (Fokker).		Uric Acid (Hopkins).
Nov. 20th.	0·768 grm. per diem.	...	0·775 grm. per diem.
,, 25th.	0·787 ,, ,,	...	0·835 ,, ,,
,, 26th.	0·734 ,, ,,	...	0·734 ,, ,,

These figures are somewhat higher, but still do not exceed the physiological maximum, which is usually fixed at 0·8 grm. per diem.

My investigations seem to show that uric acid is more readily deposited when the percentage is large: as the amount of uric acid reached on the 8th February, 1892, 0·891—0·985 grm., and on the 15th, 1·098 grms., by means of rather active physical exercise, uric acid crystals were deposited in large numbers as the urine was passed; and on microscopic examination (100 diameters), were to be seen as large acicular crystals, arranged in rosettes, as large as a pin's head. A similar action, with respect to the proportion and deposition of uric acid, appeared when alcohol, in the form of wine, was taken. On the 20th January, 1893, the excretion of uric acid by this means rose to 0·9947 (Fokker), 0·9918 (Hopkins) grm. In this case the uric acid was held in solution by alkalies; but in a similar experiment on the 6th January, 1892, in which alcohol, but no alkalies, were taken in addition to the food, numerous rosette-shaped aggregations of crystals were deposited.

Eichorst* makes mention of a medical man, with whom he was well acquainted, who could at will produce

* *Pathologie und Therapie*, Bd. ii., p. 604.

in himself uric acid gravel by taking a small quantity of alcohol.

The reaction of the urine plays a much more important *rôle* in the solubility of uric acid: neutral and alkaline urines can hold in solution a very considerable quantity of uric acid, while in an acid urine it is readily deposited. The degree of acidity depends upon the existence of phosphoric acid, which unites with the alkalies in the urine to form monobasic compounds; it never occurs as free acid. The uric acid has no direct bearing upon the reaction of the urine, as it always exists in solution in combination with alkalies, and gives a neutral reaction, and immediately crystallises when it comes into the free state. Uric acid can, it is true, indirectly influence the reaction of the urine. As already shown, it is formed from the nuclein, which contains phosphorus in the form of phosphoric acid,* so that by its disintegration this phosphoric acid becomes free, is taken up by the blood, and excreted in the urine.

This is confirmed by the discovery of Peiper,† that the alkalinity of the blood is less in children than in adults, and that it becomes also diminished by very active muscular exercise, convulsions from strychnine, leucocythæmia, cachexia from cancer, destructive diseases of the liver, and fever; conditions which are all accompanied by an active disintegration of nucleated cells, and the liberation of uric acid, as well as phosphoric acid from the nuclein. On the other hand, according to the same authority, the alkalinity of the blood rises during digestion, probably because a larger quantity of

* *Vide* Weyl: "Organische Chemie," p. 548.

† *Virchow's Archiv*, Bd. 116, p. 337.

acid is drawn from the blood by the acid gastric juice. Rumpf * gives similar results from his examinations of the alkalinity of the blood. This agrees with what Roberts and several writers have found, namely, that shortly after a meal the urine becomes neutral or even alkaline, while after prolonged fasting it is strongly acid. The maximum acidity is reached in the morning before the first meal. This is specially the case in England, where dinner, taken about 7 or 8 o'clock, is the last meal of the day, and twelve hours, or more, elapse before breakfast the next morning. The morning urine is therefore particularly liable to deposit crystals, even when it does not contain an excessive quantity of uric acid.

Roberts found, moreover, that urine containing a large proportion of saline constituents, especially neutral or basic salts of phosphoric acid and potash or soda, and sodium chloride, could more readily retain uric acid in solution, than urine poor in saline matter. This agrees with the experience that uric acid concretions frequently occur in people who live on a diet preponderating in vegetables, like the Hindoos, poor agricultural labourers, etc.; while they are seldom met with in those who partake of a large amount of common salt such as sailors and the inhabitants of the marshlands, where the drinking water is brackish.

When diabetics show a strong tendency to uric acid gravel, it may perhaps be because the urine is always acid and poor in pigment. It is not clear why this disposition should occur in obesity; probably it arises from a strong tendency to kidney disease in this state.

The quantity of pigment in the urine is also of some

* *Centralblatt für klin. Medicin.*, 1891, p. 756; 3, loc. cit.

importance. Various chronic kidney affections, in which a very pale urine, poor in pigment, is passed, are frequently complicated with uric acid gravel.

It is likewise evident that the formation of uratic concretions does not alone depend upon the fact that uric acid becomes deposited in the kidney, and by the aggregation of the crystals a calculus, apparent to the naked eye, gradually developed.

Ebstein's examinations both of the large and small uric acid calculi, have clearly shown what was believed to be the case by older authorities, namely, that the small, fine uric acid crystals are held together by an organic cementing substance which is of the nature of an albumen.

Although the larger uric acid calculi, the size of an almond, are found in the pelvis of the kidney, we must recollect that their foundation is laid in the kidney tissue, and that Ebstein has found their origin in the tubuli contorti. Here, and perhaps also in the loop of Henle, and in the junction of these with the collecting tubules, probably all the small and fine concretions are formed, which later become voided by the flow of urine into the collecting tubes and the pelvis of the kidney, where, under favourable conditions, they become the starting point of larger calculi.

Ebstein has endeavoured to explain how the albumen which holds the crystals together is formed in the kidney. In his opinion the uric acid, being deposited in the epithelia lining the tubules, acts as a chemical irritant and causes necrosis of the cells. The degenerated cells fall off, and then supply the cementing substance for the calculi. In correspondence with this theory he mentions the uratic deposits in newborn children, in gouty and other affections of the

kidney, as the chief predisposing cause of uric acid calculi.

Again, according to Ebstein, uric acid deposits must be considered the first sign of the uric acid diathesis, and in his opinion it is followed in a large number of cases by a pathological condition of the kidney which later on tends to give rise to concretions. On the examination of a kidney which had deposits of uric acid in it, he found in the tubules and in the cavities formed by dilatations of them collections of an albuminous substance showing concentric layers, and which, consequently, might be considered the basis of the larger uric acid stones, which are formed in layers.

Ebstein thinks that the gouty kidney further predisposes to calculus by precipitation of biurate of soda taking place in the kidney; and then portions of the necrosed and infiltrated kidney tissues, breaking through into the lumen of the tubules, become the starting point of further deposits; or that the gouty kidney is complicated with similar morbid processes as found by him in the case of uratic deposits, and in the same way may lead to the formation of concretions. Such pathological changes, however, have not been demonstrated by him in the gouty kidney. In conclusion, he thinks that all diseased conditions which lead to necrosis of the kidney tissue may also be the cause of concretions.

