

Gout : its pathology, forms, diagnosis and treatment / Originally founded on the Goulstonian lectures on "The chemistry and pathology of gout," delivered by the author before the Royal College of Physicians of London in 1897.

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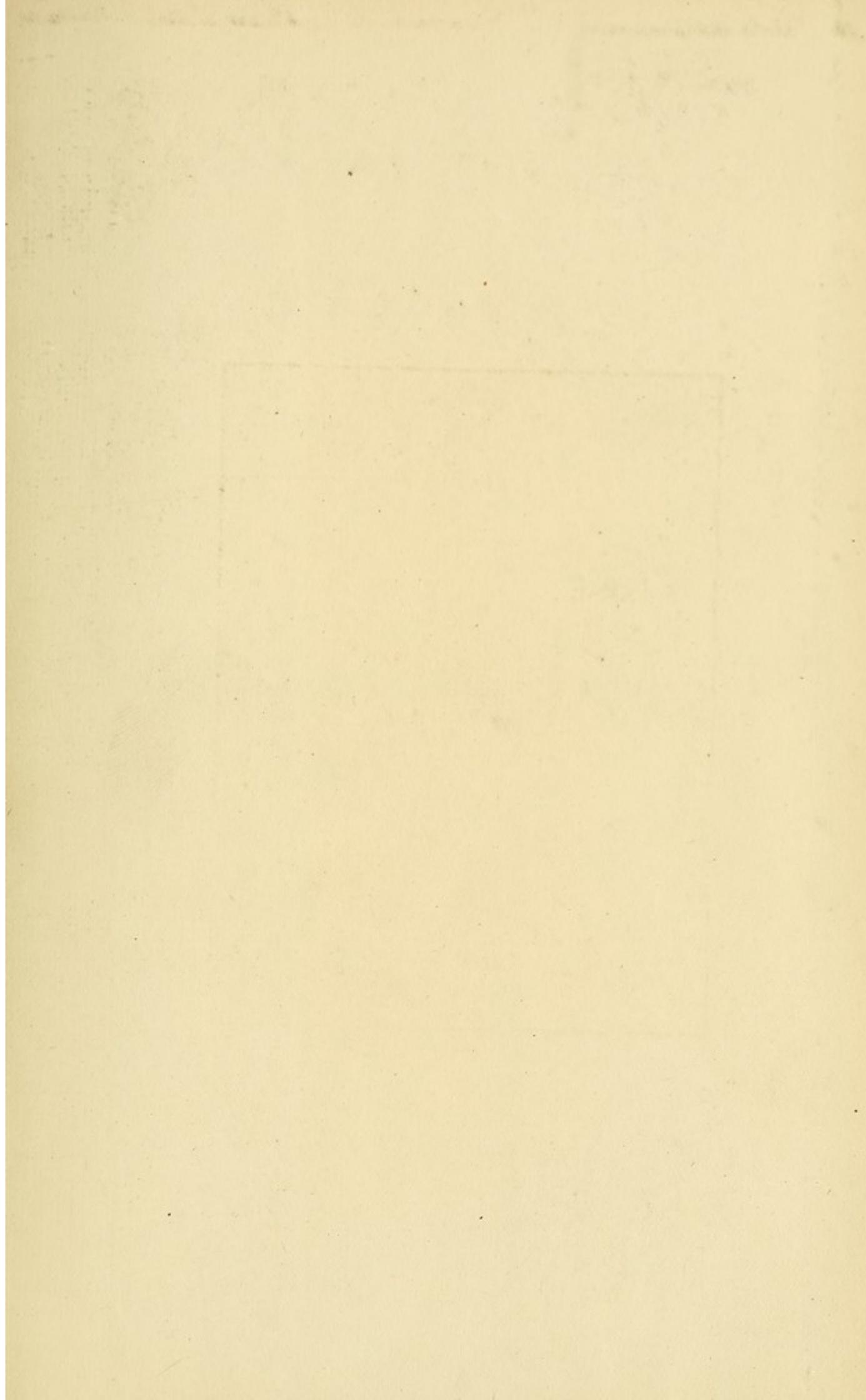
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GOUT

ITS PATHOLOGY, FORMS, DIAGNOSIS
AND TREATMENT

*Originally founded on the Goulstonian Lectures on "The
Chemistry and Pathology of Gout," delivered by the author
before the Royal College of Physicians of London in 1897*

BY

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THIRD EDITION

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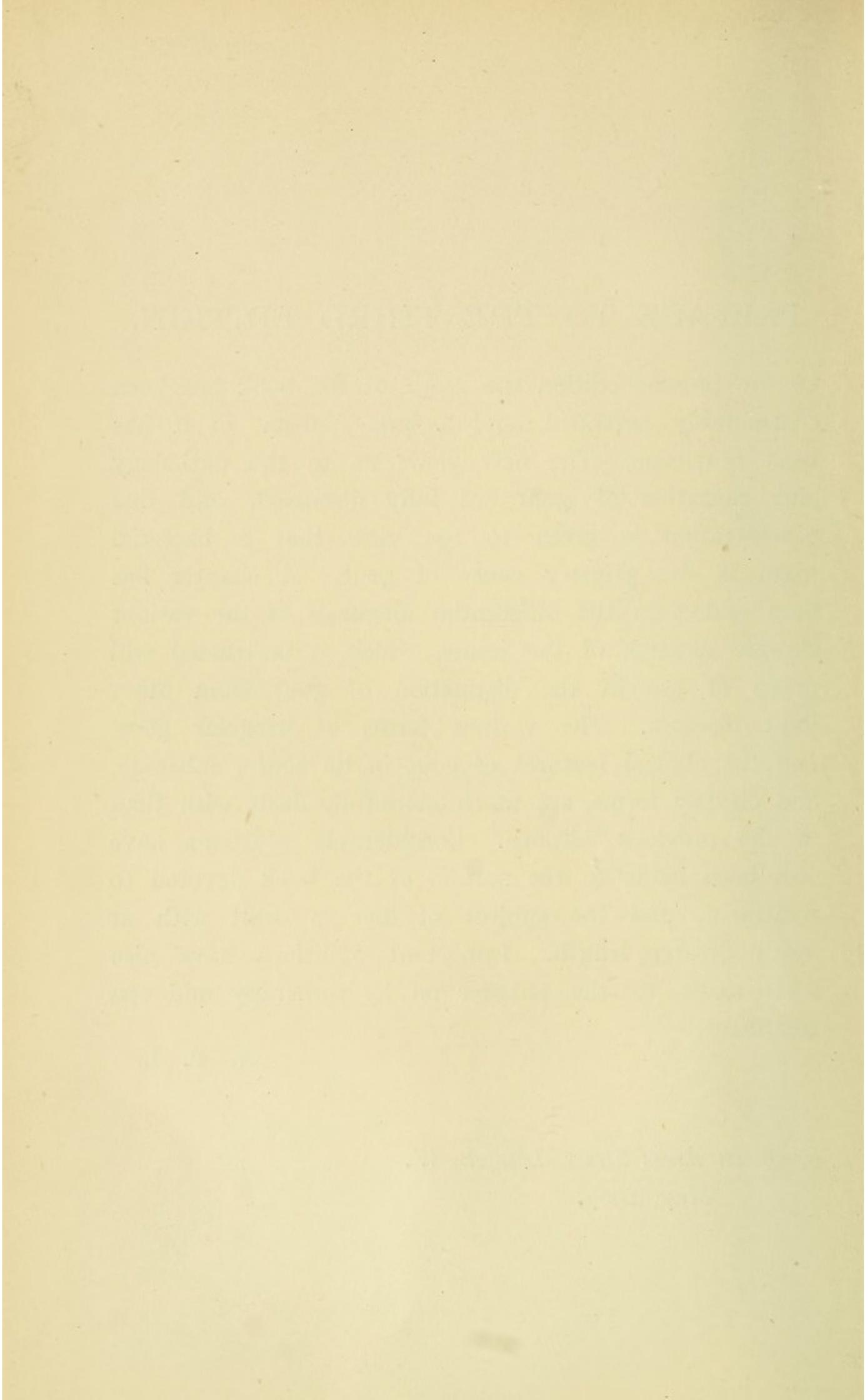
PREFACE TO THE THIRD EDITION.

IN the present edition the scope of the book has been considerably extended, and a large portion of it has been rewritten. The new views as to the pathology and causation of gout are fully discussed, and due consideration is given to the view that a bacterial toxin is the primary cause of gout. A chapter has been added on the differential diagnosis of the various chronic diseases of the joints, which it is trusted will prove of use in the distinction of gout from other joint diseases. The various forms of irregular gout, and the clinical features of gout in its acute, subacute, and chronic forms, are much more fully dealt with than in the previous editions. Considerable additions have also been made to the section of the book devoted to treatment, and the subject of diet is dealt with at much greater length. Important additions have also been made to the chapter on hydrotherapy and spa treatment.

A. P. L.

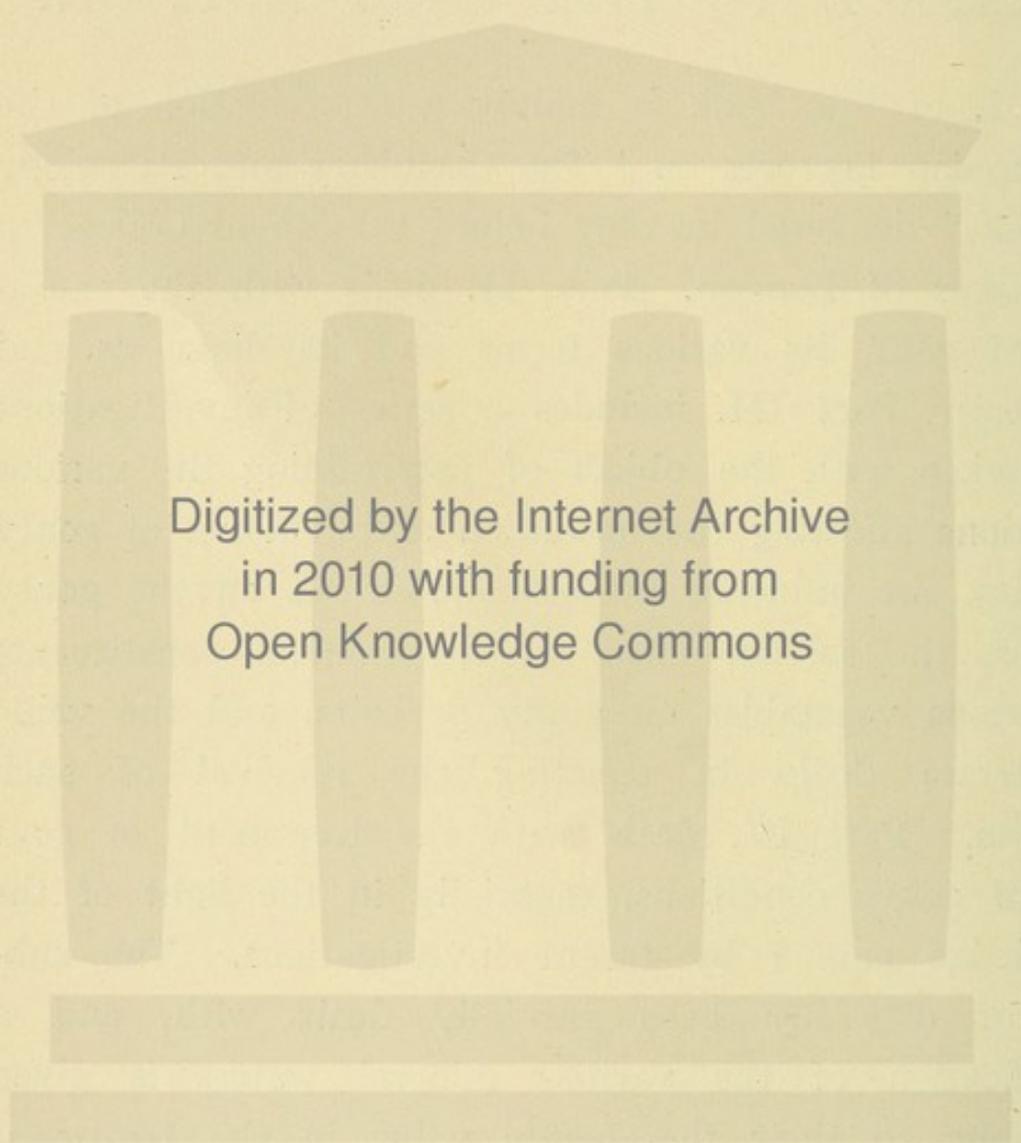
9, *Queen Anne Street, London, W.*

May, 1907.



PREFACE TO THE FIRST EDITION.

PART I. of this book is mainly a reproduction of the Goulstonian Lectures on "The Chemistry and Pathology of Gout," delivered in 1897 before the Royal College of Physicians of London. Part II. deals with the causation of gout, its various forms and its diagnosis and prognosis. Part III. includes a series of investigations undertaken with the object of ascertaining the various conditions affecting the formation and removal of gouty deposits, the influence of alcoholic drinks on the gouty process, the solvent effect of the mineral constituents of various vegetables on gouty deposits, and the value of certain drugs in effecting the removal of such deposits. Part IV. deals with the treatment of gout and of gouty conditions, especially in the light of the knowledge gained by recent investigations. The subject of diet has been carefully dealt with, and a classification of the various mineral waters is given according to their therapeutic value in the treatment of the various forms of gout.



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PART I.

THE PATHOLOGY OF GOUT.

CHAPTER I.

URIC ACID AND THE PURIN BODIES.

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GOUT is the manifestation of a number of morbid tendencies, some of which may be inherited and some acquired. If the joints are affected, articular or regular gout results; if other organs or tissues are affected, then irregular gout is produced.

It is a disease which is due to faulty metabolism, probably both intestinal and hepatic, as the result of which some toxin or toxins are produced and lead to an auto-intoxication, which is an early factor in the development of the gouty condition. This auto-intoxication coincides with or is followed by, in the majority of cases, a deposition of sodium biurate in certain of the joints or tissues, which constitutes the climax of the gouty attack. I cannot but think that with our increasing knowledge and experience of the disease uric acid and its salts will in all probability have to be relegated to a position of subsidiary importance in the pathogenesis of gout. The joint manifestations are dependent upon much more general and

much larger conditions than a mere excess of uric acid in the blood. The deposition of sodium biurate is merely the sign of the disease, not the essence of it. The generally accepted belief that the primary development in gout is the heaping up and deposit of uric acid in the tissues must be regarded as quite inadequate. The accumulation of uric acid in the tissues is simply one of the symptoms of gout, and must not be taken as its cause.

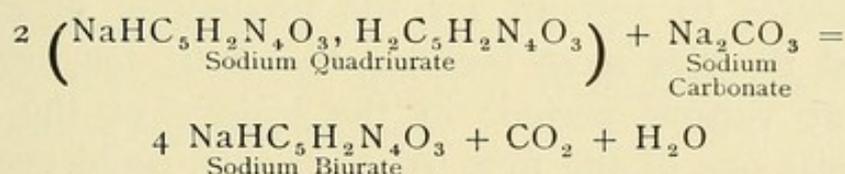
Walker Hall states that gout cannot be regarded as a state of simple malnutrition; it is rather a condition of insufficient cellular resistance against the absorption of intestinal poisons or auto-toxins, characterised by the production of imperfectly formed metabolites, which act upon some tissues as irritants and in others excite degenerative changes that permit uratic infiltration.

Gout is associated with the presence of an excess of uric acid in the blood, and the questions that will be first dealt with mainly resolve themselves into the mode or modes by which the uric acid is produced and introduced into the blood, the source or sources of its production, the relationship that it bears to the gouty paroxysm and to the other manifestations of gout, and the factors or conditions which influence its formation and its injurious action.

Uric acid and its compounds.—Uric acid is a bi-basic acid, the formula of which is $H_2(C_5H_2N_4O_3)$. This acid forms the following three classes of salts:—(1) The *neutral urates*, in which a metal takes the place of all the displaceable hydrogen, such as $Na_2C_5H_2N_4O_3$, the neutral sodium urate. (2) The *biurates*, in which a metal takes the place of half the displaceable hydrogen, such as $NaHC_5H_2N_4O_3$, the sodium biurate. The biurates, although acid salts in constitution, are not acid to test paper. (3) The *quadriurates*, in which a metal takes the place of one-fourth of the displaceable hydrogen of two molecules of uric acid, such as $NaHC_5H_2N_4O_3$, $H_2C_5H_2N_4O_3$,

the sodium quadriurate. Of these three classes of salts the neutral urates cannot exist in the living organism, and therefore take no part in the pathology of gout. It is also important to understand that uric acid does not and cannot exist in the blood in the free state under any conditions whatsoever. The sodium quadriurate is the soluble uric acid compound which is originally contained in the blood of gouty subjects, and this substance, as just mentioned, is a derivative of two molecules of uric acid in which sodium is substituted for one-fourth of the displaceable hydrogen, or, in other words, it is a molecular combination of sodium biurate with uric acid. This sodium quadriurate is, however, an unstable body, and after a certain time it unites with some of the sodium carbonate of the blood to form sodium biurate, which, if produced in larger quantities than the fluids of the body can retain in solution, becomes deposited in various structures in the crystalline form.

This conversion of sodium quadriurate into the biurate by the sodium carbonate of the blood is shown in the following equation :



The sodium quadriurate is, therefore, to be regarded as a comparatively soluble but very unstable compound, whilst the sodium biurate is comparatively insoluble but very stable.

Tunncliffe and Rosenheim* have published a series of experiments from which they conclude that there is no evidence of the existence of quadriurates as a third order of uric acid salts. They consider that the so-called quadriurates consist of mixtures in varying proportions of uric

* *Lancet*, 1900.

acid and biurates, and that their property of showing the formation of uric acid crystals under the influence of water is due to the dissolving out of the more soluble biurate moiety and a change in physical state of the remaining uric acid.

It would appear, however, that it is quite an immaterial point whether the quadriurates are regarded as molecular combinations of uric acid and biurates, or as physical mixtures of these substances.

Murexide Test for Uric Acid.—If two or three drops of strong nitric acid are added to a fragment of uric acid in a porcelain dish, and heat is gently applied until all the nitric acid is driven off, a reddish-coloured residue (alloxan) will be left. If, when the dish is cold, a few drops of solution of ammonia are added to this, a beautiful crimson-purple colour is developed, due to the production of murexide by the action of the ammonia on alloxan. This is an extremely delicate test, and the one-hundredth part of a milligramme of uric acid may be detected by this reaction.

Theories as to the causation of gout.—Of the various theories to account for the production of gout the humoral theories have been to the front for many centuries at various periods in the history of the disease. Galen was one of the first to teach that tophi arose from the desiccation of collected and pathologically altered humours.

Cullen, who was the great opponent of the ancient humoral theory of gout in the latter half of the last century, admitted, however, that in some instances a peculiar matter appears in gouty patients, but he considered that it was the effect and not the cause of the malady. Uric acid was discovered in the urine by Scheele in 1775, and in 1787 Wollaston demonstrated its presence in gouty concretions. These discoveries did not, however, bring to light the important part played by uric acid in gout.

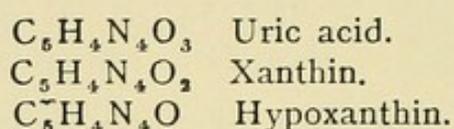
It was in 1847 that Sir Alfred Garrod first found uric acid in the blood of gouty subjects in the form of a sodium salt. The discovery of uric acid in the blood of gouty patients eventually led to the much-discussed question as to whether it was the cause or the result of gout. Those who held the former view were in their turn divided as to whether the uric acid compound only exerted its baneful effects when it had crystallised out of the blood and had become deposited in the affected tissues, or whether, while still circulating in the blood, it exercised a true toxic influence.

Cause of the presence of uric acid in the blood in gout.—The next question to consider is whether the excess of uric acid present as quadriurate and biurate in the blood in gout is the result of deficient excretion, of over-production, or of deficient destruction. All observers are agreed that an abnormal quantity of uric acid in the form of one or other of its salts is found in the blood in gout. This overcharging of the blood with uric acid must be due to one or more of the following causes :—(1) Normal production and deficient excretion of uric acid ; (2) over-production and normal excretion of uric acid ; and (3) diminished destruction of uric acid by imperfect oxidation, or by some other means.

Admitting then an excess of uric acid in the blood in the form of quadriurate or biurate, and that its deposition therefrom as the sodium biurate in cartilages and other tissues is connected with the gouty paroxysm, the two questions that naturally arise are : (1) Where is the uric acid formed ? (2) How is the uric acid formed ? It will be well, therefore, first to consider the various views as to the seat or seats of formation of uric acid.