This opinion of his, however, is purely theoretical. Even if occasional calculi can originate from the deposition of uric acid crystals in or around portions of necrosed tissue, and if in new-born children they can form by additions to the uratic deposits, his explanation will not tally with the great majority of cases.

It has already been stated that, according to the researches of other authorities, uric acid crystals are not

deposited in the epithelial cells, but in the lumen of the tubes, within the row of epithelia; it is equally untrue that the uric acid acts as a chemical poison. This is shown by the fact that a considerable quantity of uric acid may be in the blood in various kidney diseases, in leucocythæmia, and pneumonia, etc., without giving rise to necrosis of cells anywhere.

Many authors have declared themselves opposed to Ebstein; and Roberts distinctly says that in gravel uric acid acts only as a mechanical irritant, and that the same probably is true in gout.

The origin of the albuminous basis of the uric acid concretions admits of a much simpler explanation. When uric acid crystals are precipitated from the urine in the urinary tubules they act like a foreign body, as a mechanical irritant to the epithelia, which in turn react by morbid changes, proliferation, and the formation of casts. There is thus supplied an albuminous basis, which is then infiltrated with crystals. These smaller concretions are carried by the urine into the collecting tubes, where the same process again takes place, but on a larger scale, and at last they reach the pelvis of the kidney. Here they may lie and become the nucleus of a true kidney stone, which increases in size by continued fresh depositions of uric acid, while the mucous membrane of the pelvis takes upon itself the excretion of the albuminous substratum from which the concentric layers are formed, and in which the crystals are deposited.

Various researches indicate that this explanation is correct. Martin and Ruge* found on microscopic examination of the urine of twenty-four new-born children, that it contained hyaline casts in fourteen cases; and,

* *Zeitschrift für Geburtskunde*, 1875. *Schmidts Jahrb.*, 1876, i. p. 169.

on the first day of life, it contained albumen in all the cases examined. As the authors remarked, this must certainly be explained by irritation of the kidneys resulting from the precipitation of uric acid.

Ultzmann has noticed in men, otherwise healthy, periodic albuminuria simultaneous with the evacuation of uric acid crystals.* He mentions that Leube had often found crystals of uric acid in the urine of patients who were affected by periodic albuminuria, and he satisfied himself that several individuals described by Leube as having "physiological albuminuria" had afterwards undoubted attacks of renal colic, and thereafter passed uric acid concretions. Ultzmann, therefore, thinks the deposition of uric acid crystals in an acid urine, in combination with temporary albuminuria, a first step to the formation of uric acid concretions.

Henoch† states that the urine of children may sometimes contain albumen, and in a few months the health and condition of the urine may be normal.

Jolles,‡ who made use of Gaertner's centrifuge for the examination of the solid constituents of the urine, immediately after its elimination, found the continuous evacuation of uric acid crystals often accompanied by the presence of hyaline casts, although there were no other signs of kidney disease.

Da Costa § has often seen uric acid crystals in the urine in combination with crystals of oxalate of lime, especially in boys.

Sutherland ‖ found, in children with a tendency to

* Eulenburg's "Realencyclop." Artikel "Albuminuria."

† *Kinderkrankheiten, Vorlesungen über*, 1881.

‡ *Interat. klin. Rundschau*, 1893, p. 12.

§ *Americ. Journ. of Med. Science*, Jan., 1893.

‖ *Brit. Med. Journal*, 1892, ii. p. 856.

uric acid gravel, slightly periodic attacks of hæmaturia, or albuminuria of very variable degree; casts were frequently present at the same time, though seldom in any quantity.

A number of very interesting observations have been made by Mygge.* He investigated the condition of the urine of 232 individuals, taken without selection from the patients of the Kommune-hospital in Copenhagen. The urine of the twenty-four hours was collected and examined every second day. He made notes of 3,287 urine examinations; of these, 2,786 (from 127 patients) showed no precipitation of uric acid crystals; in 501 examinations (of 105 persons) there was a decided deposition, and in 262 testings (of fifty-nine patients) the crystals were very numerous. In forty-three patients the gravel was a transitory symptom; in sixteen it was continuous. In twenty-seven out of fifty cases mentioned, the uric acid gravel was accompanied by albuminuria; in twenty-two there was a trace of albumen, and in the remaining cases a chemical examination had not been made. The sediment was examined microscopically in twenty-five cases, fourteen of which contained casts and kidney epithelia, and three casts only.

In addition to the sixteen cases of continuous uric acid gravel, referred to above, Mygge collected sixteen similar cases from his hospital practice, *i.e.*, thirty-two cases altogether. Nine of these suffered from kidney disease, ten from rheumatic affections, ten from pulmonary tuberculosis, one from pneumonia, one from typhoid fever, and one from emphysema. In twenty-one of these cases the gravel was associated with albumen, but only in small amount, and temporary in character.

* *Nordiskt Med. Archiv*, Bd. 18, No. 23.

The sediment was microscopically examined in twenty-five cases, and in every one, without exception, kidney structures were found; in twenty-four, casts and epithelial cells, and in one epithelia only. In certain cases it was established that the number of casts was in proportion to the quantity of gravel. Eight of the patients here referred to died, and were examined post-mortem; in seven of these there were undoubted signs of advanced kidney disease; in the eighth case the kidneys were not examined microscopically; it is therefore an open question whether in this case also there was not organic disease of the kidney.

During the last few years I have always used the microscope in the examination of those urines which contained crystals of uric acid on elimination, or where such were deposited very shortly afterwards. It has struck me that this condition was very frequently accompanied by casts in the urine. These were sometimes granular, sometimes hyaline. As I did not at first realise the importance of this condition, I did not take notes of all the cases in which such observations were made. Some of the most characteristic observations of this kind, chiefly made during the last year and a half, are given below.

As soon as the urine to be tested was obtained, it was placed in a warm room in a conical urine-glass, and examined when the deposit had formed: latterly the sediment was separated by Gaertner's centrifugal machine.

Case I.—Ingrid C., ten years of age, suffered from very pronounced renal colic. Between the attacks rosettes and aggregations of uric acid, mixed with hyaline casts, were found in the urine.

Case II.—Tage B., nine years of age, marked here-

ditary uric acid diathesis. On March 21st, 1892, innumerable crystals of uric acid were found in the urine immediately it was passed: the smallest the size of a blood corpuscle, the largest twenty to thirty times as large; among them isolated hyaline casts; no amorphous urates.

Case III.—Mrs. M. had suffered from severe pain in the region of the kidneys for a few days before the 18th March, 1892. On this day she passed urine clouded with a large quantity of uric acid crystals. The crystals occurred partly isolated, partly arranged in large groups or rosettes; there were also a few granular casts and numerous kidney epithelia, in or round which crystals were deposited. No urates.