View that uric acid is formed from nuclein.—Mares showed a few years ago that the greatest increase in uric acid excretion occurs in a few hours after a meal, whereas general nitrogenous catabolism, as indicated by

the amount of urea excreted, increases more slowly, and does not reach a maximum until some hours later. This was explained by Horbaczewski to be due to a digestive leucocytosis, and the consequent increased liberation of nuclein within the body. Horbaczewski * has shown that uric acid, as well as xanthin and hypoxanthin, can be prepared from spleen pulp. The close relationship of these three bodies to one another is shown by a comparison of their formulæ :



By digesting fresh spleen pulp with hot water till changes set up by bacterial agency are started, he found that the fluid, when freed from albuminous bodies, contained xanthin and hypoxanthin, but no uric acid. By treating this fluid with arterial blood and keeping the mixture at 40° to 50° C., uric acid forms in it after several hours. A similar result is produced by using as the oxidising agent either a dilute solution of hydrogen peroxide, or an abundant supply of atmospheric air. Horbaczewski found that the nitrogen contained in the uric acid so formed was about equal in amount to the nitrogen contained in the xanthin and hypoxanthin (xanthin bases). So that there exist in the spleen nitrogenous substances which can be transformed, at all events in part, into xanthin bases or into uric acid. The xanthin bases when once formed cannot be further oxidised into uric acid. Horbaczewski brings forward proof that the substance which yields xanthin bases and uric acid is the nuclein of the spleen cells. It was found that when pure nuclein, prepared from spleen pulp, was dissolved in very weak alkali, and digested with blood at 40° C., uric acid was formed. Sadowenj and Formanck have shown that uric acid can be prepared in a

* *Beiträge zur Kenntnise der Bildung der Harnsäure und der Xanthinbasen.*
Sitzungsbericht der K. Acad. d. Wiss. in Wien. C., iii., 1891.

similar manner from almost all the tissues and organs of the body, and conclude that the nuclein contained in the cells is the mother-substance.

It having thus been shown that uric acid could be prepared from nuclein outside the system, an attempt was next made to ascertain whether a similar decomposition could also occur in living human beings. Horbaczewski found that the excretion of uric acid can be increased either by the administration of nuclein with food, or by the subcutaneous injection of a solution of it. Umber* found that the administration of a large amount (500 grammes per diem) of food like thymus, which contains a considerable quantity of nuclein, increases the excretion of uric acid as compared with its excretion when a similar amount of flesh is given. The same amount of liver given to one person caused an effect similar to that caused by thymus, but in others its action was less marked. Kidney and brain administered as food yielded nearly the same amount of uric acid as flesh.

From his experiments Horbaczewski concludes that uric acid is formed in health by the disintegration of nuclein, and that sudden variations in uric acid production may be due to the breaking up of leucocytes and conversion of their nuclein into uric acid or xanthin bases within the system. It has been shown by many observers that a temporary or permanent leucocytosis is always accompanied by an increased excretion of uric acid. A relationship between the number of leucocytes in the blood and the excretion of uric acid is observable in human beings during fasting and after taking food. During fasting the number of leucocytes diminishes, and the amount of uric acid excreted falls; after taking food the number of leucocytes increases, and the amount of uric acid excreted rises. The increase in the number of leucocytes in the blood after a meal appears to be due, at all events in part,

* *Zeitschrift f. klin. Medicin*, 1896, xxix., pp. 174-189.

according to Hofmeister,* to the rapid increase of lymph cells in the adenoid tissue of the stomach and intestines during digestion, whence they are discharged into the lymph stream, and finally into the blood. Gamprecht †—who uses the term “alloxur bodies” in Kossel and Krüger’s sense as meaning those bodies which have an alloxan and urea nucleus, and therefore as including, besides uric acid, xanthin, guanin, hypoxanthin, adenin, and their derivatives—found that in the exceptional cases of leukæmia in which the uric acid excretion is normal or diminished, the alloxur bases are increased, and that their amount varies directly with the amount of leucocytosis. He gives one case of his own in which this is shown very clearly, and points out that it forms an additional support to Horbaczewski’s view that uric acid comes from degeneration of leucocytes, and is formed from their nuclein.

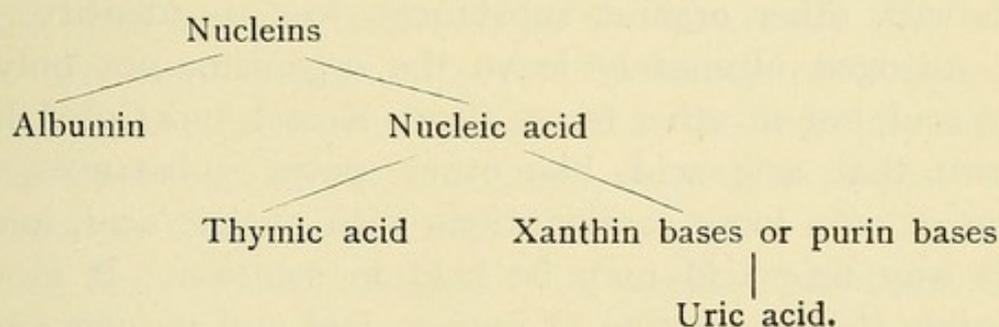
The opponents of Horbaczewski’s views have shown that a well-marked digestive leucocytosis may occur after a diet of egg white, or even after a non-nitrogenous meal, and yet there is no rise in uric acid excretion. Moreover, it has been shown that the amount of disintegration of the leucocytes could be measured by the amount of phosphoric acid secreted, for this substance is also a product of the breakdown of nuclein. The proportion of the uric and phosphoric acids, however, does not always run parallel, and in a case of leukæmia recorded by Milroy and Malcolm there was even a diminution of phosphoric acid. Kühnau in an extensive and careful research showed that following the crisis of lumbar pneumonia, at which period there is an increased destruction of the white cells, there is an increase in the daily amount of uric acid excreted. From observations that he made in various other diseases he found that a decrease in the leucocyte count is generally followed by a corresponding increase in the

* *Arch. f. Exper. Pathologie und Pharmakologie*, Bd. xxii., p. 306.

† *Centralblatt f. allgemeine Pathologie und pathologischen Anatomie*, 1896, vol. vii., p. 820.

excretion of uric acid, an increase which he considers is caused by the increase in the destruction of the white corpuscles. O. K. Williams* has made a series of observations in pulmonary tuberculosis in order to ascertain whether an increase of the white cells is followed by an increase in the amount of uric acid excreted, and in order to show that such an increase in the excretion of uric acid is due to an increase in the destruction of the white cells, he made a determination of the amount of phosphoric acid excreted as well as uric acid. He found as a result of his investigations that in the majority of cases in which an increased excretion of phosphoric acid follows an increase of destruction of white corpuscles there is associated with this increase a corresponding increase in the amount of uric acid excreted.

Uric acid and thymic acid.—By the splitting up of the nucleins, as shown by Schmoll, there are produced : (a) albumin, and (b) the nucleic acid group : thus—



The nucleins when split up by digestion yield simple albumin and nucleic acid, nucleic acid again yielding thymic acid and the xanthin bases. Since nucleic acid, by splitting up, yields ultimately uric acid and thymic acid, Minkowski and Kossel advanced the hypothesis that thymic acid is the substance which, combined with uric acid, renders the latter soluble, and that this combination cannot readily be broken up, so that uric acid cannot be recovered, after it has once combined with thymic acid, without prolonged boiling. According to this view uric

* *Lancet*, 1903.

acid, as soon as formed, combines with thymic acid. In this combination it circulates in the blood and is excreted by the kidneys, partly in its combined state and partly after the breaking up of this combination. Regarded in this light, the presence of uric acid in gouty fluids and tissues is explained by the absence of a proper proportion of thymic acid combined with it and keeping it in solution. In the normal state uric acid is produced by the oxidation of the purin bases; in the gouty state the combination with thymic acid does not take place.

It is erroneous to regard the amount of uric acid in the urine as synonymous with the amount produced in the body. The uric acid produced in metabolism in great measure leaves the body by the urine, but all of it certainly does not. Some may be retained within the body for a time (an exaggeration of this is seen in gouty concretions); some may be further oxidised and converted into urea and simpler products; some may enter into combination with other organic substances, lose its identity, and the nitrogen ultimately leave the organism, not only as uric acid, but in other forms also. Kossel and Goto* have shown that uric acid, like other purin substances, will form *in vitro* loose combinations with nucleic acid, and in this way uric acid may be held in solution. It is thus possible that the action of nucleic acid and its compounds in the body may be a factor in determining the solubility of uric acid there.

The purin bodies.—The term “purin” has been applied by E. Fischer to a nucleus C_5N_4 , and all bodies constructed upon such a base are included under this name. The purin bodies of ordinary occurrence are Hypoxanthin ($C_5H_4N_4O$), Xanthin ($C_5H_4N_4O_2$), Uric Acid ($C_5H_4N_4O_3$), Guanin ($C_5H_5N_5O$), Adenin ($C_5H_5N_5$), Caffein ($C_5HN_4O_2(CH_3)_3$), and Theobromin ($C_5H_2N_4O_2(CH_3)_2$). By some writers these bodies are styled alloxur bodies (or

* *Sitzungst. Gesellsch. gesammt. Naturwissensch. Marburg, 1900, April 6th.*

bases), or xanthin bodies. Kossel was the first to establish the close chemical connection between nucleins and the xanthin or purin bodies.

The purin bodies exist either in a free state or combined with albumin in the form of nucleic acid. Hypoxanthin and xanthin occur in muscle extracts. Adenin is yielded chiefly by the decomposition of the nucleic acid present in thymus, and guanin by the nuclein prepared from pancreas.

Uric acid and the purin group of bodies are derived from the "nucleins" or materials of which the cell-nuclei consist. The breaking-up of these nuclei gives rise to uric acid and the purin or alloxur bodies. Now, it is clear that two possible origins of these substances as met with in the body are thus conceivable: viz., from the nuclei of the cells of the living body itself, and from those of the animal and vegetable matter consumed as food. Both of these may give rise to uric acid in the system, the food-nuclei causing what is known as the exogenous, the body cells the endogenous, supply. An excessive supply of nuclear products may thus arise from the consumption of kinds of food rich in these elements, or from some perverted metabolism of the body-cells.

The daily "wear and tear" or metabolism of cell constituents leads to the production of a certain amount of purin bodies. Whether this occurs in the vegetable, animal, or human organism, these substances constitute the endogenous purins of the excreta. When tissues containing nucleins or free purins are eaten by lower animals or by man, the endogenous purins of the food ingested become exogenous to the system which absorbs them. As endogenous purins are practically waste products on their way to excretion, so when they become exogenous to another organism, they have little nutritive value, and demand early and rapid elimination. This is generally effected by the oxidation of the oxy-purins, hypoxanthin

and xanthin, to uric acid, and then the purin ring or chain in the uric acid is in the liver partially split off and a portion of the uric acid excreted as urea.

All purins are therefore primarily of an endogenous origin. What, then, are the sources of the endogenous purins? At the moment the lack of definite evidence precludes a definite reply, but for purposes of discussion we may perhaps formulate their probable sources with some show of precision, and thus consider them as arising (1) by synthesis; (2) from the destruction of leucocytes; (3) from the breaking-up of nucleo-proteids during cell processes.

Endogenous purins.—The sources of endogenous purins are probably numerous, and the quantities derived from each may vary with the hourly activities and daily needs. The endogenous purin is partly derived from leucocytes, but mostly from the cell changes which result in the maintenance of bodily functions. Hence, as the cell-nucleus is the dominating factor in metabolism, the cleavage of cell nucleins may incite the decomposition of proteid matter. It is possible that the endogenous urinary purin represents about one-half of the total endogenous purin produced, and that the latter quantity indicates the extent of metabolic processes more completely than any other factors at present available.

In regard to normal leucolysis as a probable source of endogenous purins, it is only possible for this condition to contribute a very small proportion of the total output. True it is that in leukæmia the enormous increase of leucocytes is accompanied by an increased output of uric acid; but it is known that in leucopenia, even when the leucocytes are lowered to 1500 to 3000 per cm., the uric acid or purin excretion is practically unaltered. To produce one gram of purin bodies large numbers of leucocytes are necessary—numbers out of all proportion to the leucocytosis of febrile and acute inflammatory conditions;

so that, while we may include leucolysis in a list of the sources of endogenous purin and uric acid, it cannot be considered as an important factor.

So far as experimental results can suggest normal action, one portion of the total endogenous purins is broken down to urea and the remainder excreted as uric acid. Abnormal endogenous purin metabolism may, therefore, consist in an increased production with excessive or diminished destruction, or in decreased production with excessive or diminished destruction.

It is quite possible that the conception of the existence of the quadriurates will have to be abandoned, and that it will be necessary to substitute therefor the view of uric acid organic combinations as a necessity for their normal circulation. If we allow such a possibility, then some idea may be gained of the resultant effect of the presence of the imperfect metabolites in the tissues, and our therapeutics be directed to the restoration of normal metabolised bodies, rather than to the attempted solution and elimination of uric acid.

The destruction of uric acid, according to recent work upon the subject, takes place mainly in the liver; but Wiener, working with organ extracts, showed that such prepared from liver, kidneys, and muscles were able to decompose uric acid. If his methods were reliable and his experiments correspond to intra-vitam processes, the tissues generally may share in the uric acid destruction. But the rôle of the latter must be small compared with that of the liver, and to this conclusion the later experiments of Burian and Schur distinctly point. Probably, therefore, the exogenous purin remainder is decomposed chiefly in the liver, perhaps partly in the tissues, and finally excreted as urea, or as bodies intermediate.

Exogenous purins.—Every healthy adult excretes a certain amount of purin substances which is independent of his diet; this is the result of tissue metabolism

(endogenous urinary purin). Its amount may be directly estimated by examining the urine after a diet of substances which are practically free from purin compounds ; such articles of diet are milk, cheese, white bread, potatoes, rice, green vegetables, etc. This method of examination is much better than that of analysing the urine during hunger. In inanition the upset produced in metabolism generally is sure to give untrustworthy results. When a man takes his ordinary diet, which includes articles containing nuclein, or purin compounds, the amount of urinary purin is increased by a part of the purin derived from his diet, and this increase may be termed "exogenous urinary purin." The "nutrition purin" does not pass wholly into the urine ; a certain fraction remains in the organism, the purin double ring being broken down. The amount of the remainder (exogenous urinary purin) differs for different forms of food, and is but little affected by the individuality of the subject of the experiment. The following table by Burian and Schur * gives some of the results obtained by them :—

TABLE I.

Diet.	Total percentage of purin substances in diet.	Percentage of exogenous urinary purin.
Beef	0.06	0.030
Coffee	0.20	0.075
Calf's liver	0.12	0.060
Calf's spleen	0.16	0.080
Calf's thymus	0.40	0.100

By subtracting the exogenous from the total urinary purin, the endogenous urinary purin is obtained, and the numbers come out closely with the results obtained by direct estimation ; it varies in the majority of people from 0.1 to 0.2 grammes daily, but values both higher and lower than these were obtained.

* *Pflüger's Arch.*, 1900, vol. lxxx., pp. 241-343.

In white bread, rice, eggs, salad and cauliflower, Burian and Schur found no xanthins. By use of these foods they determined the endogenous urinary purins in a number of cases, and obtained results of individual constancy. When the endogenous urinary purin was estimated, and the amount of the food purin also known, they were able to explain the relation of the food purin to the urinary purin, and knowing the amount of the food purin and the total urinary purin, they were able to calculate the quantity of endogenous urinary purin. To obtain the average amount of endogenous purin excretion, Walker Hall employed a fixed purin-free diet, consisting of eggs, bread, milk, cheese, butter, rice, and sugar. Neither tea, coffee, nor beer was taken. His results, which are in accordance with those of Burian and Schur, show that upon an almost purin-free diet an average of 0.1623 grammes purin-N. per day was excreted, or 0.4869 grammes in terms of uric acid and xanthin bases.

The further results of Walker Hall's experiments after the consumption of purin-containing foods show that:—(1) with chicken 54.4 per cent. of the food purin appears in the urine as exogenous purin; (2) with plaice 58.7 per cent. of the food purin appears in the urine as exogenous purin; and (3) with beef 47.4 per cent. of the food purin appears in the urine as exogenous purin. It thus appears probable that, allowing for the variations which occur in different animals, as well as in separate species, the system excretes in the urine (within forty-eight hours) about one-half of the fish, fowl, or beef purins contained in the food. An additional experiment, made to determine the exogenous purins after ingestion of haricot beans, showed that 55 per cent. of the food purin appeared in the urine as exogenous purin.

Walker Hall's results, together with those of Burian and Schur, show that roughly 50 per cent. of the purin contained in the food reappears in the urine; but such amount can only be taken as a broad average, and is

applicable only to healthy individuals upon perfectly assimilable diets. All foods containing purin bodies thus appear to increase the excretion of uric acid and the xanthins. On the other hand, the consumption of milk, a purin-free food, was found by Burian and Schur to result in a very low uric acid excretion. Amongst foodstuffs, the purin bodies, with the exception of uric acid, are widely distributed. They exist in all forms of meat extracts, in the flesh meats of ordinary consumption, and in larger quantities in the glandular organs—thymus, pancreas, etc. In lesser amount they occur in many vegetables, as oats, potato, and sugar beet.

So far only that portion of the food-purin has been considered which, after oxidation to higher forms in the tissues or liver, or in both, appears in the urine in quantities representing about half of the amount ingested. The next point to consider is what is the fate of the other 50 per cent. ? Swain considers that allantoin may be looked upon as an intermediary product between uric acid and urea, and that under ordinary circumstances about 50 per cent. of the uric acid produced is almost completely oxidised to urea, but that when the metabolic organs are unable fully to decompose the purin radical more allantoin and less urea appear in the urine.

It may therefore be inferred, according to the views just enunciated, that uric acid is now more generally regarded as an intermediary metabolic product, and that its appearance in the urine is due to incomplete decomposition.

It will be seen that the exogenous nucleins simply pass through the body. Their phosphorus may be retained for synthetic or organic purposes, and the small amount of albumin they contain may be used up in the tissues ; but their purin contents are not employed in the synthesis of cell nucleins. Through some decomposition of the purin ring, a definite proportion of the purin bodies is liberated, oxidised, and excreted as uric acid, and the remainder

eliminated as urea or as bodies intermediate. The results of Sœtbeer and Ibrahim also support the statement that 50 per cent. of the exogenous purin bodies are oxidised to uric acid, and 50 per cent. are further broken down and excreted as urea or intermediate bodies. Since the definite division of purin bodies into "endogenous" and "exogenous," too little time has elapsed for the record of many observations; but from the studies of Reach, Kaufmann, Vogt, and Chalmers Watson, it may be shown that in gout exogenous nuclein is more slowly excreted than in health, and that in some cases there is distinct retention.

In leukaemia the formation of endogenous purin is excessive, and the urine contains very large quantities of uric acid. In this case the endogenous purins are probably diminished by the anaemia and its consequent tissue malnutrition, and augmented by the formation and destruction of enormous numbers of leucocytes. Chalmers Watson has recorded the appearance of a peculiar type of white cell, large in size (15 μ), with a large oval or horseshoe-shaped nucleus, poor in chromatin, the protoplasm vacuolated and imperfectly stained. These cells could be readily differentiated from the ordinary finely granular oxyphile leucocyte, and also from the lymphocyte; in form and general appearance they resemble degenerated myelocytes. During the acute attack these cells were considerably increased in number, and their presence suggested the possibility of their having an important relationship to the alterations in the uric acid and phosphoric acid excretion observed in the same case.

Purin bodies and blood pressure.—Walker Hall's experiments upon the effect of the purin bodies showed that they did not lead to any alterations in the general blood-pressure. As to the form in which uric acid circulates in the tissue-fluids, much conjecture exists; the quadriurate may occur in some parts of the blood-stream, but as the presence of these exogenous purins in the blood-

stream in the form of uric acid and xanthin-bases is not indicated by the usual tests for those substances, it is probable that they exist in the blood in some loose organic combination. A considerable amount of evidence has lately accumulated, which suggests that the purin-bases, mono- and di-oxypurin alike with the tri-oxypurin, uric acid, exist in the blood-stream in combination with a complex organic body ; hence the views as to different forms of circulating inorganic urate combinations may ultimately require revision.

George Oliver has shed very clear light upon some of the processes which take place in the lymphatic and tissue spaces. Amongst other results, he shows that the purin bodies increase the exudation of lymph, and consequently affect the lymph flow. Now, it is beyond question that uric acid and the purin bases are present in excess in the blood and tissue spaces of the gouty individual, so that we may appreciate Oliver's contention that the hypertonic circulatory conditions in the patient affected with gout are associated with persistently increased lymph pressure, the consequent depression of metabolic processes, and the resultant increased arterial pressure with its usual vascular changes.

Purin bodies and absorption.—Walker Hall has shown that the fæces of gouty patients frequently contain increased quantities of fat, and the percentage of unabsorbed nitrogen rises from about 1 per cent. to 2.5 per cent. Further, the researches of His, Von Noorden, and Kaufmann and Mohr show that the powers of absorption diminish as the disease progresses. This increase of nitrogen, however, is not due to food-nitrogen alone, for it may arise from augmented quantities of digestive secretions, from excessive epithelial desquamation, or as a result of intestinal putrefaction. The actual loss of unabsorbed food is of less importance than the evident cellular deficiency which may permit the passage of extrinsic toxins

or imperfectly digested substances into the general tissues. An estimate of the exact extent of intestinal derangement is hence of more value than a determination of the quantity of unabsorbed proteid. The amount of shed epithelium, and perhaps of certain intestinal juices and bacterial products, may be better appraised by investigations into the purins of the fæces, since these in part represent the nuclein-contents of the desquamated cells. Results show that the healthy intestinal epithelium manifests certain selective powers, and that the absorbed food-nucleins depend either upon the individual nuclein-base or upon the constitution of the particular nucleo-proteid.

Vogt compared the results of rich purin-holding food upon a gouty patient and a healthy individual at the same time. The gouty patient showed retention, and delayed excretion of purin bodies. These studies confirm clinical experiences, and there is thus little doubt that the gouty individual does not well metabolise exogenous purins.

The presence of large amounts of purin bodies in the tissue fluids produces no ill effects if the kidney is normal ; for instance, gouty symptoms do not always accompany rich nuclein-intake, nor appear in leukæmic patients. The molecular concentration of the blood is generally normal ; there is neither distinct leucocytosis, altered numbers of red blood corpuscles, nor change in the hæmoglobin coefficient.

Croftan examined the uric acid-destroying quotient of the liver, kidney, muscle, blood, and spleen after the removal of these tissues from the body. The human kidney appeared to destroy more uric acid than the liver, and the muscles more than either the liver or kidney. He ascribes these results to the action of unorganised soluble ferments, and considers that his experiments favour the renal theory of gout.

Conclusions concerning the purin bodies.—The most recent investigations tend to show that uric acid is

in no sense longer to be regarded as a product of the imperfect combustion of proteids into urea, that no mere excess of nitrogenous foods as such is capable of producing it, but it closely depends upon the amount of nucleins, purins, and the alloxur group in the food. Excess of nitrogenous food has been shown by Burian, Schur, Horbaczewski, and Minkowski to result in the increase, not of uric acid and the urates, but of urea ; while by the administration of bodies rich in nucleins and purins, such as roe, sweetbread, thyroid extract, etc., the uric acid output could be increased in a marked degree. Finally, by a careful selection of nitrogenous bodies which were especially poor in nucleins and the alloxur group, the urea could be largely increased while uric acid was actually diminished in amount. About half our normal output is probably due to this source—the exogenous uric acid.

The experiments of Minkowski, in which by ligating the ureters of birds he succeeded in producing an accumulation of urates in the tissues, resembling tophi, gave rise to no other gouty or lithæmic symptom, not even to local reactions round the deposits, and only such toxic symptoms as were due to the retention of all urinary excreta. Woods-Hutchinson in his necropsies at the London Zoological Gardens repeatedly found small masses of urates just under the surface of the pericardium and the peritoneum, and even upon the valves of the heart itself, in birds and reptiles without giving rise to any symptoms of local irritation.

During a gouty attack there is a marked increase of phosphoric acid in the urine. As has been shown by Futcher, the curve of uric acid output runs in a striking parallel with that of phosphoric acid, and as all nucleins are composed of a phosphoric acid element, nucleic acid united with a purin or adenin base, we have here the other moiety of the nuclei of the cells which have been destroyed in the toxic process.

Woods-Hutchinson, in an interesting paper,* comes to the following conclusions: The uric acid produced in health comes exclusively from two sources—the larger moiety, or exogenous uric acid of Chittenden, from the nucleins and purin bases of the food; the smaller, or endogenous moiety, from the destructive metabolism of the nucleins of the body tissues. It is the endogenous moiety alone which is increased in gout and lithæmia.

The uric acid of gout, like the phosphoric acid which invariably accompanies it, is merely a result and measure of the destructive metabolism of the nucleins of the body cells, chiefly probably of the leucocytes, in response to the invasion of poisons or toxins. Parallel examinations of the blood and urine have, however, subsequently shown that leucocytosis does not regularly accompany increased uric acid excretion, and Hutchison and Macleod have recently reported a case of leucopenia in which the alloxuric urinary nitrogen was of an average normal amount. Whilst we may thus regard leucocytic destruction as one source of urinary purin, it probably does not play such an important rôle as was formerly thought.

Attempts have lately been made to prove that the excretion of uric acid and phosphoric acid (two end products of nuclear disintegration) go hand in hand. It is very doubtful if this is the case. Chalmers Watson's observations are strongly opposed to this view. It is true that uric acid and phosphoric acid are two end products of metabolism of the nucleins, but it must be remembered that the uric acid formed in the body is probably capable of further and ready transformation into urea, while there is nothing to indicate that phosphoric acid can undergo any further change in the economy.

The origin of uric acid from the nuclein of the food is one factor, its origin from the nuclein of the leucocytes is another, and, as pointed out by Halliburton, the

* *Lancet*, 1903.

catabolism of the nuclei of other animal cells, such as those of secreting glands, may contribute to the formation of the acid.

Estimation of urinary purins.—It is possible to obtain the purins in the form of a silver-magnesium precipitate, and, by measuring the amount of the precipitate, to ascertain the quantity of purins present. The following is a description of the process devised by Walker Hall. Two solutions are necessary :

<i>No. 1 solution.</i>		<i>No. 2 solution.</i>	
Ludwig's Magnesium*		Silver Nitrate . . .	1 gm.
mixture	100 cc.	Ammonia (strong) . .	100 cc.
Ammonia solution 20%	100 cc.	Talc	5 gms.
Talc	10 gms.	Distilled Water . . .	100 cc.

The only instrument employed is the "purinometer." It consists essentially of three parts:—

1. A closed graduated tube.
2. A stop-cock, with a bore of the same diameter as the upper tube.
3. A small glass reservoir of known cubical capacity.

It is used in the following manner: With the stop at a right angle to the tube, urine is poured in up to 90 cc. The stop-cock is then turned parallel with the tube, and the lower chamber and the bore of the tap become filled with the urine; 20 cc. of solution No. 1 are then added, and the precipitate is allowed to settle. If the reagent contains no talc, the precipitated phosphates take a long time to settle and there is some loss of uric acid. The precipitate of phosphates sinks into the lower chamber of the purinometer, and immediately this has happened the tap is again turned at right angles. To the clear fluid now remaining in the upper tube, solution No. 2 is added to make the total fluid 100 cc. The resultant precipitate consists of a mixture of

* This mixture consists of—

Magnesium Chloride	110 gms.
Ammonium Chloride	110 "
Ammonia	250 "
Water to	1000 cc.

silver chloride and silver-purin. The apparatus is then inclined backwards and forwards until the precipitate is yellowish-white, by which time the silver chloride will have been dissolved out by the excess of ammonia. This can be readily seen by comparison with the white phosphate precipitate in the lower tube. The instrument is now allowed to stand twenty-four hours, when the percentage of purin may be read off at the upper level of the precipitate.

An advantage may be claimed in the case of an excess of chlorides, which solution No. 2 or even a few added drops of strong ammonia will not dissolve. The silver chloride is heavy and falls rapidly (within a minute), whilst the lighter purin precipitates take an hour or so to settle. It is possible, therefore, to allow the silver chloride to fall, turn the stop-cock, let the precipitate pass into the bore of the tap, and immediately return the tap to a right angle. The loss of any purin-silver is by this means exceedingly slight, and the silver chloride excess does not interfere with the estimation. The temperature of the room in which the estimations are made should be between 10° and 15° C.

By use of the centrifuge, the precipitates become constant in a few minutes, and in such case there is no necessity for the addition of talc. Where such apparatus exists, the convenience of the method is increased and the results are more regular. A graduated centrifugalising tube is, however, necessary.

The number of cc. occupied by the silver-purin precipitate is then multiplied by a factor issued with the purinometer, and gives the percentage amount of purin nitrogen, which can be converted, if desired, into terms of uric acid.

CHAPTER II.

THE FORMATION OF URIC ACID.

View that uric acid is formed in the kidneys—Views as to the association of gout and kidney disease—View that the liver and spleen produce uric acid—View that uric acid is produced in various tissues—View that excess of uric acid is the result of an animal diet.

Uric acid and the kidneys.—Until 1847 it was supposed that uric acid was formed in the kidneys themselves, as up to that time none had ever been detected in the blood. In that year Sir Alfred Garrod demonstrated the presence of uric acid in the blood of gouty subjects, which discovery led to the conclusion that uric acid was formed in certain other organs and tissues of the body, and was merely eliminated by the kidneys. The view that then arose was that the uric acid eliminated in the urine originated in the system by the metabolism of the nitrogenised tissues, and was then thrown out by the kidneys. Sir Alfred Garrod * originally held this view, but in later years he came to the conclusion that uric acid is produced by the direct action of the kidneys from urea and other nitrogenised bodies contained in the blood and conveyed to the kidneys. From the experimental evidence that he put forward, Sir Alfred Garrod † concluded that the presence of the salt of uric acid in the blood of gouty subjects, provided it is not introduced *viâ* the alimentary canal, must be accounted for by absorption into the blood from the kidneys after its formation in those organs, the

* Trans. of the Royal Medical and Chirurgical Society, 1848, p. 93.
† Proceedings of the Royal Society, 1893, pp. 482-484.

salt being changed by the blood from ammonium quadriurate, which is the form in which uric acid is mainly present in the kidneys, to sodium quadriurate, which is the form in which uric acid first appears in the blood. He therefore held that uric acid is normally formed in the kidneys, and that when present in the blood it is a result of its having been absorbed after formation in those organs. Kolisch* regards the kidneys as the most important of the uric acid-forming organs. Latham considers that the final formation of uric acid takes place in the kidneys, where it is produced by the conjugation of substances manufactured in the liver, and conveyed in the blood to the kidneys.

The following experimental evidence has been put forward in support of the view that uric acid is formed in the kidneys. Zalesky experimented on serpents, who eliminate all their urinary nitrogen as uric acid. He found that after removal of the kidneys of serpents they lived about as long a time as when the ureters were tied, and that after death no uratic deposits were found in any of the tissues. As he found, after ligaturing the ureters of other serpents, that uratic deposits were to be seen after death in most of the organs and tissues, he concluded that the kidneys were the producers as well as the eliminators of uric acid. The following experiments also seem to be opposed to the view that the kidneys, with regard to uric acid, merely act as filters, which separate the uric acid brought to them in the blood. Sir Alfred Garrod gave from fifteen to thirty grains of potassium urate daily, and similar daily doses of sodium urate, without producing any increase of uric acid in the urine. Wöhler and Frerichs found that the administration of potassium and sodium urates increased the amount of urea, but did not augment the quantity of uric acid in the urine. Neubauer found that the administration of large quantities of uric acid to rabbits, either by the stomach or by injection into the veins, was followed by a

* *Wien. klin. Woch.*, 1895, viii., p. 787.

corresponding increase in the excretion of urea, but no uric acid was discovered in the urine.

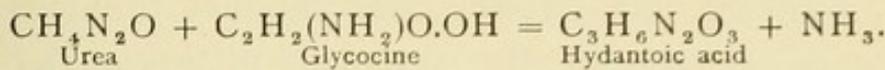
The blood of the renal artery is much richer in urea than the blood of the renal vein; according to Picard, in the proportion of about two to one, according to Sir Alfred Garrod in the proportion of about three to one. From his most recent observations, Sir Alfred Garrod concludes that in birds and other uric acid-excreting animals the metabolism of the nitrogenised tissues is exactly the same as in mammals. He believes that urea is the ultimate product of this metabolism, and that the uric acid is a subsequent product of the union of urea with some other principle or principles, glycocine probably being one of them. He regards the kidney as the organ whose function it is to manufacture uric acid from the nitrogenised matters brought to it in the blood, and considers it possible that the kidney contains different cells—some for the formation of urea, and some for the formation of uric acid—and that the ratio between the two may vary in different classes of animals.

P. W. Latham's explanation of the formation of uric acid in the animal economy is that the amido-bodies, glycocine, taurine, leucine, and tyrosine, are normally converted in the liver into urea; but if from any cause the metabolism of glycocine be interrupted, there would then be present in the liver glycocine and urea, which would produce hydantoic acid, and then hydantoin, and the latter, which is freely soluble, would pass on in the circulation to unite in the kidneys with urea or with biuret to form an ammonium salt of uric acid. Therefore, according to this view, the imperfect metabolism of glycocine is the primary and essential defect in connection with the abnormal formation of uric acid in the human system.

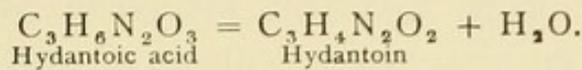
According to Latham,* the synthesis of uric acid from urea and glycocine takes place in the following steps:

* Croonian Lectures, 1886.

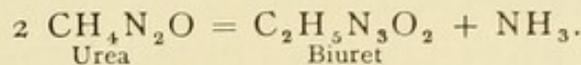
1. The urea and glycocine produce hydantoic acid—



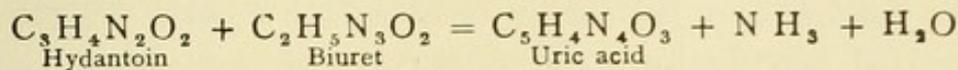
2. The hydantoic acid becomes dehydrated, and forms hydantoin—



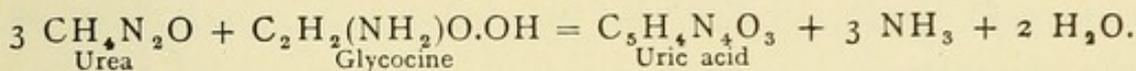
3. From more of the urea biuret is produced—



4. By combination of hydantoin and biuret, uric acid is produced—



The production of uric acid from urea and glycocine may be shown in a single equation as follows:—



Facts supporting the view that uric acid is formed from urea and glycocine.—There are several reasons for believing that uric acid may be formed from urea and glycocine in the living organism. Horbaczewski produced uric acid by the interaction of urea and glycocine, and this result was confirmed by Latham. Glycocine is certainly formed in the human body, and probably is one of the antecedents of urea, for in man, glycocholic acid, a compound of glycocine and cholic acid, passes in the bile into the intestine, and having served its purpose, and its constituents having been set free, the glycocine, together with the other amido-bodies, taurine, leucine, and tyrosine, pass in the portal blood to the liver, and probably in the hepatic cells are converted, or mainly converted, into urea.

That glycocine is concerned in the production of uric acid is somewhat probable from the fact that in the carnivora, whose urine contains little or no uric acid, the bile contains no glycocholic but only taurocholic acid, and

therefore yields no glycocine. The experiments of Hahn, Massen, Nencki, and Pawlow also support the view that glycocine is concerned in the formation of uric acid. They shut the livers of dogs almost completely off from the general circulation by diverting the portal circulation into the inferior vena cava, and so caused an increased amount of glycocine to be sent to the kidneys by preventing its conversion into urea in the liver. They found that, although the dogs passed less urea (the nitrogen being mainly eliminated as ammonium carbamate), the uric acid voided was considerably increased. Latham * believes that if an excessive amount of nitrogenous material is introduced into the portal circulation, the portion which is least readily acted upon is the glycocine, the presence of which promotes the formation of uric acid. He considers that the primary defect in gout consists in the imperfect metabolism of glycocine.

Uric acid formation and liver disease.—If uric acid be formed in the kidneys from urea and glycocine brought from the liver, it can be readily understood that alterations in the metabolism of the liver must necessarily affect the formation and excretion of uric acid. This would explain why liver trouble of some kind or another is so commonly associated with gouty dyspepsia, and also renders intelligible the fact that several observers have been unable to dissociate the connection between liver troubles and gout, and have therefore attributed the formation of uric acid to the liver. For instance, Murchison considered that gout is an hereditary disease by virtue of the transmission by parents to their offspring of a defective power of the liver, in consequence of which its functions are deranged with unusual facility; as a result of this derangement of the liver the metabolism of the albumen is to a great extent arrested at the stage of uric acid formation, instead of going on to the final stage of urea formation. George

* *Loc. cit.*

Harley considered that a strong relationship existed between gout and hepatic derangements. Sir Dyce Duckworth is of opinion that "the liver is the organ in which in health uric acid is chiefly formed, and it is probably to derangement of function in this gland that we must look for over-production of this substance." All these views are rendered equally, if not more, intelligible by regarding the liver as the seat of production of the antecedents of uric acid (urea and glycocine), the final conjugation of those bodies taking place elsewhere.

Association of kidney affections with gout.— An interesting point to consider is whether gout ever occurs without preceding kidney mischief of some kind or other. That is, whether, if the kidneys remain sound, it is possible for such an accumulation of uric acid to occur in the system as to produce an attack of gout. We will first ascertain whether there is any evidence that an affection of the kidneys (functional or organic) is associated with or precedes gout. To begin with, it is time that the old idea should be abandoned that the healthy kidneys can only eliminate a certain amount of uric acid. That the healthy kidneys are capable of separating from the blood and excreting large quantities of uric acid is shown by the observations of Laache, Bartels, Stadthagen, and Bohland and Scherz, on the excretion of uric acid in cases of leukæmia. In this disease the blood is laden with uric acid, and all these observers found a greatly increased daily excretion of uric acid, varying from twice to over six times the normal amount. This large excretion of uric acid by the kidneys shows that urates do not themselves cause damage to kidney tissues.

Sir Alfred Garrod, Sir William Roberts, and Levison all attribute the accumulation of uric acid in the blood of gouty persons to deficient excretion rather than to increased production. Sir Alfred Garrod holds the view that among the causes exciting a gouty fit is a functional

failure of eliminating power for uric acid on the part of the kidneys. He also considers that this early functional failure is followed in cases of chronic gout by structural kidney disease. His view is that the uric acid present in the blood of gout is formed in the kidneys, and is absorbed from them into the blood. This view is quite compatible with the theory that a defective capacity of the kidneys for the excretion of uric acid is the primary pathological cause of gout. Levison * states that gout is not accompanied by leucocytosis, and therefore the nuclein of leucocytes is not available for the production of uric acid. He considers that gout cannot be developed unless a primary renal lesion is present, and that this is almost invariably of the nature of an interstitial change. Vogel † estimated, in three cases of chronic gout, the intake of nitrogen by analysis of the food and the output of nitrogen in the urine and fæces. He found that there was a nitrogen retention greatly in excess of what could be attributed to a retention of uric acid. Vogel states that his patients behaved, in this respect, like sufferers from renal disease, although the clinical signs of granular kidney mischief were wanting in all the cases. In connection with this, it must be borne in mind that the absence of the clinical signs of disease of the kidneys does not necessarily imply integrity of those organs.

Association of renal disease with the presence of uric acid in the blood, and with uratic deposits in the joints.—Von Jaksch found considerable quantities of uric acid in the blood of all the cases of diseases of the kidneys that he examined, and his results were confirmed by Klemperer. It is well known that uratic incrustation of articular cartilages is not uncommonly found at the post-mortem examinations of subjects who have never been known to suffer from ostensible gout during life.

* "The Uric Acid Diathesis," 1894.

† *Zeitschrift f. klin. Medicin*, xxiv., p. 512.

Ord and Greenfield* examined a number of bodies in the post-mortem room for the existence of uratic deposits in the joints, and the presence of kidney disease. Among 96 cases presenting lesions of the kidneys, uratic deposits were found in the joints of 18. Norman Moore,† who bases his observations on the results of a large number of post-mortem examinations, states that chronic interstitial nephritis is found in a large proportion of those bodies in which sodium urate is to be seen in the joints. He found that chronic interstitial nephritis is not invariably accompanied by the presence of sodium urate in the articular cartilages, though it is usually accompanied by traces of degeneration in some of the articular cartilages. He examined the following number of cases, all of which, as far as could be ascertained, had never suffered from ostensible gout :—

Kidney disease.	No. of cases.	Uratic deposit in joint or joints.
Chronic interstitial nephritis . . .	53	25
Chronic parenchymatous nephritis	11	2

Levison ‡ is a strong supporter of the view that there is always some degree of antecedent renal disease connected with gout. In reply to criticisms of this view he points out that the post-mortem examinations of gouty patients have generally shown renal lesions, and that the few exceptional cases are open to criticism. He states that all the post-mortem examinations of patients dying of granular kidney disease at the Communal Hospital, Copenhagen, during a period of fourteen months, showed uratic deposits in one or other of the joints, although most

* Trans. of the International Medical Congress at London, 1881, vol. ii., p. 107.

† St. Bartholomew's Hosp. Reports, 1887, vol. xxiii.

‡ *Zeitschrift f. Klin. Medicin*, 1894, xxvi., p. 293.

of the patients were not known to have had any definite gouty attack.

I thought that it would be a matter of interest to ascertain the proportion of cases of uratic deposition in the joints occurring in subjects in whom granular disease of the kidneys was found at the post-mortem examination, and in connection with whom the previous history as to the occurrence or not of gout was known. For this purpose I obtained the help of some of the pathologists at the London hospitals, who kindly examined the joints in such cases whenever they were able to do so. I have collected altogether the results of 77 such examinations, for which I am indebted to the kindness of Cyril Ogle, F. J. Smith, Hebb, and Jackson Clarke. These 77 cases were all cases of granular kidney disease, and in 41 cases uratic deposits were found in one or more of the joints. The distribution of uratic deposits among the gouty and non-gouty cases is shown in the following table:—

TABLE II.

Showing the results of the examinations of the joints of 77 cases of granular kidney disease.