Case IV.—Mrs. R. had suffered for some time from pain in the loins, radiating into the left hypochondrium and the abdomen. Her morning urine was examined on the 24th March, 1893, and found to be very acid. In a tall urine glass there formed a cloudy sediment about three centimetres high. On microscopic examination this was found to contain a large amount of uric acid crystals, partly isolated, partly arranged in rosettes or in mosaic-like plates, apparently held together by some cementing substance. Further, there were cylindrical aggregations of uric acid crystals, like small sticks of candy sugar, having the shape and size of the larger collecting tubes of the kidney. Besides the crystals the sediment contained innumerable epithelia, partly separate, partly hanging together in plates; many of these appeared to have come from the calices of the kidney; there were also occasional hyaline casts, but absolutely no urates.

Case V.—Grosshändler R, forty-eight years of age, suffered from a very mild form of diabetes; the quantity of

sugar never being more than 1 per cent. and often below 0·5 per cent. He had often shown symptoms of gravel, which were treated with alkalies. After the pain of one of these attacks had disappeared, he passed on the 27th March, 1892, a slightly alkaline urine, which rapidly deposited a white flocculent sediment; in it there were found many large and beautiful crystals of uric acid, some of them free, some of them deposited in or round granular casts. In one of the specimens, bodies like sago grains were to be seen, containing a quantity of crystals and clumps of uric acid; these bodies were very numerous, rather small, surrounded by whetstone-shaped crystals, which had apparently been deposited round them. After a further attack of pain there formed, on the 14th June, 1892, in an almost neutral urine (the treatment being Fachinger water), a sediment composed of a few uric acid crystals and several large hyaline casts, one of which was branching, and in one of the branches deposits of uric acid crystals.

A similar case is reported by V. Hösslin.* An epileptic, thirty-five years of age, after violent colick-like pains, lasting eighteen hours, passed urine in which there formed a sediment of urates, mixed with flakes and threads. On microscopic examination these proved to be branching casts, inside which was a fine granular deposit, considered by Hösslin to be urates, but probably uric acid. The casts were dissolved in a solution of potash, and according to their shape and size must have been formed in the collecting tubules.

Casts are found not only in combination with deposits of uric acid crystals, but also with oxalate of lime crystals in the urine.

* *Münchener med. Wochenschr.*, 1889, No. 48. Vide *Hirsch-Virchow's Jahresb.*, 1889, i. p. 229.

Case VI.—Mrs. G., after several years of persistent and violent colic, passed a calculus in the urine. At a later period she again showed symptoms of gravel. The urine was examined on the 2nd April, 1892, after an attack of pain. It was clear, contained a light cloudy sediment of epithelial cells, a few granular casts and fragments of them, together with a large number of small oxalate of lime crystals which, when magnified 100 times, looked like fragments of broken glass, but had the characteristic envelope-like appearance under a power of 250 diameters.

Case VII.—Herr K. Urine examined on the 2nd May, 1892. It contained a large number of oxalate of lime crystals, besides numerous "round cells" and several granular casts, in which many small oxalate of lime crystals were deposited.

After I had met with this frequent combination of casts and crystals of different kinds in the urine, I endeavoured, as far as lay in my power, to prove experimentally that casts may really originate by the deposition of crystals in the urinary tubules. I conducted this experiment upon myself, as I have a marked predisposition to uric acid gravel, which can be controlled only by the continuous employment of alkalies.

On Saturday, the 18th February, 1893, I stopped taking alkalies, while the usual diet and mode of living remained unchanged; the urine was slightly alkaline, contained no deposit of any kind, and no albumen. On Wednesday, the 22nd, the urine on evacuation was strongly acid, contained a few medium sized and innumerable very small crystals of uric acid, also many round cells, with large and small fragments of granular casts. As the experiment had brought on pain in the

region of the right kidney it was not continued. After taking bicarbonate of soda for several days the urine again became slightly alkaline, contained no casts, and no uric acid crystals, even several hours after evacuation.

An investigation by Glaser * may be mentioned here. By the careful use of the centrifuge in the examination of the urine of fifteen different patients, he found that in most cases (thirty-three out of forty) the number of leucocytes could be considerably raised above the normal, if the individual under examination was allowed a large quantity of beer. On twenty-five occasions casts and cylindroids appeared in the urine, and if the large amount of beer was continued a very marked increase in the solid elements of the urine resulted, very frequently crystals of uric acid or oxalate of lime being found in the sediment.

Glaser thinks, however, that the formation of casts can be explained by the direct action of the alcohol upon the kidneys; but probably the action is an indirect one. By the large quantity of alcohol consumed a greater proportion of uric acid is formed, which, becoming deposited in the tubuli uriniferi, gives rise to the formation of casts.

The facts stated above all seem to indicate that the deposition of uric acid in the tubules can set up desquamation of the epithelia and the formation of casts. Further, crystals may then be deposited in the various casts formed in this way, and so lay the foundation of a true kidney concretion.

From the facts here discussed we may conclude that

* *Deutsche med. Wochenschr.*, 1891. Vide *Centralblatt f. klin. Med.*, 1891, p. 957.

the pathology of kidney concretions is as follows: When the chemical composition of the urine is such that uric acid becomes deposited in the kidney, the crystals are first of all laid down in the tubules of the cortex, tubuli contorti, etc. As long as they are not numerous they may be washed out by the flow of urine without giving rise to any particular inconvenience. Under special conditions, as for instance when the proportion of uric acid in the urine becomes suddenly increased, a large number of crystals are at one time deposited in the kidney tubules, and act there like a foreign body. There is then set up an irritation of the epithelia characterised by the formation of casts of various kinds, which are in turn infiltrated with crystals and lay the foundation of a concretion which may reach a certain size even in the collecting tubes. If such a minute calculus lies in the calices or in a hollow of the pelvis, it increases in size and causes a diseased condition of the mucous membrane. By means of this an albuminous substance is excreted, and deposited in consecutive layers as the concretion grows in size from the additional deposits of uric acid. If uric acid is deposited in an already diseased kidney, and if casts have already formed in the tubes, the concretions will form more rapidly; this will also be the case when pieces of necrosed tissue or foreign bodies exist in the kidney, as they lend themselves to the infiltration of uric acid crystals.

If this pathological process continues for some time it will not only tend to the formation of larger concretions, but may also cause chronic disease of the kidney by extension from the epithelia to the kidney tubes themselves, and later on may also attack the interstitial tissue. For this reason granular atrophic kidneys are very frequently found at the autopsy of patients who

have suffered from stone of the kidney for many years.

This chronic kidney affection may early interfere with the excretory power of the kidney, and, as Charcot states, the uric acid appears to be partly retained in that stage of the kidney affection in which the urea and other easily soluble constituents of the urine can pass off.

Here, perhaps, lies the explanation of the fact that symptoms of gravel or stone of the kidney very often occur in younger men who later in life are affected with typical gout.

SYMPTOMS AND COURSE.

Almost all writers who have dealt with the symptomatology of gravel have confined themselves to a description of the true renal colic. This colic ensues when a concretion of some size enters the ureter, and being wedged in is pushed farther on by morbid contraction of its wall, giving rise to great pain. It is everywhere very fully described, with accurate pictures of all the associated symptoms, such as nausea, vomiting, radiating pains, etc.

It is only exceptionally intimated that these concretions, the origin and growth of which must in most cases have occupied a long time, make themselves known long before the occurrence of colic through symptoms which can lead the physician on their track at the right time.

Ewald* states that gravel may be in existence without showing any symptoms, but that it is often accompanied by a number of obscure and indistinct symptoms which cannot be referred to any known cause. Among these, he mentions as the most frequent pain in the loins, sometimes occurring continuously, sometimes in paroxysms, and also irritability of the bladder.

More accurate accounts are to be found in the works of several specialists on diseases of children, such as Henoch,† and some English and American writers—Sutherland,‡ Goodhart,§ Dana,‖ and Da Costa.¶ The Danish author Lange** has also contributed valuable information on the symptomatology of the uric acid diathesis.

Numerous symptoms are in reality associated with uric acid gravel from its commencement, and are more or less constantly present, when examination of the urine reveals the objective symptoms of precipitation of uric acid crystals in the urinary passages.

The nature and locality of the symptoms undoubtedly indicate that precipitation of the crystals sets up an irritation of the kidneys, which shows itself in various ways. It is quite possible that crystals of uric acid may be deposited in the bladder also. Here, however, the conditions favourable for the accumulation of crystals to form a true concretion very rarely occur, and the precipitation of uric acid in this locality is therefore devoid of symptoms,

* Eulenburg's "Realencyclopädie," Bd. xv. p. 229.

† "Vorlesungen über Kinderkrankheiten," 1881.

‡ *British Medical Journal*, 1892, i. p. 856.

§ *British Medical Journal*, 1891, ii. p. 251.

‖ *Medical Record*, 1886, No. 3.

¶ *American Journal of Medical Science*, 1883, p. 313, and 1893, i., Heft.

** "Periodiske Depressionstelstande," Kopenhagen, 1886, and "Hospitaltstidende R.," 3 Bd. ix.

as the crystals readily pass out through the urethra; at most, they attract attention by a slight burning sensation in the urethra, or irritability of the bladder.

As the symptoms show themselves in rather different ways, according as the disease occurs in adults or in children, I shall now endeavour to represent these two types, relying on what I have gathered from my own experience and the various writings on the subject.

Henoch * states that he met with in two children, two to four years of age, paroxysms of violent pain, accompanied by shivering, and later by feverishness. The attacks lasted several hours, recurred at several days' interval, and ended with the evacuation of a turbid urine loaded with urates, and containing albumen. Subsequently the health of the children was good, and the urine normal in several months. As the attacks of pain were accompanied by sickness and constipation, the condition was at first believed to be intestinal colic, but as soon as the state of the urine was noticed attention was directed to the kidneys. Henoch has never observed true uric acid gravel in children, but has seen temporary albuminuria with attacks of pain. He attributes the pain to irritation of the kidneys arising from the morbid constitution of the urine, and states that the disease is cured by the use of alkaline mineral waters, like Vichy, Wildungen, etc., or by prolonged administration of bicarbonate of soda.

Kjellberg † mentions several cases of hæmaturia in children, which he considered due to gravel. A girl, ten years old, who had not suffered from scarlatinal or any other inflammation of the kidney, had relapsing hæma-

* "Vorlesungen über Kinderkrankheiten," p. 541.

† *Nordiskt. Med. Archiv*, 1870, No. 28.

turia, which was not relieved by hæmostatic medicines. It was then noticed that the urine contained a large sediment of uric acid crystals, and on the administration of Carlsbad water both the deposit of uric acid and the hæmaturia disappeared, but returned again when the alkalies were discontinued. The disease totally disappeared on the prolonged administration of Carlsbad water. In a boy seven years of age a similar condition existed, but there was also present frequent desire to pass water and a scalding sensation in the urethra while the hæmaturia and precipitation of uric acid lasted. Kjellberg mentions also several cases of albuminuria accompanied by uric acid crystals in the urine. In one of these the urine was examined microscopically immediately on elimination. In the sediment epithelia, round cells, and uric acid crystals were found, but no casts. In these cases also by the employment of Carlsbad water the crystals disappeared, after them the albumen.

Sutherland * has given a most complete account of the symptoms of uric acid gravel in children, though his explanation of them is certainly incorrect. In his opinion, some symptoms may arise from an abnormal proportion of uric acid in the blood, others by the formation of crystals and small concretions in the kidneys. His description of the patients and their symptoms corresponds fully with my own experience, at least in a large number of these young people.

According to Sutherland, these children are usually precocious, with small restless bodies, very changeable and nervous, sometimes extremely lively, sometimes very depressed; they fall asleep with difficulty, sleep is short and restless, and they often talk in it. They eat little,

* *British Medical Journal*, 1872, i. 856.

and show pronounced dislike for certain foods, they catch cold readily, giving rise to attacks of pain, usually, however, of short duration, especially should the child be kept in bed.

Various catarrhal affections, headache, and intercostal neuralgia, are common in such constitutions, and some have irregular action of the heart; liver and spleen may be enlarged; sometimes there is no other complaint than pain in the abdomen, located at the umbilicus or in the right iliac region.

Attacks like colic may likewise be met with, as Goodhart also mentions; but as the pain is usually referred to the umbilicus, the disease is often misunderstood. In the more severe cases, nausea, vomiting and hæmaturia also occur; in the milder cases, pain alone is complained of. Albuminuria may be present along with the paroxysms of pain or immediately after them, and sometimes casts in the urine, though seldom many at one time. Sometimes the presence of uric acid or oxalate of lime concretions in the kidney may give rise to intermittent albuminuria or hæmaturia. Enuresis and pain on defæcation are rarer symptoms.

I have myself not unfrequently met with gravel in children, and have detailed notes of seven such cases, 5 boys and 2 girls. They do not all belong to the same class as Sutherland's patients, for dull, slow, partly scrofulous children are also in evidence; all belong to families in which the uric acid diathesis is hereditary, either on the father's side, or the mother's, or on both. Several of my patients correspond so thoroughly with Sutherland's description, that he might have had them before him while he wrote, as will be seen by the following account of one.

Ingrid C., 11 years of age, with a neurotic family

history; mother suffered from time to time with gravel for many years; small for her age, muscular system weakly developed; extremely lively and agile, easily inclined to mirth or sadness, and tending to extremes in both directions; rather pale-faced than rosy, but subject to sudden changes, on which follow paleness and languor; she has no symptoms of scrofula or rickets. With the exception of the customary diseases of childhood, which have been passed through several years ago, she shows no other symptoms than frequent attacks of pain, of greater or less intensity and duration. The pain may come on at any time, is felt in the umbilical or left hypochondriac region, but never in the situation of the kidneys. The attacks may last several hours, and be repeated at intervals of several days; during them she is pale, devoid of energy, low-spirited, eats very little, and suffers from nausea without vomiting.