	No. of cases.	Uratic deposit in joint or joints.
Known to have had gout . . .	10	10
Never known to have had gout .	67	31
Totals	77	41

In the 10 cases known to have had gout, uratic deposits were found in one or more of the joints of all, and the kidney condition was in every case described as “markedly granular” or “fairly granular.”

Among the 67 cases of granular kidney disease not known to have suffered from previous gouty attacks,

uratic deposits were found in one or more of the joints of 31—that is, in 46 per cent. of the cases, which closely agrees with the 47 per cent. found under similar conditions by Norman Moore. In these 67 cases are included all cases which showed the existence of any granular kidney disease, but several of the cases in which no uratic deposits were found were described as only “slightly granular” or “faintly granular.”

If from the 67 cases a selection is made of those described as “markedly granular” or as “typical granular kidneys,” then the proportion of cases in which uratic deposits were found in the joints appears as follows:—

	No. of cases.	Uratie deposit in joint or joints.
Marked granular kidney disease .	26	20

Thus it is seen that among the cases of marked granular disease of the kidneys occurring in persons who were never known to have suffered from ostensible gout during life, uratic deposits were found in the joints of 77 per cent. These results, taken in conjunction with those of Norman Moore and of Levison, show that kidney disease exercises a powerful influence in causing an accumulation of uric acid in the blood, and consequently in producing uratic deposits in the joints.

Gouty affections of the kidneys not always revealed clinically.—It has been urged that if kidney disease, with the consequent diminished excretion of uric acid, be the primary factor in the causation of gout, signs of kidney mischief would always manifest themselves prior to an attack of gout, and that very few such cases have ever been recorded. But, in the first place, it must be remembered that such signs are not usually looked for, and, in the second place, they need not necessarily

reveal themselves clinically. It is well known that contracted granular kidney is not always evidenced either by the occurrence of albuminuria or of dropsy. The contention that if organic renal failure existed the urea excretion would probably be equally affected with that of uric acid does not hold good, if the view is adopted that uric acid is produced in the kidneys, while urea is only eliminated by them. It is well known that in gouty subjects the kidneys have been found at the post-mortem examination in a diseased condition, when there have been no external manifestations during life of the existence of such renal mischief. That uratic deposits are frequently found in the kidneys of gouty subjects is a matter of common experience, but in the absence of such deposits the kidneys may still be affected. Sir Dyce Duckworth believes that changes occur in the kidneys of gouty subjects quite independently of uratic deposits in these organs. It has been urged that the renal theory is difficult to harmonise with the hereditary character of gout. It is quite possible, however, that there may be in gouty subjects an hereditary tendency to the renal affection, since both Dickinson and Eichorst have shown that there is an hereditary tendency to granular kidney.

Kidney disease and gout alike caused by certain toxic agents.—Certain toxic agents which predispose to or which excite kidney disease are also known to produce gout. Lead gives rise to both chronic kidney disease and gout. In chronic lead-poisoning proliferation of the epithelium of the urinary tubules first occurs, followed by granular atrophy and excessive formation of interstitial tissue. In numerous cases of chronic lead-poisoning gout has developed. Very similar changes occur in the gouty kidney, and to the advocates of the renal theory it seems reasonable to assume that the changes in that organ in both chronic lead-poisoning and in gout so affect the excreting apparatus of the kidneys as seriously to

diminish their power of eliminating uric acid. That lead-poisoning gives rise to the accumulation of uric acid in the blood has been shown by Sir Alfred Garrod. Gout subsequently developed in two cases of plumbism in which the blood was found by him to be rich in uric acid. He also determined the excretion of uric acid in the urine of two patients to whom acetate of lead had been medicinally administered. In both patients a well-marked diminution of uric acid in the urine occurred. It was also noticed that after the lead had been given for a day or two, the excretion of the uric acid in the urine was suddenly diminished to a very small amount—a condition which usually lasted for a day or two. This points to the fact that lead exercises a marked inhibitory effect on the cells of the kidneys concerned in the excretion of uric acid. The action of the lead is not due to inhibition of the formation of uric acid, since in cases of plumbism the blood becomes charged with uric acid. Alcohol is another body which in excessive quantities gives rise to kidney mischief, and which may also give rise to gout.

View that the liver and spleen produce uric acid.

—The view that the liver was the seat of production of uric acid probably originated in the knowledge that the excretion of uric acid in the urine is most abundant during digestion, when the liver is most active. This view is, however, equally compatible with the idea that the liver merely produces the antecedents of uric acid. The investigations of Schröder and Minkowski apparently were strongly in favour of the view that uric acid was formed in the liver. Schröder* states that the liver of birds contains a high percentage of uric acid, and that after removal of the kidneys uric acid continues to be formed, and accumulates in the liver and blood. The last-mentioned statement is utterly opposed to the results of Zalesky's experiments on the extirpation of the kidneys of serpents.

* "Ludwig's Festschrift," 1887, p. 89.

Minkowski * succeeded in keeping geese alive from six to twenty hours after extirpation of the liver; after the operation, their urinary excrement contained only 2 to 3 per cent. of uric acid, instead of the normal 60 or 70 per cent. This diminished excretion of uric acid after extirpation of the liver is, however, no proof that the liver is the seat of formation of uric acid. The results are equally compatible with the view that the liver is the seat of production of the antecedents of uric acid only.

Murchison regarded the liver as the seat of production of uric acid, and considered that the presence of the latter in the blood or tissues was due to functional derangement of the liver, in consequence of which the metabolism of some of the albumen became arrested at the stage of uric acid formation, instead of going on to the complete stage of urea formation. Charcot regarded the liver as the principal seat of production of uric acid. He considered that a functional derangement of the liver caused the production of excessive quantities of uric acid, and its consequent accumulation in the blood. Meissner regards the liver of fowls in the normal condition as the principal source of uric acid, but considers that the spleen and the nervous tissues share in the formation. Ranke was of opinion that his experiments led to the conclusion that the spleen was the principal organ concerned in the production of uric acid. It has, however, never been possible to show that the spleen takes any active part in developing gout. On the contrary, the large amount of uric acid found in the blood of cases of leukæmia and severe anæmia shows that an exaggerated production of uric acid does not by itself exert any influence on the origin of gout.

There is a good deal of experimental evidence to show that uric acid is synthetically formed in the liver of birds, but it is doubtful whether the mammalian liver possesses

* *Arch. Exp. Path. u. Pharmak.*, xxi.

a similar power. Indeed, the experiments of Sir Lauder Brunton on the liver of the cat tend to show that uric acid can be destroyed in the liver, and is converted, in part at least, into urea. Rose Bradford * contends that in the case of birds, notwithstanding the presence of urea in the blood, the evidence would seem to be conclusive that the uric acid is really formed by the liver. Removal of the liver in birds is followed by the diminution, or even the disappearance, of uric acid from the urine, and, on the other hand, the ligation of the ureters and—what is, perhaps, more conclusive—destruction of the kidney cells by the injection of bichromate of potash is followed by the accumulation of uric acid in the blood, and even by its deposition in the form of urates in various organs and cavities of the body, as, for instance, the liver on the one hand and the pericardium on the other.

The disappearance of uric acid from the urine after extirpation of the liver might, of course, be due to the urea no longer being formed in the liver, and is not conclusive evidence of the formation of uric acid in that organ; but Rose Bradford thinks that Ebstein's results showing the accumulation of uric acid and its deposition after destruction of the renal cells with bichromate of potash would seem to negative the idea that this substance is formed in the kidney. In his opinion, it would not seem to be probable that a function which is discharged by the liver in one set of vertebrates, such as birds, would be discharged by another organ, as the kidney, in another set of vertebrates, such as mammals, and therefore it is improbable that the kidney is the seat of the formation of uric acid in mammals and in man.

Rose Bradford, therefore, concludes that there is really but little, if any, evidence in favour of the view of the kidney having a special secretory activity, although perhaps it would be unwise to deny the possibility of it.

* *Lancet*, July 16, 1904.

Views that uric acid is produced in various tissues.—Ebstein, who attributes in cases of gout the main production of uric acid to the muscles and bone-marrow of the affected extremities, admits, however, that the kidneys may take a part, not only in the secretion, but also in the manufacture of uric acid. Robins was the first to formulate the view that uric acid is formed in connective tissues generally, and that the pathological condition is merely an exaggeration of the physiological one. This view therefore regards normal fibrous tissues as the seat of production of uric acid, and considers that in gout this production is increased. Chrzonszczewsky also concludes that uric acid arises in connective tissue, and that it is conducted thence through the lymphatic vessels. Cantani considers that the connective tissues take an active part in the formation of uric acid, and that in cases of gout it is especially produced in the cartilages and peri-articular tissues (ligaments, tendons, etc.). Senator also inclines to the opinion that at least part of the uric acid is formed in cartilaginous tissue. Most writers and observers on the subject, however, consider that it is only certain that uric acid deposits in substances of the connective-tissue class, and that there is no proof that uric acid is formed in connective tissue.

Views that excess of uric acid is the result of an animal diet.—Another commonly received notion is that gout is accompanied by an excessive formation of uric acid, which is usually attributed to the ingestion of a too highly nitrogenised diet, and especially to an animal one. Virchow, however, considers that a too highly nitrogenised diet is not necessarily the cause of gout, because he has often observed gout in poorly-fed convicts. Gout is certainly not incompatible with a vegetable diet, as, amongst certain birds kept in captivity and living exclusively on grain, uratic deposits have been observed around the joints. On the other hand, animal

food does not necessarily produce uric acid in a healthy system, as is shown by its absence from the urine of some of the carnivora. It has for a long time been held that the ingestion of very large quantities of proteid matter is followed by an increased production of uric acid, and *vice versa*, but in 1899 Taylor showed that the amount of ingested proteid has absolutely no constant relation to the quantity of uric acid excreted, and Jerome concluded from the results of a long experiment that there is at present no proof that uric acid can arise in man independently of a substance containing an alloxur or purin group.

That the production of uric acid is not dependent, at all events to any great extent, on diet is also shown by the fact that the same diet which in one class of animals will produce uric acid will in another class produce urea. Thus, in the urine of the carnivorous lion and tiger there is a quantity of urea and but very little uric acid; on the other hand, the carnivorous python and boa excrete uric acid and no urea. Graminivorous birds excrete uric acid and no urea, whilst herbivorous mammals excrete quantities of urea and but little or no uric acid.

Haig claims that, in addition to the formation of uric acid in the animal economy, the gradual introduction of small quantities of uric acid in the food leads to its gradual accumulation, and that consequently very large amounts may be stored in the body without any excessive formation having taken place. Haig, however, does not produce any proof that uric acid is stored up in the system apart from gout. The contrary is proved by the fact that in diseases such as leukæmia, severe anæmia, etc., although large quantities of uric acid are formed, yet they are readily eliminated without the occurrence of storage in the system.

Haig, who in my opinion wrongly ascribes to uric acid an almost universal rôle in the causation of disease,

claims that the uric acid excreted in the urine comes from two sources:—(1) The uric acid which is formed in the body out of nitrogenous food; (2) the uric acid introduced into the body ready-formed in certain articles of diet, such as meat, meat extracts, soup, tea, coffee, etc. He considers that flesh diet increases both the introduction and the formation of uric acid, a view which is opposed to the previously quoted experimental results obtained by Bleibtreu and by Hirschfeld. Haig * gives the quantities of uric acid which a man may introduce into his system with an ordinary dinner as follows:—

	<i>grain.</i>
8 oz. soup . . . containing 0.02 per cent. uric acid	= 0.70
2 oz. fish . . . „ 0.03 „ „	= 0.26
3 oz. meat . . . „ 0.04 „ „	= 0.52
$\frac{1}{2}$ drachm meat extract „ 0.80 „ „	= 0.24
	1.72

As far as I can ascertain from Haig's writings, he has never identified by the murexide test this uric acid reported to be present in these various articles of diet. These estimations depend solely on the application of Haycraft's process to the articles of diet, and the subsequent calculation of the silver precipitate so obtained in terms of uric acid. Recently Haig has shown a tendency to shift the responsibility from uric acid to xanthin, and therefore refers to the amounts of uric acid or xanthin which he states are present in various foods. This assumption, that the substance stated to be present in foods, if not uric acid, is xanthin, is however untenable, since xanthin is not estimated by Haycraft's process.

* *Brit. Med. Journ.*, 1894.

CHAPTER III.

PRIMARY CAUSATION OF GOUT.

The uric acid compound regarded as acting passively and physically—The uric acid compound regarded as acting as a poison or irritant—Uric acid not a poison—Necrotic changes as the primary cause—Inflammatory or degenerative changes as the primary cause—Nervous disturbance as the primary cause—Excess of carbonaceous material as the primary cause—A bacterial toxin as the primary cause—The liver as a toxin destroyer.

THE various views held as to the primary cause of gout may be classified into the following groups:—

1. The uric acid compound regarded as acting passively and physically while in the crystalline state.
2. The uric acid compound regarded as acting as a poison or irritant while in the dissolved state.
3. Necrotic changes in the affected tissues regarded as the primary cause.
4. Inflammatory or degenerative changes in the affected tissues regarded as the primary cause.
5. Nervous disturbance regarded as the primary cause.
6. Excess of carbonaceous material in the blood regarded as the primary cause.
7. A bacterial toxin regarded as the primary cause.

These various views will now be considered and discussed.

1. The uric acid compound regarded as acting passively and physically while in the crystalline state.

—Sir Alfred Garrod and Sir William Roberts have been the two principal exponents of this view, which regards gout—in so far as its phenomena depend on uric acid—

as a disease the manifestations of which are approximately due to mechanical injury. Sir Alfred Garrod holds that every paroxysm of gout is attended by a crystalline deposit of sodium biurate, and that this deposit exercises chiefly a mechanical effect. He explains, in connection with articular gout, that when the blood, for some reason or other, is incapable of holding the uric acid compound in solution, it is deposited in an articular cartilage which is specially predisposed for its reception. Such predisposition is generally caused by its being the seat of former injury or disease. The crystallisation of the biurate within the interstices of the cartilage then provokes the inflammatory changes, so that the deposition is the cause of the inflammation. Sir William Roberts was of opinion that uric acid probably does not possess any inherent poisonous quality, and that as long as it remains in solution it produces no harmful results. The mischief that it is capable of producing only results from its precipitation or crystallisation as sodium biurate in the tissues or fluids of the body. He considered that the inflammation, pain, swelling, and the remoter secondary degenerative changes of regular gout are quite explicable by regarding the crystalline biurate, which is precipitated in the cartilaginous and fibrous structures of the joints, as exerting a mechanical action as a foreign body. Cornil and Ranvier also favour the idea that the crystalline uratic deposit in cartilages produces inflammatory changes by its mechanical irritation.

Sir William Roberts even held that the manifestations of irregular gout may be due, like the arthritic manifestations, to uratic deposition—that is, to actual precipitation of crystals of sodium biurate into the connective and fibrous structures of the implicated organs, whether the liver, heart, lungs, or brain, or into the fibrous sheaths of the nerves controlling the functions of the affected viscera. He was further of opinion that the presence in the blood

of scattered needles of sodium biurate might constitute foci around which clotting might take place, and that the thromboses not unfrequently observed in gouty cases might thus be accounted for. The various localities in the body, apart from the joints, in which uratic deposits have been found, will be referred to later, but as regards the possible deposition of sodium biurate in nervous structures constituting the exciting cause of some of the pains and affections of different viscera peculiar to irregular gout, it may be of interest to mention here the following facts:—Crystals of sodium biurate have been found by Watson, Gairdner, and Dafour on the cerebral meninges; by Schroeder van der Kolk in the neurilemma of peripheral nerves; and by Cornil in the cerebro-spinal fluid.

With regard to the manifestations of irregular gout being due to uratic deposits in the affected viscera, it is true that observations on the subject are very limited in number. But, in the first place, it should be remembered that such irregular uratic deposits are extremely likely to escape observation in the post-mortem room, unless very carefully looked for with the aid of the microscope; and, in the second place, it is highly probable that such deposits would become dissolved during life as the attack of irregular gout passes off.

The question might be raised that if the crystalline biurate always acts as an irritant, why should not the semi-solid urinary excrement of birds and serpents set up kidney mischief by acting as an irritant to the kidneys during its excretion? The reason is that the urinary excrement of birds and serpents is composed of an amorphous quadriurate, and that in the amorphous condition it is incapable of acting as an irritant. Moreover, it is possible, as Sir William Roberts has suggested, that the uratic excrement passes through the tubules of the kidneys of birds and reptiles in the gelatinous form, which could

not produce the mechanical irritation that a crystalline deposit would be liable to cause.

To the view that a sudden deposition of crystals of sodium biurate in the tissues surrounding the joint causes the severe pain and inflammatory symptoms of acute gout, it has been objected that if sodium biurate were an irritant and the inflammation were produced by its deposition in the tissues, then that inflammation would not subside as long as the irritant remained. If an irritant foreign body remains in an organ, it is impossible that the inflammation caused by that irritant should subside while the irritant actually increases, for after each attack, and in the intervals between the attacks, the deposits of sodium biurate enlarge. Therefore the fact that the inflammation of the joint or tissue in which sodium biurate is deposited subsides while the deposition remains and increases serves to negative the theory that such deposition is the cause of the inflammation. It is much more probable that inflammation precedes deposition of biurate, and that the deposition of sodium biurate, which takes place in the tissues of and around a joint after an attack of gout, is subsequent to the attack. During an attack the joint is distended with synovial fluid rich in sodium quadriurate or biurate; the spaces in the periarticular areolar tissue are also distended with blood-serum containing one or both of the uric acid salts. As the attack subsides and the local temperature falls, crystallisation of sodium biurate occurs in the effused fluid, brought about in part by the fall of temperature, in part by the conversion of the more soluble quadriurate into the less soluble biurate, and in part by the absorption of the more watery part of the effused fluid.

2. The uric acid compound regarded as acting as a poison or irritant while in the dissolved state.—This view, while holding that the uric acid compound is the primary cause of gout, regards it as producing morbid

changes in the structure of tissues while remaining in the dissolved state. Many writers and observers have supported the view that, apart from the local trouble in the joints caused by the deposited sodium biurate acting as an irritant, the soluble uric acid compound which is circulating in the fluids of the body acts as a poison, the toxic effects of which are responsible for a number of the symptoms associated with the gouty state. Pfeiffer holds the somewhat peculiar view that a compound of uric acid is deposited in both healthy and diseased portions of the body—apparently without producing any marked symptoms—and that an acute attack of gout is caused by the blood re-dissolving this deposited uric acid compound, owing to a temporary increase in the alkalinity of the blood, and that dissolved in the blood in this concentrated form the uric acid compound acts as a chemical poison. That this view is untenable is evident when it is remembered that uric acid is deposited as the sodium biurate, and, as will be shown later, the solubility of this body in a fluid medium is not heightened by an increased alkalinity of that medium.

Uric acid not a poison.—Sir William Roberts* argues that the acceptance of the theory that uric acid possesses a toxic action is difficult for the following two reasons:—(1) That there is no direct experimental proof that uric acid is a toxic agent; and (2) that although the fluids of the body of a gouty man, on the eve of an outbreak of acute gout, are impregnated with sodium biurate to saturation, yet such a person does not show any signs of poisoning, but enjoys complete immunity from toxic symptoms until the sudden advent of the arthritic attack. Another fact which is strongly opposed to the view that uric acid is a toxic agent is that in cases of leukæmia and severe anæmia the blood is frequently highly charged with uric acid in the form of sodium quadriurate without the pro-

* Croonian Lectures: "Uric Acid Gravel and Gout," 1892.

duction of any toxic symptoms that could be referred to the uric acid compound.

When Sir Alfred Garrod discovered that uric acid was present in the blood of patients during an attack of gout it was naturally supposed that the symptoms of gout were due to the presence of this body in the blood and tissues. If uric acid is the cause of gout, it must be shown that uric acid will produce toxic effects or produce some of the symptoms of gout. This, however, has never been done.

In support of the belief that uric acid is practically devoid of toxic properties, the following facts may be put forward :—(1) Animals have been made to ingest large quantities of uric acid with their food, and urates in solution have been freely injected into their veins, without eliciting any signs of poisoning ; (2) experiments on frogs' muscles have shown that muscle rigidity and tetanus are produced by hypoxanthin, but that uric acid is inert ; (3) after carefully searching the literature on the subject, the only evidence I can find of discomfort following the ingestion of uric acid is the statement of Walker Hall, who, after taking large doses of uric acid, had malaise and headache lasting for several hours : almost any substance, however (common salt, for example), will produce toxic effects if taken in very excessive quantities ; (4) in leukæmia the blood contains, for a long time, a large quantity of uric acid, more than double the amount present in most cases of gout, yet there are no symptoms whatever in common between the two diseases, and no symptoms that could be referred to uric acid are ever present in this disease—this in itself shows that uric acid can have no toxic effect ; (5) Ransom, of New York, has demonstrated the non-toxic properties of uric acid by the following experiments. In two cases of chronic nephritis three grammes of uric acid were given by the mouth in twenty-four hours for three days in succession. A decided increase was found in the urine during the time, but there was no sys-

temic disturbance. In one case of chronic nephritis, three grammes were given in twenty-four hours for three days in succession, and on the fourth day six grammes were given, without producing any systemic disturbance. In four cases of chronic gout, a diet of shad roe was given for five days, which caused a decided increase in the excretion of uric acid in the urine, but no disturbance of the health. In two rabbits, two successive intravenous injections of one gramme each of uric acid were made without systemic disturbance, though a large part of the acid was recovered from the urine. In two dogs, two successive intravenous injections of two grammes each of uric acid were not followed by any disturbance, while the urine showed a large increase.