In the summer of 1892 the paroxysms of pain were so severe, that they gave rise to typical attacks of hysteria in which the patient screamed, threw her arms about, and was partially unconscious. Concretions of any size have never been noticed in the urine. It has often been examined immediately on elimination; it was pale, acid, and contained, during and after the attacks of pain, large quantities of uric acid crystals of a particularly large size, and arranged partly in rosettes; it frequently contained also hyaline casts, but never in large numbers. It has never deposited urates while standing before being examined. The bowels have always been natural, and no objective signs of any organic disease, etc., can be detected.

This history also helps to show that children almost never refer the pain to the region of the kidney; the seat of pain is generally stated to be about the umbilicus,

in other cases in the left hypochondrium, or sides of the abdomen; it may radiate into the thighs or round to the back. Strangury may be present, especially in the case of boys.

Usually the pain commences quite suddenly and without perceivable cause; sometimes the children wake in the night with pain and screaming. Very often constipation is present, and then the pain is apt to be attributed to an intestinal affection or to worms.

A symptom almost as constant as pain is the sudden onset of unaccountable indisposition, tiredness, and depression, which may advance to a state of complete melancholia, and alarms the parents, because it stands in no proportion to the other apparently mild change in the condition of the child.

The mother of one of these patients, Paul G——, twelve years of age, described his illness as follows:— "The boy complains of a frequent desire to make water, accompanied by a scalding sensation. He wakes once every night to pass water, and complains of a pain near the navel, and has frequent desire to go to stool. He is changeable in his play and work, easily tired and depressed, and this state may later on advance to one of marked low-spiritedness without any conceivable cause."

The urine was quite clear, acid, and, as far as one could see, had no sediment. On using the centrifuge there were at the bottom of the glass a number of medium-sized and several very large aggregations of uric acid crystals, but no signs of urates.

A similar great mental depression has been shown by Lange* to occur in adults. In his treatise on this con-

* "Periodiske Depressionstande," Kopenhagen, 1886.

dition he says that he has really had no opportunity of observing it in children, but, judging from the statements of patients, he is disposed to think that indications of it may also be found in children.

The description of the disease varies more in adults, perhaps because they are in a better position to notice and describe the symptoms.

The most constant symptom is a dull pain in the loins, occupying the seat of one or both kidneys. In the text-books of the pathology pain is the only symptom mentioned as the forerunner of true colic; it has, however, little similarity to the pain in renal colic, as it is continuous and generally not very severe, being more like a feeling of tenderness without being augmented by pressure over the painful spot. It is very often aggravated when the patient occupies the same position for a considerable time, especially if it is rather a strained position, as in continuous work at a writing table; the patients then experience pain when they straighten themselves, although at the same time they have a constant desire to do so, to change their position or place. It disappears generally on the application of warmth, or on recourse to the recumbent position, and so does not disturb sleep.

Patients often attribute the pain to a rheumatic lumbago, which is treated in vain, and often indeed aggravated by massage, warm baths, Russian baths, etc. This treatment is almost as harmful as vapour baths and prolonged warm baths, which, according to Horbaczewski, increase the production of uric acid, and so directly minimise the chances of the patient.

The pain may radiate from the loin in various directions, sometimes towards the left hypochondriac region, and in this way the disease is frequently mistaken for

some stomach disorder, especially in young women for simple ulcer of the stomach. Sometimes it radiates to the back, between the shoulder-blades, and occasionally down the arms. Very often it goes down one or both thighs so intensely and continuously as to simulate sciatica. It is distinguished from this, however, by being confined to the outer and anterior aspects of the thighs, appearing to follow the distribution of the external cutaneous nerve. It, therefore, extends only as far as the knee, and there are neither tender points nor pain along the posterior aspect of the thigh, or below the knee.

Several authors have stated that various neuralgias, migraine, attacks of angina, asthma, etc., may arise from kidney irritation due to gravel. Da Costa * mentions them as associated with uric acid gravel; Cantani † and Kisch ‡ as symptoms of the precipitation of oxalate of lime crystals.

I have myself met with in one female patient feelings of oppression, palpitation, and shortness of breath ending in syncope, without being able to account for them on examining the heart and other organs, and without being able to find any other affection which could account for them, except a hereditary uric acid tendency in both parents and a well-established uric acid diathesis, with symptoms of gravel. I naturally drew no conclusion from this single case, as these symptoms might well be explained in another way.

Constipation is not unfrequently met with in these patients, and must be regarded as a nervous symptom.

* *American Journal of Medical Science*, 1893.

† *Pathologie und Therapie der Stoffwechsellkrankheiten*, 1880, Bd. 2.

‡ *Berl. klin. Wochensch.*, 1892, p. 317.

In one young lady, who had suffered for a number of years from obstinate constipation, for which innumerable strong purgative medicines and mineral waters had been employed in vain, treatment directed against the existing uric acid precipitation very quickly brought back the normal action of the bowels, which remained normal for more than two years under continuous employment of small doses of bicarbonate of soda.

Lange* has called attention to the existence of a considerable and persistent itching of the skin, as a result of uric acid gravel; this symptom has also been mentioned by Da Costa.† In the four cases referred to by Lange, the success of treatment of the diathesis was very apparent, as the itching disappeared when the patient continued to take alkalies, but reappeared when the treatment was stopped for some time.

Lange‡ has, moreover, collected a number of observations, which show that the uric acid diathesis is able to occasion a peculiar mental affection, showing itself by periodic states of depression, without hallucination tendencies. They do not lose the ability of comprehending their condition as purely morbid, but they are completely unable to shake off the disinclination and dislike for all things and all people, which makes their existence so unbearable. Along with the depression of spirits there is usually tiredness, some sleeplessness, and loss of flesh.

Among my adult patients I have seen only in one case a morbid condition accurately corresponding to Lange's description, and this occurred in a patient with

* *Hospitalstidende*, R. 3. B. ix. p. 553.

† *Americ. Journal Med. Science*, 1883, p. 313; u. 1893, i. Heft.

‡ *Periodiske Depressionstilstande, etc., Kopenhagen*, 1886.

mild arthritic symptoms, but with no signs of gravel. I have seen, in three cases of uratic precipitation in the kidney, slight symptoms of periodic depression; one of these had onsets of rather severe pain, not, however, typical of renal colic.

A certain depression of spirits almost always accompanies the repeated painful sensations characteristic of the formation of gravel; but this rarely is of so pronounced a character as to appear quite separate from the existing lesion, and so to come within the category of mental affections.