Not only in the medical world has an unmerited importance been attached to uric acid as a factor in the causation of disease, but unfortunately, among a considerable section of the public there has arisen a fetichism of uric acid, which has been pandered to and fostered by the proprietors of the various quack remedies that are so persistently advertised as being capable of dissolving or removing uric acid from the system. The time has come clearly to recognise that uric acid possesses no toxic properties worth speaking of. The joint manifestations of gout are dependent upon much more general and much larger conditions than a mere excess of uric acid in the blood. The deposition of sodium biurate is merely the sign of the disease, not the essence of it. In fact, the rôle of uric acid in gout may well be compared with that of sugar in diabetes. Ringrose Gore has well pointed out that uric acid can be no exception to the general law that a substance acts as a poison in direct proportion to the amount of it present in the circulating fluids.

Alloxur bases regarded as the poison of gout.—Kolisch * considers that some antecedents or allies of

* *Wien. klin. Woch.*, 1895.

uric acid are responsible for the toxic effect which he believes constitutes the primary cause of gout. His view is that the graver manifestations of gout only make their appearance when the functions of the kidneys become impaired from any cause, and since he finds that in the urine of the gouty there is an increase of alloxuric substances, and also that alloxur bases cause changes in the kidneys resembling parenchymatous degeneration, he infers that these bases are concerned in the production of the kidney affection which precedes the development of gout. His theory is that during normal action of the kidneys the greater part of the alloxur bases is excreted as uric acid; but when the structures which form uric acid are enfeebled there is an increased excretion of alloxur bases, with concomitant toxic effects. Kolisch's views have received some confirmation by Weintrand,* who has also found an excessive excretion of alloxuric substances in the urine of gouty patients. On the other hand, they are controverted by the observations of Schmoll,† His,‡ Laquer,§ and Mafatti,|| who failed to find any increased excretion of alloxuric substances in the urines of gouty patients.

3. Necrotic changes in the affected tissues regarded as the primary cause of gout, the necrosis being due to the presence of dissolved urates.—Ebstein,¶ who has devoted a considerable amount of time to the experimental study of the causation of gout, is the great exponent of this view. His theory is that a destructive or, as he terms it, a necrotising process is produced in the cartilages or other implicated tissues by uric acid in one form of combination, and that, following this, the uric acid in another form of combination is deposited in the necrosed areas. In other words, that a destructive process always precedes

* *Charité Annalen*, 1895, xx.

† *Zeitschrift f. klin. Medicin*, 1896, xxix.

‡ *Berlin. klin. Woch.*, 1896, xxxiii.

§ *Verhandlungen des Cong. f. innere Med.*, 1896, xiv.

|| *Wien. klin. Woch.*, 1896, ix.

¶ "Die Natur und Behandlung der Gicht," 1882.

the process of deposition, both processes being due to uric acid, but in different states of combination. Ebstein maintains that uratic crystals only form in necrotic tissues, never in healthy tissues. He regards the necrosis of tissue and the subsequent uratic deposits as together constituting the characteristic *ensemble* of the gouty process. His theory assumes that the irritant is the neutral sodium urate in the dissolved state, and that the first step in the gouty process consists in a stasis of the lymph stream, followed by the infiltration of the tissue in circumscribed areas by the lymph containing the dissolved neutral urate. The neutral urate, according to his view, acts as a chemical irritant, and sets up a necrotising process in the implicated tissues, and finally produces complete necrosis of the tissues in the affected areas. The necrotising and necrotic portions of the tissues provoke irritation of the surrounding parts, and so produce the inflammatory phenomena of gout. Ebstein assumes that the process of necrosis generates a free acid, which converts the neutral urate present in the fluids of the body into the acid urate, which substance is then deposited in the crystalline form in the fully necrosed areas. No mention is made of the nature or name of this hypothetical acid.

Ebstein's experiments.—To support this theory Ebstein relies upon two different classes of experiments conducted by him. One class consists of his examination of the organs and tissues of birds that he considered he had rendered gouty, by preventing the elimination of their urinary secretion. The other class of experiment consists of observations on the irritant effect of a solution of a sodium urate on the delicate corneal tissue of the eye. As I venture to differ from the deductions that Ebstein has drawn from his experiments and observations, I propose to describe his methods of experimentation, and briefly to criticise his deductions therefrom.

Ebstein's experiments on birds.—Ebstein's first series

of experiments consisted in an endeavour to induce in cocks a condition which, from the anatomical point of view, he considered was analogous to the gouty state in man. This he effected by preventing the elimination of their urinary uratic secretion in two ways—(a) by ligaturing the two ureters, and so damming back upon the circulation the urates which would otherwise have passed away ; and (b) by administering to the cocks small and repeated subcutaneous injections of the neutral potassium chromate, which Ebstein considers inhibits the passage of uric acid through the kidneys by its action on the renal parenchyma, and so causes a damming back upon the circulation of a portion of the urates, which normally are excreted in their entirety by the kidneys. In the bodies of the birds experimented on uratic deposits were found in the articulations, in the tendon-sheaths, in the liver, and in the muscular tissues. Ebstein found that the deposition of urates was much more copious and more widely spread in the cocks experimented on by injection of potassium chromate than in those whose ureters were ligatured. This difference he referred to the fact that he could keep the birds alive for a long time while subjecting them to the action of potassium chromate, whereas after ligaturing both ureters they, as a rule, only lived for about twenty-four hours. As the result of these experiments Ebstein came to the following conclusions :—(1) That necrosing and necrotic processes are developed in various organs as the result of some irritant ; (2) that uratic deposits form in the necrotic areas which in appearance resemble the gouty deposits of man ; (3) that a reactive inflammation, with infiltration of small cells, is set up in the neighbourhood of these necrotic areas.

Criticism of Ebstein's experiments on birds.—This class of experiments consisted of observations of the uratic deposits formed in fowls when the elimination of their uric acid is prevented either by ligaturing the ureters, or by the progressive disablement of the kidneys

by repeated subcutaneous injections of potassium chromate. I do not think that the morbid processes occurring under these conditions in fowls can be considered as, in any sense, comparable with those occurring in connection with gout in man. Ebstein found uratic deposits in the liver and muscular tissues of the birds experimented on, localities where they are not found, at all events to any appreciable extent, in human gout. From this one may fairly conclude that the two processes cannot be considered as comparable. Moreover, since the fowl produces and eliminates by the kidneys so large a quantity of urates, the more or less sudden stoppage of kidney excretion must necessarily result in the damming back of it and the rapid accumulation of it in the blood and tissues, where, as Sir William Roberts suggests,* it would probably first collect in a state of solution as the quadriurate, which would then be precipitated in the tissues as the gelatinous biurate, and this in its turn would be changed into the crystalline biurate.

Ebstein's experiments with urates.—It is on the second class of experiments that Ebstein depends for proof of his assumption that the neutral sodium urate is capable of acting as a chemical irritant to the tissues, and of producing in them the necrotising changes which subsequently lead to complete necrosis of the affected areas of the implicated tissues. In order to show that a combination of uric acid with sodium acted as an irritant, Ebstein took a saturated solution, prepared at 100° F., of uric acid in a 5 per cent. solution of sodium phosphate, and injected it into the peritoneal cavity, into the kidney, into the anterior chamber of the eye, into the cartilage of the ear, and into the cornea of a rabbit. Powdered uric acid was also introduced by insufflation into the conjunctival fold of one eye. Very appreciable changes were produced in the cornea only, and it was in this structure that Ebstein studied what he considers were the irritant or toxic effects of uric acid.

* Croonian Lectures: "Uric Acid Gravel and Gout," 1892.

He found that these injections produced a modified form of inflammation in the tissues of the cornea. As a control experiment he injected into the cornea of the other eye a simple solution of sodium phosphate, or water containing calcined magnesia in suspension, neither of which produced any inflammatory changes. He therefore inferred that the inflammatory changes were set up in the cornea by the urate in solution acting as a chemical irritant.

Criticism of Ebstein's experiments with urates.—The objection to this method of experimentation is that, in the first place, the solution of uric acid in sodium phosphate does not contain the neutral sodium urate, which is the body on which Ebstein relies for the production of the initial irritant effects leading on to the necrotising process. The solution would contain the sodium quadriurate or the biurate, or a mixture of the two. Moreover, as Sir William Roberts has pointed out, such a saturated solution would soon begin to deposit its urate in the form of the gelatinous biurate, which, infiltrating the affected area of the corneal tissue, would act as a mechanical irritant. It is, therefore, clear that all the corneal changes observed by Ebstein can be accounted for by the assumption that they are caused by a mechanical irritant. The experiments of Neubauer are opposed to the view that a soluble urate circulating in the blood can act as a poison or irritant and start necrosis. He found that the administration of large quantities of uric acid to rabbits (as much as twelve grammes in some cases) did not seem to cause any inconvenience. Moreover, is it likely that solutions of urates should act as irritants, when their passage through the kidneys is part of the natural elimination of nitrogen in man? If solutions of the urates are to be regarded as irritants, then the kidneys would never escape damage.

Another important argument which militates against the acceptance of Ebstein's theory is that not only is there no proof that the neutral sodium urate, upon which he

depends for the starting of the gouty changes, ever exists in the human body, but, on the other hand, there is strong evidence to show that it never can exist in the human body. The neutral sodium urate is an extremely caustic and unstable compound, and is decomposed in the presence of carbonates, so that it is impossible for it to exist in the blood. The first factor upon which Ebstein relies for his theory of the causation of gout therefore disappears. Moreover, the responsibility for the assumed necrotic changes cannot be transferred from the neutral sodium urate to the biurate, since Pfeiffer has shown, by means of subcutaneous injections of a solution of a biurate, that although it can produce pain and irritation, yet it cannot cause necrosis, especially when in so weak a solution as must occur in the human body. The assumption by Ebstein that the process of necrosis generates an acid which is supposed by him to convert the neutral urate into the acid urate is based on an imperfect acquaintance with the chemistry of the urates. Sir William Roberts has shown that uric acid is primarily taken up by the blood and lymph as a quadriurate—not as a neutral urate—and he has also proved that the formation and deposition of the crystalline biurate are not favoured by the intervention of an acid. Moreover, in connection with leukæmia, severe anæmia, and other diseases, to which reference will be made later, we know that a considerable quantity of uric acid may be present in the blood in the form of sodium quadriurate without giving rise to necrosis of tissues anywhere.

4. Inflammatory or degenerative changes in the affected tissues regarded as the primary cause of gout, such initial changes not being caused by urates.—Ord in 1872 considered that gout was due to a special form of degeneration in some of the fibroid tissues, resulting in an excessive formation of sodium urate, which is then discharged into the blood, and is subsequently deposited in those parts least freely supplied with vascular and lymphatic structures.

Ord, whose views, in this particular, have been supported by Norman Moore and Bowlby, also considers that uratic deposits only occur in tissues which have previously begun to degenerate.

Berkart * considers that the severity of the local symptoms attending an attack of acute gout is inconsistent with the assumption that they are produced by a primary chondritis, due to irritation set up by the deposition of sodium biurate in the articular cartilages. He considers that the rôle of the uric acid is one of a humbler kind than that which has hitherto been attributed to it. In his opinion the uratic deposits are most frequently connected with a form of panarthrititis, or a general inflammatory affection of the joints, which chiefly affects the smaller joints of the extremities. Without assuming any identity between arthritis deformans and gout, he considers that in both instances the disease probably originates in some kind of atrophy of the substance of the bone, that the degenerative process then attacks the cartilages and fibrous tissues of the joints, and that following on this there occurs a necrosis of the tissues close to or within the joint. This necrosis, he considers, is the primary cause of the pain, hyperæmia, collateral œdema, and desquamation of the skin of the affected joint. The degeneration and necrosis of the tissues are the result of a profound disturbance of nutrition. Berkart attributes the presence of the urates in the blood in part to leucocytosis, and in part to the formation of uric acid from the disintegration of the tissues ; so that he regards the uratic deposits as an epiphenomenon, and not as the cause of the gouty paroxysm.

George W. Balfour † holds that an acute attack of gout is not truly inflammatory, but results from thrombosis of small vessels around the affected joint. According to his view, the occurrence of such thrombosis accounts for the

* *Brit. Med. Journ.*, 1895, vol. i.

† *Edinburgh Med. Journ.*, 1898, iii.

sudden onset of acute pain in the affected joint. The events which follow are due to the formation of an anæmic area in and around the joint, viz., early visible turgidity of the veins leading from the affected part, followed by swelling due to accumulation of plasma within the anæmic area, and, lastly, tension of the skin. He considers that the deposition of sodium biurate is simply due to the accumulation of blood plasma containing it in solution within the anæmic area of the joint, and that the deposit is neither the result nor the cause of any inflammatory action.

5. Nervous disturbance regarded as the primary cause of gout.—The view that gout is intimately connected with disturbances of the nervous system has many supporters. Cullen, the great opponent of the humoral theory in the latter half of the last century, considered that gout mainly depended on an affection of the nervous centres. Sir Dyce Duckworth,* while accepting the view, as previously mentioned, that uric acid has some connection with gout, considers that gout is primarily dependent on a functional disorder of a definite tract of the nervous system, and that the part specially involved is possibly situated in the medulla oblongata, where it may be that there is a trophic centre for the joints. One reason that Sir Dyce Duckworth gives for considering this possible is the relationship of gout to diabetes, the consideration of which has led him to the belief that the portions of the nervous system involved in the two diseases cannot be far apart from one another. In consequence of this disorder of the neurotrophic system defects of nutrition arise which not only cause undue formation of uric acid, but also inhibit the normal destruction of that body in the tissues ; at the same time the renal excretory power for uric acid appears to be temporarily inhibited as part of the process of the gouty paroxysm.

* "A Treatise on Gout," 1889.

Sir Dyce Duckworth, therefore, regards gout as belonging to the class of neuro-humoral diseases, but he does not at present insist on the localisation of the primary disturbance in a limited portion of the cerebro-spinal axis. He draws the following distinction between inherited and acquired gout. In primary or inherited gout the toxæmia is dependent on the inherited gouty neurosis. In secondary or acquired gout the toxæmia arises from the digestive and excretory organs becoming overloaded, and then, if with this toxæmia there is depression and exhaustion of the nervous system, the gouty neurosis may be established by the morbid blood condition affecting the nutrition of the nervous system. Sir Dyce Duckworth claims that the suddenness with which an acute attack of gout comes on, preceded as it is usually by a sense of well-being in the patient, is indicative of the nervous origin of the outbreak, and that it is to the instability and undue sensitiveness of the nervous system in the gouty that the manifestations of the paroxysm are due.

Edward Liveing * considers that there is much to be said in support of the view that gout is the manifestation of a disorder which has its primary seat in the nervous system. He remarks that the view that uric acid exerts a toxic influence upon the nervous centres, and that the particular character of the disorder is determined by the territory involved, is one that presents real obstacles, on account of the limited operation attributed to a cause so general in its nature.

P. W. Latham † regards some change in the nervous system as the most important factor in the etiology of gout. He thinks that such change is localised in the medulla oblongata, or in the spinal cord, or in both, and that this nervous disorder may be either hereditary or acquired. He argues that if a portion of the medulla

* "On Megrism and Sick Headache," 1873, pp. 404-405.

† Croonian Lectures, 1886.

oblongata involving some of the roots of the vagus be the part affected, the metabolism of the liver may be interfered with, and so lead to the formation of uric acid. He also considers that if, from any cause, uric acid is circulating in the blood, it would act as a poison upon any weak spot in the nervous system, and that it is intelligible that it might act upon portions of the spinal cord which control the nutrition of the joints, and so cause nutritive changes or inflammation in the joints connected with that portion of the cord. In consequence of the inflammation or nutritive changes in the joints, sodium biurate becomes deposited in them, or in the tissues around the affected joint. Latham explains the phenomena of a gouty paroxysm by direct stimulation of sensory nerves by uric acid. He considers that the gout associated with chronic lead poisoning may be explained by the lead acting, in such cases, more particularly on those portions of the spinal cord which are concerned in gout.

6. Excess of carbonaceous material in the blood regarded as the primary cause of gout.—Francis Hare* has put forward the view that excess of carbonaceous material in the blood, or, as the author terms it, “hyperpyræmia” (Gr. *πυρεῖα*, fuel), is an essential, though by no means the sole factor in many disorders, such as common paroxysmal neuroses, migraine, asthma, epilepsy, and gout. It has frequently been shown that the paroxysms of acute articular gout are interchangeable with the paroxysms of migraine, asthma, and epilepsy, and many cases have been reported in which the onset of acute gout has been exactly coincident with the complete subsidence, temporary or even permanent, of long-standing migraine, asthma, and epilepsy, and others marked by converse substitutions.

Hare therefore considers that it is reasonable to suppose that the accumulation which precedes, and the discharge which accompanies, the acute gouty paroxysm,

* “A Common Humoral Factor of Disease,” 1905.

are similar in nature to the accumulations and discharges which occur in connection with the migrainous, asthmatic, and epileptic paroxysms. He considers that the carbonaceous compounds have a greater tendency to accumulate in the blood than the nitrogenous. For while the ingestion of proteid food, whether in small or large quantities, is quickly followed by a corresponding increase in the elimination of nitrogenous excreta, such as urea, there is no such rapid and commensurate increase in the elimination of carbonic acid after the ingestion of carbonaceous food ; indeed, the capacity possessed by the organism for increasing catabolism in response to the absorption of an excess of carbonaceous food is strictly limited. It is a remarkable fact that for adequate carbonaceous catabolism the organism is largely dependent on muscular exercise and exposure to cold—conditions which influence but slightly nitrogenous catabolism. Hence it follows that a liberal supply of carbonaceous food, combined with deficient exercise, especially in warm weather, favours an accumulation of the carbon contents of the blood. Such an accumulation would, of course, be precluded by an adequate increase in the rate of fat formation, but the capacity for fat formation is conspicuously deficient in many persons, and may, moreover, have already attained its limit. In these days of warm clothing, warm rooms, and little exercise, when starch and sugar are consumed in such truly enormous quantities, the conditions are, it is contended, all favourable for the induction of the hyperpyræmic state.

Hare maintains that an excessive ingestion of starch or sugar may lead to “glycogenic distension” of the liver, which, by compressing the intrahepatic portal capillaries, causes mechanical congestion of the whole retrohepatic portal venous system, and consequently of the whole gastric and intestinal mucosa. Hence digestion and absorption are inhibited, and in this way the liver tends to restrict the whole nutrient income, and therefore the carbonaceous

income of the blood. On the other hand, undue accumulation of the carbon contents of the blood may be prevented by an increase in the carbonaceous expenditure of the blood, the main items of which are fat formation, combustion or carbonaceous catabolism, and in women utero-gestation, lactation, and menstruation. He considers that hyperpyræmia may, under different conditions, culminate in acute gout, and that the pyrexia of acute gout, lasting as it may do many days, is curative of the underlying hyperpyræmic condition, and of all those hyperpyræmic manifestations (irregular or suppressed gout) which so often precede the articular paroxysm.

7. A bacterial toxin regarded as the primary cause of gout.—If the symptoms of gout are not due to uric acid, yet they must be caused by some other constituent of the blood. The normal constituents of the blood are well known, and there is no increase in any of them in gout sufficient to cause its symptoms; so that it must be due to one of those bodies, such as the toxins, which we know to be present in many diseases, but are not able to separate in analyses. In differentiating the symptoms of gout it can be noted that the principal symptoms are similar to those produced by toxins in diseases in which the symptoms are caused by the action of bacterial toxins on the tissues. For instance, the joints are peculiarly liable to be affected by the toxins of rheumatic fever, septicæmia, scarlatina, and allied diseases, and an attack of inflammation from this cause is more likely to be attended by great pain and constitutional disturbance than if due to the deposition of sodium biurate, which is non-irritating when deposited in other regions of the body.

The bacterial view of the pathogenesis of gout was very ably dealt with by Ringrose Gore in a paper read before the British Medical Association in 1900. In that paper the author stated his view that gout was caused by some product of digestion, either absorbed from the digestive

tract or produced by some alteration of metabolism going on in some of the digestive organs ; that there must be some body formed in the intestinal canal capable both of causing the symptoms of gout and also of so altering the metabolism of the liver as to cause an increased formation of uric acid. He went on to state that he considered a toxin was the cause of the disease, a product of a definite bacillus, and a product of one of the bacilli normally found in the intestinal canal.