As already remarked, the objective symptom of this disease is the precipitation of uric acid crystals in the urine, either immediately after or before its evacuation.

Mygge* has given a very good and characteristic description of the urine of such patients, when it is collected for twenty-four hours. One of the peculiarities of this urine is that it is very rarely turbid, and apart from a crystalline sediment and an extensive cloud of mucus, which quickly falls to the bottom, it is surprisingly clear, and as a rule remains so, although left standing for days or even weeks, under conditions supposed to favour alkaline decomposition. When the urine passed during the twenty-four hours is collected in a urine glass, and the portion at the bottom of the glass poured into a conical glass, in a short time there forms at the bottom a dense layer of uric acid crystals, from two millimetres to one and a half thick; above this is to be seen a considerable cloud of mucus, intermixed with minute sparkling crystals of uric acid, which sometimes also form on the sides of the glass a diamond-dust-like layer.

* *Nordiskt. Med. Archiv*, Bd. 18. No. 23.

Above the cloud of mucus the urine is, as a rule, perfectly clear and often remarkably bright.

The urine is best examined immediately on being passed, so that there can be no doubt that the precipitation of uric acid is a primary phenomenon, and not due to the secondary disintegration of the quadriurate deposited. The best plan is for the patient to pass the water in presence of the physician, or where this is impracticable, to let him get it as soon after elimination as possible. As the morning urine is always the most liable to deposit uric acid crystals, I have in most cases asked for a sample of it. The urine is poured into a conical glass, and may be examined in the course of 15 to 20 minutes. Since I have had Gärtner's centrifuge at my disposal, I have preferred to let the urine stand in a conical glass for 5 to 10 minutes, then to carefully pour off the upper part, and put the lower portion in the centrifuge. When in the sediment so obtained large or very numerous crystals of uric acid are found, mixed together with round cells, kidney epithelia, or casts, one is warranted in attributing the existing symptoms, such as pain in the loins, radiating neuralgia, depression of spirits, etc., to the commencing formation of gravel in the kidney.

When precipitated uric acid is not immediately found, it is advisable, as recommended by Roberts, to let the urine stand in a warm place (about 20° C.), in order to observe if in the course of a few hours a deposition of crystals takes place; when this happens the urine must be considered to possess an abnormal tendency to deposit crystals, and this along with an accidental increase of uric acid production can cause precipitation in the kidney. When, on the other hand, only a layer of amorphous quadriurate forms, no conclusion can be

drawn from the presence of many or few crystals of uric acid along with it, as these may be formed by the decomposition which normally takes place when the urine sediment stands for a long time.

It must always be remembered in examining the urine that the degree of acidity, which plays so important a *rôle* in precipitation of uric acid, is influenced by many circumstances; after fasting the urine is acid, after a meal it is neutral or even alkaline; moreover the taking of alcohol or medicines may render the examination fruitless.

Roberts,* who carefully investigated this subject, found that the urine of a healthy man was strongly acid, and contained the greatest percentage of uric acid in the morning, after 14 to 16 hours' fasting: and as already stated, the examination of the morning urine is to be preferred for this reason.

It can hardly be doubted that the pain in the loins, neuralgia, etc., are symptoms of an irritable condition of the kidneys, and are caused by the uratic precipitate acting as a foreign body. Lange, in his treatise on the states of depression which may arise from the uric acid diathesis, comes to the conclusion that they cannot be attributed to a reflex condition, but result from an excess of uric acid circulating in the blood, and are a direct expression of the diathesis. I cannot quite follow this explanation; it has been already shown that an excessive proportion of uric acid in the blood is present in many diseases, without giving rise to depressed mental condition. Further, Roberts has demonstrated by his researches, that precipitation of uric acid may take place without the urine, and probably without the blood, containing an

* *Edinburgh Med. Journal*, 1860, p. 877.

excess of uric acid, and my own investigations have given a similar result (see page 110); and, in addition, various authors as for instance Cantani * and Kisch † have described a number of symptoms, as characteristic of the deposition of oxalate of lime in the kidneys, very like the above-mentioned group of symptoms, namely: loss of flesh, muscular weakness, pain in the loins, frequent micturition, depression of spirits, etc., and finally, in more advanced cases, renal colic. It is evident there are many symptoms of both diseases so similar, that one is compelled to attribute them to a common cause, and this can scarcely be any other than an irritation of the kidneys established by the deposition of crystals, which reflexly, that is, in some unknown way, gives rise to the other symptoms.

In many cases the course of the disease is extremely chronic; I have seen patients show symptoms like the above for 20 to 30 years, without true renal colic or other severe symptoms supervening. On the other hand, it is seldom that the disease totally disappears, unless the patient pays attention to his mode of living and diet.

As the object of this work is to discuss the pathology only of the milder forms of uric acid concretions, which often occupy the attention of the physician, being sometimes treated as totally different affections, I shall not deal with renal colic, which is described on similar lines in all the pathologies, and to which description I have nothing to add. Similarly, I shall not enter into the symptoms caused by larger concretions in the pelvis of the kidneys or other parts of the urinary passages.

* *Pathologie und Therapie der Stoffwechselkrankeiten*, 1880.

† *Berl. klin. Wochenschr.*, 1892, p. 317.

DIAGNOSIS.

The diagnosis of the early or slight development of uric acid gravel follows from what has been already written. The disease may be confused with simple ulcer of the stomach, lumbago, sciatica, and various kidney disorders. In children it is often regarded as intestinal colic, but careful consideration of all the subjective and objective symptoms, along with the results of the examination of the urine, will put the physician on the right track.

TREATMENT.

The treatment of this condition has three objects in view. 1. To act upon the reaction and chemical constitution of the urine in such a way as to diminish the tendency to uric acid precipitation. 2. To decrease the amount of uric acid produced when there is reason to think it is formed in increased quantity. 3. To endeavour to eliminate or dissolve concretions already formed in the kidney.

These objects are to be attained partly by the regulation of the mode of life and diet, and partly by the employment of various drugs.

The different authorities, who have dealt with this subject, have constructed certain dietaries, founded upon their theory of the formation of uric acid, which are said to be useful for diminishing its production. Accordingly,

Cantani* has recommended a diet preponderating in flesh —a kind of Banting cure; Haig,† one consisting chiefly of vegetable food; Ebstein,‡ the same diet as he prescribes for obesity and gout. As it has now been proved by the researches of Stadthagen, Bleibtreu, and Schultze, and of Horbaczewski also (see page 26) that the formation of uric acid is not diminished in an appreciable degree by a purely vegetarian diet, and that it is only slightly larger on an exclusively flesh diet than on the usual mixed one, there is no reason to afflict the patient with the extremely unpleasant restraint which a regulated diet that must not be departed from imposes. The patient may be permitted to live on the usual mixed dietary, and must be warned against excess both in the one and in the other direction. The collected statistics indicate that a diet too poor in albumen has a greater tendency to produce uric acid concretions. In support of this point Roberts has shown that they are frequently found in poor, badly-nourished children and agricultural labourers; and other authors have seen uratic precipitation during continuous fasting. Senator § states that the urine of the professional faster Cetti contained, after seven days' fasting, crystals of ammonium urate arranged like a thorn-apple, and so large as to cause a strong sensation of scalding in the urethra.