A little later in the same year Le Gendre read a paper at the International Congress of Medicine in Paris, in which he foreshadowed the possible intestinal origin of gout. A year later Chalmers Watson drew attention to this view of the origin of gout. In 1903 there appeared in the *Lancet* a most instructive paper by Woods-Hutchinson, in which he stated his view that gout was a toxæmia ; that the source of the toxin was the gastro-intestinal tract ; that owing to some catarrhal or inflamed condition of that tract, possibly secondary to some chemical changes within that tract, a toxin was produced that was absorbed into the circulation ; that if the cells, either the wandering leucocytes of the blood and the lymph or the fixed body cells, could successfully combat and neutralise that poison nothing resulted. He thought that probably such was the case in people who suffered from certain intestinal derangements which quickly passed off ; but if the cells were powerless completely to neutralise that toxin, then, as the result of the unaltered toxin that was circulating in the blood and lymph, gout resulted ; that the cells, lymphocytes and fixed body cells, which were able to neutralise part of that toxin suffered degradation and degeneration in neutralising it, and as a result uric and phosphoric acids, the *débris* of nucleinic substances, were set free, and that that was the origin of uric acid which in certain cases might be deposited as an after-effect in the form of sodium biurate.

The selective action of toxins on different tissues is

exemplified by the way in which cartilaginous and fibrous structures become inflamed in gout. These tissues are also more liable or earlier liable on account of their lower vitality. As gout becomes more advanced the higher structures become involved and various nervous symptoms occur, such as some of the cardiac attacks, which are certainly toxic in character; the various tissues and organs affected by gout, the inflamed joints, the kidney disease, eczema, catarrh, and inflammation of the various mucous membranes, gastritis, phlebitis, neuritis, cardiac gout, form a group which have marked toxic analogies, and can be best explained by the action of a toxin circulating in the blood.

If the toxin which produces gout is formed by one of those bacilli normally found in the intestinal canal, the formation of the toxin must be due to some pathogenic alteration in the character of the bacillus, which might be accomplished either by a change in the intestinal secretion or by a marked alteration in the amount or character of the food. While the intestinal bacteria may be non-pathogenic under normal conditions, a slight change in environment may make a great alteration in this respect, and the most common, such as the *Bacillus coli communis*, may produce the most virulent toxins. This is well seen, as Treves has pointed out, in acute intestinal obstruction, where a change takes place in the intestinal secretion, the intestinal bacteria becoming virulent; and the patient may die of acute peritonitis, with acute toxic poisoning, and no bacteria other than those normally present in the intestines may be found. In appendicitis, again, the *Bacillus coli communis* may be the only bacillus present.

The causes that influence the growth of bacteria in the intestinal canal are in the main identical with those that produce gout. For instance, the quantity of bacteria in the intestinal canal varies directly with the amount of proteid food, and any articles of food which produce a

dyspeptic condition in the stomach or intestine also cause a very great increase in the number of bacteria found in the intestinal canal.

Gore's view is that gout is probably produced originally by an altered gastro-intestinal secretion, which in its turn leads to an alteration of the toxins produced by one of the intestinal bacilli. A catarrhal condition of the intestinal mucosa is probably responsible for the change in the intestinal secretion, and this catarrhal condition may be either an inherited trait, or induced by errors in diet. This change in the intestinal secretion would produce a change in intestinal toxins until a point would be reached when an excess of food or alcohol would generate a sufficient amount of toxin to produce an attack of gout ; this tendency would increase unless kept in check by careful dieting, and subsequent attacks would be more easily produced ; also this tendency would be transmitted to the offspring, and those starting life with it would tend to have gout earlier, and in an aggravated form.

Woods-Hutchinson regards uric acid as purely a symptom or index of certain changes taking place in the body metabolism, and defines gout as a toxæmia of varying causation, usually of gastro-intestinal origin, accompanied by the formation of an excess of urates, this excess of urates being due to the breaking down of the leucocytes and fixed cells in the attempt to neutralise the poison ; in other words, being the measure of the resisting power of the body tissues. The formation and introduction of the toxins are by no means confined to the gouty ; it is only the nature of the resistance of the body to them that gives the character of gout. The exciting cause of gout may be the toxin of micro-organisms acting directly or indirectly, or an auto-intoxication from deficient digestion or metabolism. In many cases the exciting cause may to some extent be discovered—such, for instance, as intestinal fermentation or putrefaction, or some disorder of the teeth, or mouth, or stomach.

So far, it cannot be said that any bacterium specific of gout has been discovered.

Trautner * regards a mucous colitis as one of the first manifestations of gout, and considers that the *Bacillus coli communis* is the initial agent in gouty affections. He states that the *Bacillus coli communis* produces a reducing substance, which is transformed into xanthin and uric acid during its passage through the body. It is fairly well known that different species of intestinal bacteria secrete or excrete substances which restrict the growth of other species, and sometimes of their own. At the same time, the intestinal mucosa pours forth secretions, which also materially affect the bacteria or their products, so that the degree of the intestinal infection in gout must depend in part upon the species of bacteria present, and in part upon the integrity of the secreting cells of the intestinal mucosa. No doubt hereditary deficiency in the digestive faculties may be responsible for the production of exceptionally powerful toxins, or may diminish the resistance to the products of the intestinal bacteria.

It has been customary to regard the bacillus coli group as the most characteristic intestinal bacteria, but Houston has shown that streptococci surpass the colon bacilli in abundance in normal human faeces; they were at times present to the number of 1,000,000,000 per gramme. Streptococci are thus present in the intestine of man, and of such animals as have been examined, in vast numbers, exceeding, in most cases, all other bacteria. Andrewes has brought forward evidence to show that the streptococci are well-established saprophytes of the alimentary canal, and that to all intents and purposes they are, at the present day, exclusively attached to the animal body, and in particular to the alimentary canal. Here, and here alone, they flourish and prevail in incredible numbers. Andrewes and Horder have recently published the details of the examination of

* *Nord. Med. Arkiv.*, 1905.

more than two hundred strains of streptococci from cases of human disease.

In my opinion, the view that a bacterial toxin is the primary cause of gout is the most probable one. In a former edition of this book I supported the theory as to the renal origin of the disease, but recent advances in our knowledge of the pathology of gout have led me to abandon that theory. The view as to the bacterial origin of gout is supported by the well-known fact that adequate removal of the intestinal contents at the commencement of the gouty attack always effects rapid diminution of the symptoms. Moreover, the classic remedies for gout have only two things in common : one that they relieve gout, and the other that they check intestinal putrefaction, or diminish the absorption of its products, or promote their elimination from the system.

It must be remembered that there are two drugs which from their great influence in gout must always be taken into consideration when thinking of the origin of this disease—the action of colchicum in relieving and that of lead in inducing gout. It is suggestive that both have an action on the intestinal secretion : colchicum causes an immediate alteration in its amount and character ; lead has the opposite effect of causing a diminution and alteration of the intestinal secretion when taken in small and long-continued doses.

The liver as a toxin destroyer.—One of the most important functions possessed by the liver is that of a toxin destroyer, or poison filter, for the blood in general, and that of the portal system in particular. Attention to this was first attracted by the discovery that extirpation, or ligation, of the blood-vessels of the liver in the lower vertebrates was promptly followed, not by mere impairment of digestive power, but by a rapidly fatal group of toxic symptoms similar to those of acute poisoning, ending in coma, with or without convulsions, and in death.

The experiment was carried a step further, and the blood from the portal vein diverted, by means of a fistula, directly into the vena cava, without passing through the liver; and again symptoms of acute intoxication developed, which soon proved fatal, although less rapidly than when the hepatic artery, or vein, was also tied. The blood was taken from the portal vein of one rabbit, and injected into the tissues of another, and found to be markedly toxic; while that drawn, under similar conditions, from the vena cava on the cardiac side of the liver was found to be only very mildly so. The conclusion was arrived at, some ten or twelve years ago, that the most important and essential function of the liver was that of a reducer and detoxicator of toxic substances, contained both in the portal and in the (hepatic) arterial blood.

According to this view, the rôle of the liver in gout is a negative one, being inability to perform its chief normal functions of acting as a "poison filter" and of absorbing or transforming into harmless excretory substances the excess of toxins brought to it by the portal vein.

CHAPTER IV.

ALKALINITY OF THE BLOOD IN GOUT.

Uric acid a normal constituent of the blood—Diseases associated with an excess of uric acid in the blood—Alkalinity of the blood in gout—Alkalinity of the blood and the precipitation of sodium biurate.

Uric acid a normal constituent of the blood.—It will be evident that if uric acid is not formed in the kidneys it must be brought to those organs in the blood in some combination or other.

We know that some 400–500 grains of urea are normally excreted in the urine, and that this urea is conveyed in the blood from various organs to the kidneys, where it is excreted. But, in addition, from eight to ten grains of uric acid are daily excreted in the urine of man. The question is, does this uric acid come as such to the kidneys? In other words, is it produced in any of the organs or tissues of the body generally and conveyed in the blood to the kidneys, to be by them excreted, or is it produced in the kidneys and then turned into the urine? The answers to these questions will depend very much upon our ascertaining whether uric acid exists in the blood of man in health, and whether it exists in the blood of those animals, such as birds, the whole of whose nitrogenous urinary excrement consists of a compound of uric acid. For it follows that if uric acid be not formed in the kidneys, it must be conveyed in the blood to those organs. If such be the case, its detection in the blood, provided careful search for it be made, ought to be a fairly easy matter, considering

that in the murexide reaction we have such an extremely delicate test for the identification of uric acid.

Here it is well to bear in mind that statements as to the presence of uric acid in the blood and viscera are valueless unless the substance is proved to be uric acid by the murexide test. Haig, who asserts that uric acid is always present in the blood and tissues, bases his statements solely on the application of Haycraft's process to water-extracts of the blood and tissues, and the subsequent calculation of the silver precipitate so obtained in terms of uric acid. As far as can be ascertained from Haig's writings, he has never identified by the murexide test this uric acid reported to be present in the blood and tissues.

Garrod's thread test.—Garrod's thread test is a rough method for the detection of uric acid in the blood, and is performed as follows:—To two drachms of serum obtained from a blister (applied at a site other than the inflamed spot) add ten to twelve drops of strong acetic acid. Mix the two fluids, and immerse one or two linen threads, and set aside for twenty-four hours. Then examine with a low power of the microscope, and if a positive result is attained, numerous minute rhombic crystals of uric acid will be found on the submerged part of the thread.

As a matter of fact, the detection of small quantities of uric acid in the blood is a more difficult matter than was originally thought to be the case.

Sir Alfred Garrod,* as the result of his investigations, declares that in absolute health the uric acid in the blood is inappreciable, that in gout the blood is very rich in it, and that uric acid is found in smaller but appreciable quantities in individuals who are developing a gouty condition, or who are under the poisonous influence of lead. Von Jaksch † examined the blood of several healthy

* Lumleian Lectures, 1883.

† *Deut. medicin. Woch.*, 1890, xxxiii., p. 741.

individuals, but found no uric acid present. Klemperer* also was unable to find any uric acid in the blood of healthy persons. I too have examined the blood of healthy subjects without being able to find uric acid.

Sir Alfred Garrod examined the blood of the ox, sheep, and pig by the uric acid thread test, but could never find a trace of uric acid present.

The examination of the blood of birds and reptiles has a very important bearing on the discovery of the normal seat of formation of uric acid. As is well known, the semi-solid urinary excrement of birds consists, apart from the small quantity of water present, entirely of uric acid compounds, so that the nitrogen excreted by the kidneys of birds is eliminated entirely in the form of uric acid and none of it in the form of urea. This white mortar-like urinary excrement of birds has been shown by Sir William Roberts to consist of the quadriurates of ammonium, potassium, and sodium. Consequently birds excrete in proportion to their body-weight an enormous amount of uric acid as compared with the uric acid output of mammals. If this large quantity of uric acid be produced in the organs and tissues generally it must be conveyed in the blood to the kidneys, and it therefore should be capable of detection in the blood of birds. It has, however, until comparatively recently, escaped detection.

Sir Alfred Garrod examined the blood of the turkey, fowl, pigeon, and duck by the uric acid thread test, but never found a trace of uric acid present.

I also have worked on the blood of the turkey, goose, duck, and fowl, but have never been able to detect any uric acid in the blood of those birds.

John Davy examined the blood of two snakes (*Viper communis*) for uric acid, but failed to detect any.

Chalmers Watson, using a more improved method of extraction, has been able to detect uric acid in the blood

* *Deut. medicin. Woch.*, 1895, xxi., p. 655.

of the duck, goose, and turkey. It must, therefore, be concluded from the results of his experiments that uric acid is normally present in the blood of birds.

Croftan also states that he has found uric acid in the blood of twelve normal subjects, and Petréu has also found it in the blood of healthy human beings in very small quantities. It must, therefore, I think, be conceded that the uric acid excreted by the kidneys in the urine is brought to those organs in the blood.

Other diseases associated with an excessive amount of uric acid in the blood.—Apart from gout, an excess of uric acid has been detected in the blood in the following diseases:—Primary and secondary anæmia, pernicious anæmia, splenic tumours, leukæmia, pneumonia, malignant disease, chronic Bright's disease, contracted granular kidney, ulcerative endocarditis, acute aneurism, gonorrhœal rheumatism, plumbism, intestinal inflammation, malaria, and typhus (after the febrile stage).

Von Jaksch * found uric acid in the blood of cases of both primary and secondary anæmia, pernicious anæmia, and splenic tumour. He also found it in the blood in conditions inducing dyspnœa, notably in heart disease, pleurisy with effusion, pulmonary catarrh, pneumonia, and emphysema. Klemperer † has recently confirmed the results of Von Jaksch and others as to the presence of uric acid in the blood of leukæmia, and many observations have been made of the increased excretion of uric acid that accompanies this disease. Laache ‡ found a daily excretion of 3.7 grammes (nearly six times the average normal amount) in a patient suffering from this disease. Bartels § observed a daily excretion of 4 grammes (more than six times the average normal amount). Stadthagen || found a daily

* *Deut. medicin. Woch.*, 1890, xxxiii.

† *Deut. medicin. Woch.*, 1895, xxi.

‡ "Klin. Urinanalyse," 1892.

§ *Deut. Arch. f. klin. Medicin*, Bd. i.

|| *Virchow's Arch.*, Bd. cix.

excretion of 2 grammes (three times the average normal amount). Bohland and Scherz * found a daily excretion of 1.4 gramme (twice the average normal amount).

Von Jaksch found uric acid in the blood of all the cases of renal disease that he examined, the proportions being especially large in cases of granular kidney disease and uræmia. Von Jaksch's results were confirmed by Klemperer, who examined the blood of cases of contracted kidney and found uric acid always present.

Chalmers Watson has recorded the results of an investigation of the blood in cases of pneumonia, malignant disease, chronic Bright's disease, ulcerative endocarditis, and acute aneurism, in all of which the presence of uric acid could be determined in the limited quantity of blood examined.

Alkalinity of the blood in gout.—It is remarkable that for a very long time the view has been generally held that a diminished alkalinity of the blood is associated with gout. This view, which is a pure hypothesis, probably originated in the assumption that gout is associated with an acid dyscrasia, and that absorption of uric acid into the blood necessarily diminished the alkalinity of that medium. The hypothesis has probably been strengthened, although erroneously, by the fact that the gouty paroxysm is usually accompanied by increased acidity of the urine. Consequently some observers have drawn the conclusion that an increased acidity of the urine must necessarily be associated with, and an index of, a diminished alkalinity of the blood (it is scarcely necessary to remark that there can be no such condition as acidity of the blood).

The test of experimental investigation, however, shows that the association of a diminished alkalinity of the blood with gout is erroneous. Klemperer some years ago proved by actual determinations of the blood of gouty subjects that the alkalinity was not below that of healthy blood.

* *Pflüger's Arch.*, Bd. xlvii.

Later on Adolf Magnus-Levy found that there was no diminution of the alkalinity of the blood during attacks of gout, nor was any obvious difference observed during and apart from the attacks. The alkalinity was found to be much the same in healthy and gouty persons, and both exhibited fluctuations of alkalinity. More recently I have made a number of determinations of the alkalinity of the blood of healthy and gouty persons—using the delicate process devised by A. E. Wright, which only requires the abstraction of three or four drops of blood from the individual—with the result that so far I have found in every gouty patient whose blood I have examined a higher alkalinity than the average alkalinity of the blood of healthy persons. The results that I have, up to the present time, obtained show that whereas the alkalinity of the blood of healthy adults varies from 0.161 to 0.185 per cent. of anhydrous sodium carbonate, with an average of 0.167 per cent., the alkalinity of the blood of gouty patients varies from 0.193 to 0.251 per cent., with an average of 0.217, which is nearly one-third higher than that of normal blood.

It is well known that an attack of gout may be accelerated by ingestion of food or beverages harmful either as regards their quality or quantity. Such substances may exert a direct or indirect chemical action which facilitates the precipitation of sodium biurate—this is the chemical view—or they may possibly exert a physical action only in hastening such precipitation—this is the mechanical view. A view which is commonly held as to the influence of diet and certain beverages in accelerating an attack of gout, is that such substances reduce the alkalinity of the blood, and so hasten the precipitation of sodium biurate. It is remarkable what a number of writers incline to the view that diminution of the alkalinity of the blood causes the deposition from it of sodium biurate, and that a subsequent rise in alkalinity causes solution of the previously formed

deposits. It is assumed that a nitrogenous animal diet diminishes the alkalinity of the blood and so causes deposition of sodium biurate. It is also assumed that a similar result is caused by the acids contained in wines and beers; and that the pains in the joints that frequently occur in gouty subjects soon after taking certain wines or beers are due to deposition of biurate following on the reduction of the alkalinity of the blood by the acid so introduced.

Now, I have been unable to meet with any experimental proof that a diminution in the alkalinity of blood containing uric acid in solution either facilitates the deposition of sodium biurate from it, or diminishes its solvent power for sodium biurate or for uric acid. I therefore considered it advisable experimentally to investigate these different points, and for that purpose the following series of experiments were undertaken.

Experiments showing to what extent the rate of formation and precipitation of sodium biurate is affected by diminishing, by the addition of acids, the alkalinity of blood serum charged with uric acid.—Seven bottles, each containing 40 c.c. of blood serum, were raised to 100° F., and then charged with uric acid to the extent of 1 in 1,000. As soon as the uric acid was dissolved, varying quantities of hydrochloric acid were added to the contents of three of the bottles, and of tartaric acid to another three, so as partially to reduce the alkalinity of the serum; the contents of the seventh bottle were left unaltered. The bottles were kept in a warm chamber at 100° F., and the commencement of the precipitation of sodium biurate crystals was then looked for by examining some of the contents of the bottles under the microscope every few minutes, so as to note the time when the formation of biurate crystals commenced. The quantities of hydrochloric acid added to the contents of three of the bottles were such as to neutralise respectively three-fourths, one-

half, and one-fourth of the alkalinity of the serum remaining after solution of the uric acid. To the other three bottles corresponding quantities of tartaric acid were added to produce similar results. The following tables (Table III. and Table IV.) show the results of these experiments.

TABLE III.

Results of experiments made with blood serum charged with uric acid, to show the effect which the diminution of the alkalinity of the serum, by the addition of hydrochloric acid, has on the precipitation of sodium biurate.

Solution.	Commencement of precipitation.
Blood serum containing 1 in 1,000 uric acid.	Crystals of sodium biurate first appeared in 6-7 hours.
The same, one-fourth neutralised by hydrochloric acid.	Do.
The same, one-half neutralised by hydrochloric acid.	Do.
The same, three-fourths neutralised by hydrochloric acid.	Some crystals of uric acid appeared in 5 minutes. Crystals of sodium biurate first appeared in 12 hours.

It will be seen from the results of these experiments that the effect of diminishing the alkalinity of blood serum as far as one-half has no influence whatever in hastening the conversion of the sodium quadriurate into biurate, or, in other words, does not influence the deposition of sodium biurate from the serum. When the alkalinity is reduced by three-fourths, by the addition of hydrochloric acid, some crystals of uric acid were almost immediately precipitated, but when this precipitation of uric acid had ceased, then the deposition of sodium biurate did not begin till twelve hours had elapsed. The reason that the

deposition of sodium biurate was delayed a longer time than in the cases of the serum, the alkalinity of which was reduced respectively by one-fourth and one-half, was that the removal of some of the uric acid rendered the solution of sodium quadriurate weaker, and, as has been pointed out by Sir William Roberts, the amount of uric acid in solution exercises a very important influence on the rate of maturation of the quadriurate, and the advent of precipitation of the biurate. This early shower of uric acid crystals that occurred when sufficient hydrochloric acid was added to the blood serum to neutralise three-fourths of its alkalinity has no bearing whatever on the chemistry of the gouty attack, since the gouty deposit always consists of sodium biurate, and never of uric acid. The following table shows the results of the experiments obtained with blood serum, the alkalinity of which was partially reduced by means of tartaric acid.

TABLE IV.

Results of experiments made with blood serum, charged with uric acid, to show the effect which the diminution of the alkalinity of the serum, by the addition of tartaric acid, has on the precipitation of sodium biurate.

Solution.	Commencement of precipitation.
Blood serum containing 1 in 1,000 uric acid.	Crystals of sodium biurate first appeared in 6-7 hours.
The same, one-fourth neutralised by tartaric acid.	Do.
The same, one-half neutralised by tartaric acid.	Do.
The same three-fourths neutralised by tartaric acid.	Do.