On the other hand, the greatest moderation must be exercised in reference to alcoholic drinks. Alcohol is hurtful both by increasing the production of uric acid, and by its action on the kidney tissues, already irritated by the precipitated uric acid crystals.

* "Pathologie u. Therap. der Stoffwech.," 1880.

† *Lancet*, 1890, ii. p. 281.

‡ "Natur und Behandlung der Harnesteine."

§ *Berl. klin. Wochensch.*, 1887, p. 427.

It must also be considered with reference to diet whether the patient may be allowed much or little liquid to drink. It is, indeed, doubtful whether it is desirable to make the urine very dilute as long as it retains its physiological reaction, as the quadriurate decomposes more rapidly in water than in normal urine; a full stream of urine, however, in the kidney tubules and pelvis may be useful by washing out small concretions, and if at the same time precautions are taken that the urine is neutral or only slightly alkaline, there is no danger of uric acid crystals being deposited. On this account it may be advisable to prescribe for the patient a daily draught of one or other alkaline water, and for this purpose Fachingen, Wildungen, or Vichy water may be profitably employed.

According to Ebstein's * researches the production of uric acid is not really influenced by the quantity of liquid taken into the system. His investigations are not quite trustworthy, as they were conducted by Heintz's method; but Schönborn † obtained the same result with a reliable method.

Having regard to the general health, a sedentary mode of living must naturally be avoided; it must also be remembered that as long as the other conditions favourable for the precipitation of uric acid are present it is injudicious to increase the production, and this is a certain consequence of any active, protracted muscular exertion (see page 111).

It is, therefore, not uncommon for patients who have not felt their predisposition to the disease, or whose inaccurate conception of it has not brought them to consult

* "Natur und Behandlung der Harnsteine."

† *Pflüger's Archiv*, Bd. 44, p. 529. See *Hirsch-Virchow's Jahresbericht.*, 1891, p. 171.

a physician, to believe that they will derive benefit from active exercise, and so to begin gymnastics, cycling, or the like. Then pain in the loins, neuralgia, etc., are very quickly set up, and if these symptoms are put down to a muscular rheumatism, and treated by massage and vapour baths, which still further increase the production of uric acid, the disease may be very protracted and assume a severe character.

On the other hand, no reasonable kind of bodily exercise is to be objected to, as long as it affects the solubility of uric acid in the urine in such a way as to increase the amount excreted, without precipitation taking place.

As the degree of acidity of the urine plays such an important part in the pathogenesis of uric acid precipitation, it is necessary to keep this in view when regulating the regimen of the patient. Both the old and the more recent writers have shown that the urine is more acid and more concentrated after prolonged fasting than after a meal. Hence the rule that the patient should not take few and large meals, but the daily quantum of food should be divided up into several meals. Roberts has particularly accentuated this point, as in England usually only three meals are taken in the day, so that twelve hours or more may elapse between dinner and the first meal of the following day. With us also it is advisable to impress upon patients that they should not let too many hours intervene between meals.

In connection with dietary, it should be remembered that sodium chloride is one of the substances which hold the quadriurate in solution; patients will act wisely by partaking largely of common salt, as it rapidly passes off in the urine.

Alkalies have been recommended as the special

medicinal treatment from time immemorial. The action of alkalies, of which bicarbonate of soda is the most popular, depends on their power of making the urine neutral or slightly alkaline. It is a good plan to instruct the patient to control the action of the medicine by using litmus paper, and take care that especially the morning urine is neutral or slightly alkaline. With this in view, a practical suggestion of Roberts is to take an alkaline powder at bed-time, in order to counteract the effect which the many hours of fasting have on the reaction of the urine.

Salkowski and Spilker* have investigated whether a moderate amount of alkalies have any influence on the production of uric acid. They found that a healthy man can take a dose of 10, 15, 20 to 25 grms. of acetate of soda daily without suffering inconvenience; it is eliminated in the urine as bicarbonate of soda. While the daily excretion of uric acid before taking drugs was 0·722 to 1·0708, or on an average 0·8218 grm., it sank on regular doses of acetate of soda to 0·5925 grm. on one day, and varied between 0·605 and 0·906 (25 grm. acetate of soda being taken daily); the average excretion of uric acid was 0·6923 grm.—a small decrease.

An apparent contradiction to this is that Spilker obtained a considerable increase in uric acid excreted by giving a medium sized dog 13 to 16 grm. acetate of soda daily. According to Horbaczewski, this must be explained by the introduction of such a large quantity of alkali into the stomach of a dog setting up a kind of inflammatory condition of the follicles, which is accompanied by a plentiful new formation of leucocytes.

It follows, from all that has been brought forward

* *Virchow's Archiv*, Bd. 117, p. 570.

here, that alkalies possess a favourable action on the chemical constitution of the urine; and, moreover, that they appear to slightly decrease the production of uric acid when the amount given is not overdone in a purely theoretical fashion.

The various mineral springs act in the same way as the carbonates and acetates of the alkalies. Fachingen, Vichy, and Wildungen waters are usually employed for this purpose; no particular advantage being derived from any one of these more than another; their activity stands in proportion to the amount of alkalies contained, and to the quantity of water which the patient may consume without disturbances of digestion arising.

As the quantity of uric acid in the blood and in the urine is directly proportional to the disintegration of leucocytes, there is reason, in cases of increased uric acid production, to prescribe those remedies that will diminish the number of leucocytes. With this in view, quinine or arsenic, specially recommended by Laache,* may be ordered.

In private practice it is very difficult to get the urine of patients collected during the 24 hours, especially when it has to be continued for a considerable time. I have not succeeded in making a large number of examinations of the urine after the administration of these drugs. In several children, where the symptoms as well as the number of blood corpuscles justified the assumption of an increased uric acid production, and in whom were undoubted signs of kidney irritation caused by the deposition of uric acid crystals, I have investigated the medicinal action of arsenic and iron preparations; and it

* "Die Anämie," Christiania, 1883, und "Verh. des X. Intern. Congr. Berlin," Bd. ii. Abth. v. p. 152.

struck me that the patients who formerly suffered from constantly recurring attacks of pain, etc., had a much better appearance, and were able to remain unaffected for months, even if, after some time, they were careless in taking the alkalies.

I hope to be able to carry out more accurate investigations on this question later on. One must not forget to watch carefully the condition of the patient while arsenic is being taken; Rasch * has recently drawn the attention of the profession to the fact that the uncontrolled and unlimited administration of arsenic is fraught with great danger.