From these experiments it is evident that even the reduction of the alkalinity of blood serum by three-fourths

has no influence in hastening the precipitation of sodium biurate from blood serum impregnated with uric acid. The view, therefore, that a diminution of the alkalinity of the blood promotes an attack of gout by favouring the deposition of sodium biurate is, in my opinion, untenable. In order to give an idea of the amount of acid that would be required to reduce the alkalinity of the blood of an adult human being by three-fourths, I made the following estimation and calculation. I found that the acidity of some 1847 port, reckoned as tartaric acid, was equal to six grains of acid to the wineglassful. In order to neutralise three-fourths of the alkalinity of the blood serum of a man of average weight, it would be necessary that all the acid contained in two bottles of such port should be introduced at one moment into the circulation.

Experiments to show the solvency of uric acid in blood serum the alkalinity of which has been reduced by the addition of an acid.—The effect of hydrochloric and tartaric acids respectively was investigated. As will be seen from the results, there is a remarkable difference in the solvent power of partially neutralised blood serum for uric acid, accordingly as its alkalinity is reduced by the addition of hydrochloric or tartaric acid. The experiments were carried out in the following manner:—Four bottles each containing 25 c.c. of blood serum were taken; three of them were treated respectively with different quantities of hydrochloric acid, so as to reduce the alkalinity of the serum in one case by one-fourth, in the second case by one-half, and in the third case by three-fourths; the contents of the remaining bottle were left untouched. The bottles were placed in the warm chamber till their contents were at 100° F., and then an excess (60—70 milligrammes) of uric acid was added to each. They were kept in the warm chamber for two hours, during which time they were frequently agitated; the contents of

the bottles were then filtered from undissolved uric acid, and the dissolved uric acid in each filtrate was estimated. The following table shows the results:—

TABLE V.

Showing the solubility of uric acid at 100° F. in unaltered blood serum and in blood serum the alkalinity of which is proportionately reduced by the addition of hydrochloric acid.

Solvent.	Uric acid dissolved.
Unaltered serum	2.03 per 1,000.
Serum one-fourth neutralised by hydrochloric acid	1.48 „
Serum one-half neutralised by hydrochloric acid	1.00 „
Serum three-fourths neutralised by hydrochloric acid	0.45 „

Similar experiments were carried out using tartaric acid in the place of hydrochloric acid. The results were as follows:—

TABLE VI.

Showing the solubility of uric acid at 100° F. in unaltered blood serum and in blood serum the alkalinity of which is proportionately reduced by the addition of tartaric acid.

Solvent.	Uric acid dissolved.
Unaltered serum	2.03 per 1,000
Serum one-fourth neutralised by tartaric acid	2.01 „
Serum one-half neutralised by tartaric acid	2.01 „
Serum three-fourths neutralised by tartaric acid	2.02 „

It is seen from the results of these experiments that if the alkalinity of blood serum is reduced by the addition of hydrochloric acid, the solvency of the serum for uric acid is correspondingly altered. This is what would be expected, since the conversion of some of the sodium bicarbonate of the serum into sodium chloride renders that portion of the sodium unattainable by the uric acid, and prevents the solution of a corresponding amount of the latter as sodium quadriurate. Such a result, however, does not follow the reduction of the alkalinity of the serum by the addition of an organic acid, such as tartaric acid. It will be seen that serum, the alkalinity of which is reduced respectively by one-fourth, one-half, and three-fourths, practically does not vary at all as regards its solvency for uric acid. The explanation, no doubt, is that the uric acid is able to displace the tartaric acid from its combination with sodium, and utilise the sodium of the tartrate as readily as the sodium of the bicarbonate to form the soluble sodium quadriurate. Since the acidity of wines is due to organic acids (mainly tartaric, malic, and succinic acids), it would seem very doubtful, judging from the results of these experiments, whether, even if any alteration in the alkalinity of the blood were produced by the drinking of acid wines, the solubility of uric acid in such blood could be affected in the slightest degree.

Experiments to show the solvency of sodium biurate in blood serum the alkalinity of which has been reduced by the addition of an acid.—The effect of hydrochloric and tartaric acids respectively was investigated. The experiments were carried out in a similar manner to those just described, except that an excess of sodium biurate was substituted for the uric acid, and the digestion with the sodium biurate was carried on at 100° F. for five hours. The following tables show the results :—

TABLE VII.

Showing the solubility of sodium biurate at 100° F. in unaltered blood serum, and in blood serum the alkalinity of which is proportionately reduced by the addition of hydrochloric acid.

Solvent.	Sodium biurate dissolved.
Unaltered serum	0.05 per 1,000
Serum one-fourth neutralised by hydrochloric acid	0.05 ,,
Serum one-half neutralised by hydrochloric acid	0.07 ,,
Serum three-fourths neutralised by hydrochloric acid	0.10 ,,

These results show that sodium biurate is slightly more soluble in serum which has been partially neutralised by the addition of hydrochloric acid than it is in unaltered serum.

TABLE VIII.

Showing the solubility of sodium biurate at 100° F. in unaltered blood serum, and in blood serum the alkalinity of which is proportionately reduced by the addition of tartaric acid.

Solvent.	Sodium biurate dissolved.
Unaltered serum	0.05 per 1,000
Serum one-fourth neutralised by tartaric acid.	0.08 ,,
Serum one-half neutralised by tartaric acid	0.08 ,,
Serum three-fourths neutralised by tartaric acid	0.12 ,,

These results also show that sodium biurate is more soluble in serum the alkalinity of which has been reduced

by the addition of tartaric acid than it is in unaltered serum. I think that the view that uric acid is deposited in the liver, spleen, joints, and fibrous tissues owing to diminished alkalinity of the blood should be abandoned. It is based on an error—viz. that the deposit is uric acid, whereas it is sodium biurate. The results of the experiments that have just been described indicate that diminution of the alkalinity of the medium does not promote the deposition of sodium biurate. The other view, that increased alkalinity of the blood dissolves and sweeps out the accumulations of uric acid from the various organs and tissues, should also, in my opinion, be abandoned. It is based on the same error—viz. that the deposit is uric acid, whereas it is sodium biurate. That this body is not more soluble in highly alkaline fluids has been proved by the experiments of Sir William Roberts,* and is confirmed by the experiments that have just been described. Another erroneous idea in my opinion is that uric acid may be precipitated from the blood in the form of insoluble urates by certain metallic salts; these insoluble urates are supposed to be deposited in various tissues or organs, and yet in some mysterious manner to be subsequently redissolved when the alkalinity of the blood rises. There is absolutely no experimental proof to support such a statement.

General conclusions drawn from the investigations.—

1. The alkalinity of the blood is actually increased during a gouty attack.

2. The solubility of uric acid in the blood is not affected by a diminished alkalinity of the blood produced by the addition of organic acids.

3. The deposition of sodium biurate is not accelerated by a diminution of the alkalinity of the blood.

4. An increased alkalinity of the blood does not increase the solubility of deposits of sodium biurate.

* Croonian Lectures on "Uric-Acid Gravel and Gout," 1892.

Alkalinity of the blood and precipitation of sodium biurate.—The quadriurate is, in the dissolved state, a very unstable body, and soon changes into the sodium biurate, which, however, is not at once precipitated, since it at first assumes the form of the gelatinous biurate, in which form it is a much more soluble compound than the crystalline biurate. This gelatinous modification is afterwards converted, either slowly or rapidly, according to various conditions, into the crystalline compound.

The results will now be given of some experiments conducted by the author as to the conditions affecting the conversion of the gelatinous into the crystalline biurate; they apparently promise to throw some light on the means at our disposal for checking a gouty attack or for diminishing its severity.

Nature of the experiments.—The gelatinous form of sodium biurate is about five times as soluble in blood serum and artificial blood serum as the crystalline variety, and the following experiments demonstrate the behaviour of the gelatinous biurate in artificial blood serum. The experiments were conducted in the following manner. Five bottles containing artificial blood serum at 98° F., with 1.50 per cent. of the gelatinous sodium biurate added, were treated thus:—No. 1 was left unaltered, No. 2 had its alkalinity increased by the addition of 0.1 per cent. of sodium bicarbonate, No. 3 by the addition of 0.3 per cent., No. 4 by the addition of 0.8 per cent., and No. 5 by the addition of 1.0 per cent. The bottles were kept in a warm chamber at the blood heat, and every minute a small quantity of the contents of each bottle was removed, examined under the microscope, and the time at which the acicular crystals of sodium biurate first made their appearance was noted. The results are shown in the following table:—

TABLE IX.

Showing the time effect of sodium bicarbonate on the conversion of the gelatinous biurate into the crystalline form.

	Crystals of sodium biurate first appeared in.
No. 1.—Artificial blood serum containing 1.50 per cent. of gelatinous sodium biurate	10 minutes.
No. 2.—The same as No. 1, but containing 0.1 per cent. of added sodium bicarbonate	7 "
No. 3.—The same as No. 1, but containing 0.3 per cent. of added sodium bicarbonate	5 "
No. 4.—The same as No. 1, but containing 0.8 per cent. of added sodium bicarbonate	3 "
No. 5.—The same as No. 1, but containing 1.0 per cent. of added sodium bicarbonate	2 "

These results show that the proportionately increased alkalinity of the serum with sodium bicarbonate proportionately accelerated the conversion of the gelatinous biurate into the crystalline variety. It was also very evident to the naked eye at the end of half an hour that the higher the proportion of sodium bicarbonate present the greater was the bulk of the precipitate. The five bottles were kept in the warm chamber for twenty-four hours, when their contents were filtered, and the respective amounts of sodium biurate remaining in solution in the gelatinous form were estimated. These results were as follows :—

TABLE X.

Showing the effect of sodium bicarbonate on the conversion of the gelatinous biurate into the crystalline form at the end of twenty-four hours.

	Gelatinous biurate left in solution (in parts per 1,000).
No. 1	0.64
No. 2	0.57
No. 3	0.43
No. 4	0.24
No. 5	0.22

These results confirm those of Table IX., and show that the higher the alkalinity of the serum from the presence of sodium bicarbonate the more complete is the conversion of the gelatinous biurate into the crystalline variety, and therefore the less is the amount of the gelatinous biurate left in solution.

A precisely similar series of experiments was then conducted, with the substitution of potassium bicarbonate for the added proportions of sodium bicarbonate. The results are set out in:—

TABLE XI.

Showing the time effect of potassium bicarbonate on the conversion of the gelatinous biurate into the crystalline form.

	Crystals of sodium biurate first appeared in
No. 1.—Artificial blood serum containing 1.50 per cent. of gelatinous sodium biurate	10 minutes.
No. 2.—The same as No. 1, but containing 0.1 per cent. of added potassium bicarbonate	17 „
No. 3.—The same as No. 1, but containing 0.3 per cent. of added potassium bicarbonate	23 „
No. 4.—The same as No. 1, but containing 0.8 per cent. of added potassium bicarbonate	35 „
No. 5.—The same as No. 1, but containing 1.0 per cent. of added potassium bicarbonate	38 „

The results show that the presence of potassium bicarbonate in the serum delays the precipitation of the crystalline biurate, the extent of the delay being proportionate to the amount of potassium bicarbonate present. It was very evident to the naked eye at the end of an hour

that the greater the proportion of potassium bicarbonate present the smaller was the amount of sodium biurate precipitated. The effect of potassium bicarbonate on the gelatinous biurate is, therefore, precisely the opposite of that of sodium bicarbonate.

The five bottles were kept in the warm chamber for twenty-four hours, when their contents were filtered, and the respective amounts of sodium biurate remaining in solution in the gelatinous form were estimated, with the following results:—

TABLE XII.

Showing the effect of potassium bicarbonate on the conversion of the gelatinous biurate into the crystalline form at the end of twenty-four hours.

	Gelatinous biurate left in solution (in parts per 1,000).
No. 1	0.62
No. 2	0.69
No. 3	0.78
No. 4	1.01
No. 5	1.09

These results confirm those of the previous table, and show that the greater the proportion of potassium bicarbonate present in the serum the greater is the inhibitory effect on the conversion of the gelatinous biurate into the crystalline form, and therefore the greater is the amount of the gelatinous biurate left in solution.

As the result of these experiments it may be contended that the higher the alkalinity of the blood from the presence of sodium bicarbonate, the more rapid and the more complete is the conversion of the soluble gelatinous biurate into the comparatively insoluble and crystalline form. In connection with this point it is instructive to bear in mind that mineral waters rich in sodium bicarbonate are

well known to accelerate an attack of gout in many gouty subjects ; and it is also of interest again to mention here that, from many observations made on the alkalinity of the blood, it is invariably found in every gouty patient that the alkalinity of the blood is higher than the average alkalinity of the blood of healthy individuals.

Since this increased alkalinity is due to a higher proportion of sodium carbonate or bicarbonate, it can be understood why such blood is prone to hasten and to augment the formation of gouty deposits. On the other hand, it is seen that when the increased alkalinity of blood serum is due to the presence of potassium bicarbonate, the conversion of the gelatinous biurate into the crystalline variety is delayed as regards time, and is considerably diminished as regards quantity, thus explaining the well-known beneficial effect of the alkaline potassium salts in the treatment of acute and subacute gout. Von Loghem has also shown experimentally that increased alkalinity of the tissue fluids leads to deposition of the biurate, while diminished alkalinity lessens the tendency to uratic deposits.

CHAPTER V.

THE GOUTY DEPOSIT.

Formation of the gouty deposit—Conditions influencing the deposition of sodium biurate—Determining cause of the gouty deposit—The lymph circulation—Seats of uratic deposits in gout—Anatomical seat of the deposit in cartilages.

Formation of the gouty deposit.—Sir William Roberts investigated the behaviour of free uric acid with blood serum and kindred media, with the object of endeavouring to throw light on the mode in which sodium biurate originates in the body, and on the conditions which control the precipitation of sodium biurate in the gouty system. He experimented with solutions of uric acid in blood serum and in a standard solvent which was prepared as follows :—

Composition of Roberts's standard solvent.

Sodium chloride	0.5 gramme.
Sodium bicarbonate	0.2 gramme.
— Distilled water	100 c.c.

This solution represents the blood serum, in so far as its saline ingredients are concerned. Sir William Roberts found that it reacted with uric acid and the urates in the same manner as blood serum itself, and in the same manner as a solution comprising all the salts of the serum in their proper proportions. He found that blood serum and the standard at the temperature of the human body both dissolved uric acid to the extent of about one part in 500, thus exhibiting about twenty times the solvent power that the same media exercise on sodium biurate. The

chemical and solvent power is dependent on the sodium carbonate contained in them, and is due to that body converting the uric acid into sodium quadriurate. This sodium quadriurate which remains in solution is gradually converted by the excess of sodium carbonate into sodium biurate, and this, on account of its lesser solubility, is eventually precipitated in the crystalline form. Sir William Roberts inferred from these results that, in the normal state, uric acid is primarily taken up in the system as quadriurate, and that, as such, it circulates in the blood. The detained quadriurate, circulating in a medium rich in sodium carbonate, is gradually transformed by the latter into sodium biurate, which is less soluble and is probably less easily excreted by the kidneys than the quadriurate. This biurate is probably not precipitated at once, since it would most probably pass at first into the hydrated or gelatinous condition, which is a much more soluble modification of sodium biurate than the crystalline form ; but with due lapse of time, and increasing accumulation, it passes into the anhydrous or crystalline condition, and, as this form is almost insoluble, precipitation of it occurs, or is likely to occur.

The reason that in leukæmia and other blood diseases no uratic deposits occur is that the uric acid produced in the various organs or tissues is discharged into the blood as a quadriurate, and, as this requires some hours for its maturation before it is possible for it to deposit sodium biurate, there is abundant time for the kidneys to eliminate it, provided these organs are sound.

Time occupied in the conversion of the quadriurate into the biurate.—The period of time required for the conversion of the sodium quadriurate contained in the blood into the biurate is variable, and is doubtless dependent on several factors, such as the amount of quadriurate present, and the proportions of various saline constituents of the blood, which may either hasten or inhibit

the change. This last-mentioned group of factors is a most important one in connection with the therapeutical treatment of gout. From an experimental inquiry into the subject that I have made, I find that when the blood serum is saturated with sodium quadriurate and kept at the body temperature, deposition of sodium biurate does not commence till the end of two hours, and is not complete till many hours—sometimes days—have elapsed. Probably in no pathological condition is there so much sodium quadriurate present in the blood as to produce saturation. The smaller the proportion of quadriurate present, the longer is the deposition of sodium biurate delayed, and the longer is the time required to complete its precipitation.

Deposition of sodium biurate encouraged by concentration of medium and proportions of sodium salts present.—Sir William Roberts found that sodium biurate is very sparingly soluble in blood serum; at blood heat the amount dissolved is about one part in 10,000 (about one-tenth of its solubility in water). This lessened solubility is entirely due to the saline ingredients of the serum, as on depriving the serum of its salts by dialysis, it was then found to exercise the same solvent action on the biurate as simple water. Sir William Roberts found that the sodium salts especially diminish the solvent power of a medium for sodium biurate, and that this diminished power is mainly, if not entirely, due to the sodium, and is apparently not much, if at all, influenced by the acids combined with it, since solutions of sodium bicarbonate, chloride, sulphate, phosphate, and salicylate, prepared so that the percentage of sodium in them was the same, exhibited the same low solvent action. His experiments also show that if a medium be rich in urates, but poor in sodium salts, its tendency to precipitation is feeble, and *vice versâ*. Since structures belonging to the connective-tissue class are rich in sodium salts and are also liable to

uratic deposits, while muscle, brain, liver, and spleen are poor in sodium salts and not liable to uratic deposits, he considers that the proportion of sodium salts in a tissue is an important factor in determining the deposition of urates in that tissue.

Precipitation of sodium biurate from synovial fluid.—Another factor in facilitating the precipitation of urates is to be found in the synovial fluid. Sir William Roberts's view is that the uratic precipitation actually takes place from the synovial fluid, and does not originate in the cartilaginous substance. This view is based in part on the microscopic appearance of vertical sections of gouty cartilage, in which the deposit is seen to be greatest on the synovial surface of the cartilage and to become gradually sparser and sparser towards the deeper layers, and in part on the fact that synovial fluid has been repeatedly found heavily laden with crystals of sodium biurate. He considers (as opposed to Ebstein's view) that the process of deposition in the cartilage is a purely passive and physical one, and that the synovial fluid, charged with its dissolved urate, penetrates by liquid diffusion into the superficial layers of the cartilage, and that, when the critical moment arrives, precipitation takes place simultaneously in the synovia and in the cartilage. According to this view, the after-consequences are entirely secondary, and are due to inflammation set up by the presence of the foreign body in the tissue.

As regards the varying liability of different joints to gouty attacks, Sir William Roberts considers that it is, at all events in part, dependent on a greater concentration of the synovia of some joints, and on a variable proportion of sodium salts and possibly of sodium biurate. The experiments made by Frerichs* on the comparative composition of the synovia of animals leading idle and active existences somewhat support this view. Frerichs found

* R. Wagner's 'Handwörterbuch der Physiologie,' 1884, Bd. iii., Part i.

that the synovia of stall-fed horses and oxen leading an idle existence was more watery and contained a larger proportion of sodium salts than the synovia of similar animals doing work or roaming in the meadows. Moreover, the joints of the idle animals contained twice as much synovia as the joints of similar animals taking active exercise.

Deposition of sodium biurate encouraged by sluggish movement of medium.—It is highly probable that the very sluggish movement of fluids in the cartilaginous and fibrous tissues favours the deposition of urates from the medium in which they are dissolved. As illustrating the fact that whatever interferes with the movement of the animal fluids favours the production of gouty symptoms, or of an actual attack of gout, an interesting case has been recorded by Charcot, who observed, in a hemiplegic woman of forty, that most of the articular cartilages on the right, paralysed, side were infiltrated with urates, whereas those of the non-paralysed side showed no such deposits. Sir William Roberts considers that the chief reason why, in the post-mortem room, the cartilages figure more prominently than the fibrous structures as the seat of deposition of sodium biurate is to be found in the fact that in the fibrous tissues there is a comparatively free lymph flow, which exercises a more effective solvent action on uratic deposits than can be effected by the sluggish lymph flow in the cartilages. With regard to the reason or reasons that gouty precipitation takes place preferentially in synovia rather than in the serum of blood and lymph, Sir W. Roberts considers that the motionless condition of synovia as compared with the state of rapid movement of blood and lymph would give to synovia a priority in uratic precipitation.

Deposition of sodium biurate encouraged by injury to joints or by interference with their nutrition.—A slight injury to a joint, which in a healthy person

would speedily pass off, in a gouty person renders the part susceptible to the deposition of sodium biurate if sodium quadriurate be circulating in the blood. This susceptibility is probably in some way connected with an impairment of the nutrition of the affected tissues. Fagge, indeed, regarded a paroxysmal attack of gout in the light of an accident occurring in the course of an essentially chronic change in the joint affected.