As long as the concretions are scarcely visible to the naked eye, or still sufficiently small to pass easily down the ureter, the treatment described above will suffice. The state of affairs is quite different when the concretions have become so large that they can pass down the ureter only with difficulty and intense pain. Here it would be necessary to bring into use medicines which have the power of re-dissolving the larger concretions already in existence. For accomplishing this object innumerable drugs have been put forward, indeed so many that the suspicion at once arises that none of them can be depended on.

The compounds of lithia, the carbonate, the citrate, acetate, benzoate, and salicylate, have the greatest therapeutic properties; it must be borne in mind that large doses of these compounds are not well tolerated, and their prolonged administration, even in small doses, may set up disturbances of digestion.

The lithia salts have been recommended, because the urate of lithia is more soluble in water than the other

* "Bibliothek f. Läger," 1892, H. 8.

compounds of uric acid. The borocitrate of magnesia and the borocitrate of ammonium have also been recommended, but do not appear to be superior to the lithia salts. The latest drug, however, is the organic base, piperazine.

The method of demonstrating the advisability of these remedies has, as a rule, been conducted by mixing uric acid and the drug under examination with water, and investigating the solubility of the compound formed. In this experiment it has been quite overlooked that totally different conditions prevail in the kidney. Here the alkaline salts in the blood are excreted together with the uric acid and other acid constituents of the urine; the alkalies will form compounds with these acids, and so be placed quite beyond the sphere of exercising a soluble action on calculi, usually very resistent.

Piperazine was brought forward by Biesenthal and Schmidt * as a drug of great promise, but its action as a solvent of uric acid was tested only outside the body. It was so warmly recommended, because the urate of piperazine was soluble in 50 parts of water, while the urate of lithia required 368 parts of water. Piperazine was used on a large scale until Mendelsohn † showed that the urine of patients who for some days previously had taken the usual daily dose of piperazine, was totally unable to dissolve even minute uratic concretions, and that its solvent action disappeared whenever the solution of the drug in water was mixed with urine A mixture of 1 part piperazine, 40 of water, and 60 of urine had no solvent action whatever.

Piperazine exercises no action upon the production

* *Berlin. klin. Wochenschr.*, 1891, p. 1214.

† *Berlin. klin. Wochenschr.*, 1892, p 384.

of uric acid. Ebstein and Sprague * have prescribed it in doses of 1—2—3 grm. daily; during this time the urine of the individuals experimented on was sometimes neutral, sometimes slightly alkaline, the amount of uric acid excreted was about normal, indeed rather greater than before the administration of the drug. As the individuals referred to had never shown symptoms of uric acid gravel, and the piperazine could not bring into solution deposits of uric acid in the kidney, the increase, which, however, was small, must therefore be put down to the influence of piperazine upon metabolism.

My experiments upon myself seem to show that the usual daily dose of 1 grm. piperazine exerts no influence upon the amount of uric acid excreted; while in the same way as the inorganic bases, it makes the urine neutral or slightly alkaline. Piperazine was taken from the 7th to the 10th of February, and the amount of uric acid estimated by the Fokker-Salkowski method.

Urine of the 7th,	(active bodily exercise)			0·981	grm.	uric acid.
,, ,, 8th,	,,		,,	0·739	,,	,,
,, ,, 9th,	,,		,,	0·628	,,	,,
,, ,, 10th,	,,		,,	0·547	,,	,,

A similar examination of the urine on days when no piperazine was taken gave

Urine of the 14th Feb.,	(active bodily exercise)			1·089	grm.	uric acid.
,, ,, 16th	,,		,,	0·552	,,	,,
,, ,, 17th	,,		,,	0·621	,,	,,
,, ,, 18th	,,		,,	0·450	,,	,,

Piperazine, accordingly, appears to act exactly like the alkalies, namely, to change the reaction of the urine. As it is not tolerated by every patient, and does not

* *Berlin. klin. Wochenschr.*, 1891, p. 348.

surpass in its action the cheap and harmless bicarbonate of soda, there is no reason why the preference should be given to this expensive drug.

Glycerine was once much recommended as a solvent of urinary calculi. Colasanti * found that glycerine at an elevated temperature dissolved uric acid in the proportion of 0·74 in 100 parts glycerine, but as the uric acid is no longer held in solution by the addition of acids, alkalies, or water, it is indeed doubtful whether anything is to be expected from it. Glycerine was a short time ago recommended by Hermann,† with some success. He gave adults 50 to 100 c.c. of glycerine, dissolved in an equal quantity of water, two to three times daily. Several hours after the administration of the glycerine pain was felt in the region of the kidneys, which in some cases advanced to true renal colic, and led to the evacuation of gravel or small calculi. This treatment gave rise to no symptoms in healthy persons.

It must be remembered, in the administration of glycerine, that it usually contains so much acid (sulphuric acid) that it may do harm; one should, therefore, be sure of employing a pure preparation.

The best effect is probably to be expected from a regulated mineral water treatment.

Fürst ‡ has recently conducted a comparative estimation of the solvent action of various mineral springs upon uric acid, and this instructive investigation was worked out in the following way.

A healthy individual drank 100 c.c. of the mineral spring whose action was to be tested, and the urine

* Moleschott, "Unters. z. Naturl." See *Hirsch-Virchow's Jahresb.* 1883, i. p. 126.

† *Semaine Med.*, Dec. 10, 1892.

‡ *Deutsche Medicalzeit*, 1893, Januar.

passed was examined by adding 0·5 grm. of dried uric acid to 200 c.c. of urine, and digesting at 37° C. for fifteen to twenty minutes, after which the uric acid was filtered off, dried, and carefully weighed, with the following result:—

Normal urine				Deposited uric acid.	
Urine after drinking		Assmanshauser Brunnen		,,	,,
,,	,,	Wiesbadener Koch Brunnen		,,	,,
,,	,,	Salzschlirfer Bonifacius-Quelle		,,	,,
,,	,,	Fachinger Brunnen took up	0·043	grm.	uric acid.
,,	,,	Vichy	,, 0 025	,,	,,
,,	,,	Wildungen Brunnen	,, 0 024	,,	,,

According to this investigation Fachingen water appears to be the most active; moreover, Fürst concludes from his experiments that the solvent action on uric acid of a mineral spring appears to depend on the proportion of alkaline carbonates it contains, and that the soda salts appear to have no particular advantage over the compounds of potash and lime.

If the treatment with Wildungen, or any other mineral spring generally employed with success in this disease, is not able to free the patient from the concretions, which give rise to renal colic, or which, from their presence in the pelvis of the kidney, cause continual pain and irritation, and sometimes set up serious affections, there is no option but to confine the treatment to the alleviation of the condition by analgesic remedies, or to call in surgical assistance.

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