As regards the relation between gout and rheumatism, Sir Alfred Garrod has remarked that if gout supervene in individuals who have suffered from rheumatism, it is generally the articulations which were the seat of rheumatism that are first attacked by gout. So that joints which have been the seat of acute rheumatism are especially predisposed, in gouty subjects, to become the seat of uratic deposits.

Ebstein * considers that deposition of sodium biurate is dependent on and is produced by previous necrosis of the affected tissues, and that the uratic deposit never occurs in a normal tissue. His view is that the neutral sodium urate circulating in the blood acts as an irritant and produces necrosis of the cartilages or other tissues, in which the sodium biurate is subsequently deposited; as a result of this necrosis he considers that an acid is developed which converts the neutral urate into acid urate, which compound is then deposited in the necrosed areas. This theory is obviously an erroneous one, since the neutral sodium urate cannot exist in the circulation. Klemperer † does not consider that uric acid is responsible for the necrotic changes in tissues, nor that the phenomena of gout can be due to mere crystallisation of sodium biurate from the blood, because in leukæmia, where an excess of urate is present in the blood, neither local necrosis nor uratic deposits occur. He believes that some unknown

* "Die Natur und Behandlung der Gicht," 1882.

† *Deut. medicin. Woch.*, 1895, vol. xxi., p. 655.

substances, in gout, lead to inflammatory and necrotic processes in various tissues; these necrotic areas then attract the uric acid from the blood, the chemical affinity of the necrotic parts for uric acid being so great that the blood cannot redissolve it. Von Noorden thinks the unknown substance which starts the inflammatory and necrotic processes is a ferment, and that the uric acid crystallises out in the necrotic tissues.

Reasons for the special selection of the great toe and ear as seats of gouty deposits.—There are several reasons to account for the special causation of uratic deposits in the great toe. (1) There is the liability of the metatarso-phalangeal joint to injury from having to support the weight of the body, and from being subjected to sudden shocks. (2) The remoteness of the joint from the heart, and the force of the circulation being consequently at its minimum at that part. (3) The poor vascularity of the tissues of the joint. The liability of the joint to injury is shown by Garrod's examinations of the great-toe joints of twenty subjects known not to have had gout. In fourteen he found ulceration of the cartilages of one or both joints. Of these twenty subjects three were under thirty years of age and showed no ulceration of the cartilages; the remaining seventeen were over thirty years of age, and of these fourteen, or 82 per cent., showed ulceration of the cartilages. All the subjects over fifty years of age showed ulceration.

In the helix of the ear the sluggish circulation and the coldness of the organ are quite sufficient to account for the frequency with which uratic deposits are found in that part.

While the usual course of the disease is for the great-toe joint to be the part first affected, in not a few cases the primary attack occurs in the knees, ankles, tarsus, or hands. The actual site of the attack is frequently determined by some previous injury to the part affected, by

which its vitality has been weakened, and the part rendered more prone to the attack of the toxins. When the swelling increases the pain lessens ; later the parts pit on pressure, and the cuticle cracks and desquamates.

Determining cause of the gouty deposit.—The whole series of periartritic and arthritic changes in gout are in all probability the result of slow chronic intoxication, with local necrosis, at points of least vitality. The intoxication and the local necrosis are probably due to the action of a bacterial toxin or toxins.

The tissue lymph or lymph circulation in the areolar tissue.—This subject is one that has an intimate bearing on the production of the œdema and the formation of the gouty deposits in various forms of gout.

G. Oliver,* in the course of experiments on blood, found that the rolling of a tight rubber ring over the finger from the tip to beyond the interphalangeal joints as a rule considerably raises the percentage of the blood corpuscles, and of the hæmoglobin. From the observation of this fact he was forced to the conclusion that the ring not merely emptied the vessels, but likewise cleared away any tissue fluid present in the skin and subcutaneous tissues.

The needle, in puncturing the capillaries, liberates a certain portion of lymph from the areolar tissue which surrounds them, and this dilutes the blood. When, however, both fluids have been dispersed by the compression of the rubber ring a puncture made just before the removal of the ring yields blood from the vessels only ; for the blood instantly returns to the vessels, whereas an appreciable interval must elapse before the lymph reappears or is exuded afresh.

Oliver's method of observation is first to take a sample of blood from the first easily flowing drop derived from a puncture at the root of the nail, the object being to obtain

* *Lancet*, 1903.

the actual proportion of lymph present in the tissues around the puncture. Three stout rubber rings are then rolled in succession from the tip of the finger to beyond the interphalangeal joints, and these are then removed by placing over the finger a rigid tube, on to which the rings are rolled; in this way compression of the tissues is secured in one direction only—namely, from the tip. The original puncture will generally suffice for supplying the second sample. The finger is held upwards until the blood is made to flow, for observation shows that compression does not now alter the proportion of the corpuscles. The hæmocytometer tubes are then read in the usual way, and the difference between the readings indicates the percentage of tissue lymph. The following are some of Oliver's general conclusions:—

1. The ingestion of food produces a rapid flow of lymph into the tissue spaces, which in an hour after meals attains its maximum development, and then slowly subsides and only ceases after the lapse of from three to four hours.

2. The interchange of fluid between the blood and the tissues may be measured, and, as showing the large amount of lymph that flows from the blood into the areolar tissues, Oliver calculates that a man weighing eleven stones should exude twenty-eight fluid ounces of lymph into the interstitial spaces of his tissues after each meal. This large interchange of fluid between the blood and the body-tissues excites other fluid transfers from the blood; consequently when the maximum exudation takes place the volume of the blood will shrink considerably. During absorption it will increase, and when absorption is completed it will acquire its fullest expansion.

3. *Exudation of tissue lymph.*—Physiologists are divided as to whether tissue lymph is a pressure product or a secretion. Oliver, as well as Ludwig, Starling and others, considers it to be a pressure product, inasmuch as the amount

of lymph in normal subjects is always proportionate to the rise in the blood pressure.

4. *Absorption or disposal of tissue lymph.*—In the normal condition of circulation each exudation of lymph completely disappears before its successor is drawn out. Lymph can only be disposed of in two ways:—(1) by absorption into the capillaries, and (2) by transmission along the lymphatics. When the body is in a state of rest, the fluid exuded into the tissues is mainly absorbed directly into the blood, and an essential condition required to effect this absorption is a falling capillary pressure. Should the blood pressure remain high, absorption ceases to go on and the lymph flow from the tissues is arrested, as well as the continuous discharge of lymph in the tissues of those in whom the blood pressure is supernormal.

5. *Intermediary circulation.*—The to-and-fro transferance of fluid from the capillary to the tissue spaces constitutes a circulation which appears to suffice for all the requirements of metabolism while the body is in a state of rest. This circulation, interposed as it is between the capillaries and the lymphatic vessels, is termed by Oliver the “intermediary circulation.” It is merely an extravascular extension of the capillary circulation controlled by the forces which actuate that circulation.

6. *Physiological ends served by the tissue lymph circulation.*—Inasmuch as proteids are diffused through membranes in proportion to the pressure brought to bear upon them, it may be inferred that the physiological end served by the rise in the capillary blood pressure which produces the digestive exudations of lymph is to supply pabulum to the tissues. Proteids are therefore probably distributed to them in the exudation current which flows from the blood. Inasmuch as absorption does not commence until the blood pressure begins to fall, the current from the tissue spaces to the capillaries will not set in until after the acme of the wave has been reached. This

return stream probably consists of a solution of salts and waste products only, and any surplus of proteids not used up in construction and repair of the tissues may be restored to the blood by transmission along the lymphatics rather than by direct retransfer through the capillary wall, for there is a difficulty in explaining how proteids can be absorbed from the tissues by this direct route. If these views on the physiological purport of the lymph waves be correct it may be inferred:—(1) That the intermediary circulation provides the mechanism, as it were, for the supply of pabulum to the tissues and for the removal of soluble waste products from them. (2) That the lymph wave which follows a meal insures the immediate supply of pabulum from the blood which restores all the tissues of the body at once and long before the food itself can be assimilated into the blood. Thus it is that the ingestion of food secures the speedy renewal of the energies, which is a matter of common experience; and therefore the exhausted tissues have not to remain unsupplied with fresh nourishment until the food taken becomes part of the common store of pabulum which the blood keeps ready for distribution. (3) That beverages (tea, coffee, and alcohol) probably invigorate the body by inciting a flow of lymph into the tissues. Beverages, however, viewed from this standpoint differ from food-stuffs in that they fail to restore to the blood the outflow of pabulum which they create. They are therefore but temporary expedients of nutrition.

7. When the blood pressure becomes supernormal, as in high altitudes, in chronic goutiness, and in kindred ailments, the density of the blood rises in proportion to the increased and persistent exudation of tissue lymph; and when the pressure falls below the normal range the fluid exchange between the blood and the tissues diminishes, and the density of the blood tends to be low, and, indeed, is generally low.

8. In all the cases of undoubted gout examined by Oliver an obstructed form of the intermediary circulation was found, but whether it is invariably present in gout cannot at present be affirmed. All the remedial measures which counteract chronic goutiness liberate the embarrassed peripheral circulation by reducing the increased venular resistance, and thus they secure a rise in the venous pressure, a fall in the capillary pressure, and a reduction in the mediary circulation of tissue lymph. When the obstructed intermediary circulation in gouty subjects is thus relieved and the normal flow and ebb of tissue lymph are restored, the general health is improved and the local manifestations of the gouty state, as a rule, either disappear or are lessened.

9. Oliver considers that his experiments afford some confirmation of the correctness of the generally entertained opinion that goutiness primarily depends on the retention of some waste product or products. There may be differences of opinion as to how gout originates, but as to how it is maintained when established he considers that his observations leave no doubt. They have shown that it is essentially dependent on a derangement of the intermediary circulation, and that therefore the tissues themselves form the arena in which gouty disturbances develop and manifest themselves. Residua may accumulate and be deposited in the interstitial spaces of the tissues, because their removal is thwarted, either by an excessive capillary blood pressure limiting the absorption of fluid from these spaces, or by a diminution of that pressure reducing the fluid exchange between the blood and the tissues. Hence the two leading types of gout which are well recognised. According to his observations, the continuous presence of a large quantity of tissue lymph provides an important condition for the development of the local manifestations of gout, which were present in by far the majority of the cases observed, and those few cases

in which local signs of gout had not so far declared themselves might fairly be said to be gouty—in the sense of potential gout.

Chalmers Watson, from an examination of gouty deposits in tendons, cartilages, and bone, came to the following conclusions :—

1. The examination of gouty tendons showed that the necrotic areas had a definite relation to the vessels of the part. The appearances in the tendons indicated that the necrotic areas are to be accounted for by an infection by the blood stream.

2. The erosion of cartilage was due not to the presence of uric acid, but to the action of small round cells of the granulation tissue type.

3. In connection with the gouty deposits in the bone, there were noticed a richness of the blood supply, the presence of giant cells, and great accumulation of small round cells of the nature commonly associated with the action of bacterial toxins.

4. The general conclusion was that the *tout ensemble* of the pathological pictures is strikingly similar to that seen in chronic infective diseases. From this point of view the uric acid is regarded as the feature which gives the inflammation its specific character.

Seats of uratic deposits in gout.—Uratic deposits are found almost exclusively in structures belonging to the connective-tissue class—in cartilages, ligaments, tendons, and in the cutaneous and subcutaneous connective tissue. Although the uratic deposits are seen most characteristically in joint structures, yet they have been found in nearly all the structures of the body which contain a large amount of connective tissue. In the central nervous system crystals of sodium biurate have been found in the dura and pia mater, in the neurilemma of nerve-sheaths, in patches of cerebral softening, and in the cerebro-spinal fluid. A similar condition has been noted in the cardio-

vascular system, the aortic and mitral valves and aorta occasionally showing a deposit. Among other sites may be mentioned the eyelids, sclerotic, auricle, tendons and tendon sheaths, vocal cords, bronchi, bursæ, bone marrow, palmar and other fascia, and subcutaneous tissue generally. Indeed, it is probable that a careful examination of the various organs and tissues in pronounced cases of gout would reveal the presence of a deposit in many other places not previously described. These points sufficiently indicate that uratic precipitation is very variable in its incidence—a fact of considerable import in connection with the phenomena of irregular gout.

A deposit of sodium biurate may occur in an enlarged, thickened, and inflamed bursa, in which case the swelling may reach a considerable size. Tophi vary in size from a very minute deposit, the size of a pin's head, up to or exceeding that of a small orange. Among the more common situations are the ears, fingers, foot, ankle, and eyelids, but they may be seen in other situations. The general appearances vary according to the site, and the presence or absence of ulceration.

Although tophi originally consist of sodium biurate, yet, if they persist long enough, they come to contain both phosphate and carbonate of lime, and the gouty nodosities about a joint may ultimately form true bone.

Anatomical seat of the deposit in cartilages.—The uratic deposit first occurs in the central portion of articular cartilage—a point farthest from the network of nutrient capillaries and a point whose nutrition is more easily retarded. It is also probably the point of greatest pressure; hence a long walk, a dance, or similar violent exercise may precipitate an attack of gout. Uratic deposits occur in cartilages, ligaments, synovial membranes and their fringe-like processes. In synovial membranes the deposit is not on the surface, but in the subserous tissue. Ebstein*

* "Die Natur und Behandlung der Gicht," 1882.

states that directly under the surface of the cartilage a very shallow tissue layer exists in which crystals are wanting, and in the layer immediately beneath this the crystals are most plentiful. He agrees with Sir Alfred Garrod that only two-thirds of the thickness of the cartilage is usually infiltrated, although exceptionally—as shown by Cornil and Ranvier—the whole cartilage may be infiltrated. With regard to the exact relation of the uratic deposit to the various elements of articular cartilage, the cartilage cells are held to be the centres of primary deposit by Cornil and Ranvier, Charcot, Rindfleisch, Budd, and Garrod. Cornil and Ranvier consider that nutritive disturbances in the cartilage cells precede the deposition of sodium urate. Rindfleisch and Budd, however, consider that the cartilage cells do not take any active part. Some observers, including Sir Dyce Duckworth, consider that the deposition occurs quite indiscriminately, not selecting for its original site any particular element of the cartilage. Others, as Bramson, Rokitansky, and Auguste Fœrster, think that urates deposit in the intercellular cartilaginous substance.

When a gouty joint is examined in the earlier stages of the disease the articular cartilages show scattered or isolated points, streaks, or patches of a chalk-like material—sodium biurate. A closer examination may reveal the fact that this deposit is not really on the surface of the cartilage, but is situated interstitially in its substance, the superficial layer of epithelium being intact. Later this superficial layer is involved, and the articular surface becomes roughened, irregular, and eroded. As the primary deposits take place in the areas where circulation and nutrition are at their lowest level, we accordingly find that it is the central portion of the articular cartilage that shows the earliest manifestations. Later on the ligamentous structures may become the seat of interstitial deposit, and the synovial membranes and their fringe-like processes are involved.

The ends of the bones occasionally become enlarged, and even true bony ankylosis may occur. Changes also take place outside the joints, the connective tissues, aponeuroses, and tendon sheaths becoming the seat of a varying amount of uratic infiltration. Inflammatory changes occur in the cartilage leading to proliferation and necrosis, the former being most manifest at the periphery of the cartilage, where the deposits are smaller and the tissues more highly vascularised. As a result, outgrowths may occur at the margin of the articulation.

PART II.

ÆTIOLOGY AND VARIETIES OF GOUT-- DIAGNOSIS AND PROGNOSIS.

CHAPTER VI.

ÆTIOLOGY AND CLINICAL FEATURES.

Ætiology of gout—Heredity—Immediate exciting cause—The clinical features of acute gout—The clinical features of chronic gout—The kidneys in chronic gout.

Ætiology of gout.—*Age.*—Gout is mainly a disease of middle and late life, but it may occur earlier if there is a marked hereditary tendency. While gout is commonly a disease of adult life, not appearing as a rule under the age of thirty-five, there are numerous exceptions to this.

Sex.—Gout is much more common among males. This tendency is no doubt mainly due to the fact that the habits of men, with regard to diet and alcoholic drinks, are more conducive to the development of the disease than the more temperate habits of life of the majority of women.

Geographical distribution.—It is generally conceded that in England the disease is more prevalent than in any other country in the world. In this country there has for many generations been a large leisured class who have been over-indulgent in eating and drinking, and who at the same time have taken insufficient exercise.

There has been a general impression prevalent both within and outside the United States that gout is a rare disease in that country. It is, however, much more

prevalent there than is generally supposed. At the Johns Hopkins Hospital, Baltimore, out of the total medical cases admitted to the wards during fourteen years 0·26 per cent. were cases of gout. For a similar period at St. Bartholomew's Hospital, out of the total medical cases admitted to the wards, 0·37 per cent. were cases of gout. So that in London, the home of gout, the cases are a little less than one-third more frequent than they are at Baltimore. The disparity is, therefore, not at all marked, and is probably even less than that shown by these figures, since it has been generally conceded in the past by medical men in America that gout is not as a rule so thoroughly diagnosed as in this country, and that many cases of true gout are mistaken for rheumatism.

Hereditary predisposition.—As regards the oft-debated question of heredity, it is now generally admitted that hereditary predisposition is a most important factor in the determination of gout—that persons who have developed gout under conditions suitable to its genesis tend to have children who are liable to develop gout, but it does not follow that such children will ever suffer from gout unless the conditions under which they live are suitable for the development of that disease. The females of gouty families frequently escape the apparent development of gout in themselves, but transmit the disease, or the liability to it, to their children. It is doubtful, however, whether true atavism occurs in connection with gout; that is, whether gout entirely misses a generation. It is more probable that it appears in some form, irregular or otherwise, in the generation that it is supposed to have passed over. It is generally admitted that parents who have become gouty under conditions of ease and high living tend to have children who are liable to develop gout under like conditions. But it must not be assumed that therefore parental high living is a cause of filial goutiness. The diathesis, the inborn tendency to acquire the

disease under certain conditions, is transmissible; but there is no evidence that parental high living increases that tendency in the child. An explanation of the hereditary character of gout is that the defects of the cells (possibly the cells of the intestinal mucosa) of the progenitor are transmitted to those of the offspring through the ovum or the spermatozoa.

Scudamore states that out of 523 gouty patients, 59 per cent. gave a history of the disease in the parents or grandparents. Sir Alfred Garrod found that the predisposition was inherited in 50 per cent. of his hospital patients, but among his private cases he believed that the tendency was inherited in 75 per cent.

Heredity as a predisposing factor in the causation of gout stands out more prominently in this than in any other country. Amongst the poorer classes it is difficult to obtain reliable information as to the inheritance of gout. I have, therefore, taken from my case-books 300 consecutive cases of gout, in all of which careful inquiry had been made into the family histories. These cases were all private patients belonging to the well-to-do classes.

Of the 300 cases, 244 gave a definite family history of gout, 12 cases gave a history of what was described as rheumatism in parents or grandparents, and in 44 cases no history of any joint disease occurring in any members of the family could be obtained. As regards the 12 cases which gave a family history of what was called rheumatism, it is possible that the disease which actually occurred in the ancestors was gout; but these cases have not been included among those with a definite family history of gout.

If these figures are reduced to percentages the following numbers are obtained:—

Definite family history of gout	81·3 per cent.
Family history of what was called rheumatism	4·0 „ „
No family history of either gout or rheumatism	14·7 „ „

Of the cases that gave a definite family history of gout the following is the distribution of the heritage :—

TABLE XIII.

From one or both parents only	24·6 per cent.
From one or more grandparents only	17·6 „ „
From one or more grandparents and one or both parents	16·8 „ „
From one or both parents, and other members of the family (not grandparents)	15·6 „ „
From one or more grandparents, and other mem- bers of the family (not parents)	9·4 „ „
From one or more grandparents, from one or both parents, and other members of the family	9·0 „ „
From members of the family not grandparents or parents	7·0 „ „

If this table is examined it will be seen that in 27 per cent. of the cases the disease was transmitted from grandparents to grandchildren without the fathers or mothers suffering from active gout.

Of the cases inherited from the parents only, the following is the distribution of the heritage :—

From the father only	73·4 per cent.
From the mother only	11·6 „ „
From both parents	15·0 „ „

Of the cases inherited from the grandparents only the following is the distribution of the heritage :—

Paternal side	53·5 per cent.
Maternal side	21·0 „ „
Both sides	25·5 „ „

Habits of life.—The abuse of alcoholic drinks, especially those of the fermented class, such as wines and beers, and the excessive consumption of nitrogenous, rich, and indigestible food, are powerful factors in the development of gout. Indolent habits, inadequate physical exercise, and deficient food, with bad hygienic surroundings, also strongly predispose to gout.

Gout is more common among the rich than the poor, and has been called "*morbis divitum*" in consequence. Over-feeding and luxurious habits of life undoubtedly favour its onset; yet it may occur in the most abstemious at times, and the poor are not exempt from it. It might seem that the poor who suffer from gout would afford more favourable subjects in whom to study its causation than the rich, on account of the less varied nature of their dietary and conditions of life. Some writers incline to the view that there is one, and only one, source of the disease among the labouring classes—malt liquors. It can hardly be doubted that this class of beverages constitutes at least a potent exciting cause of gout. The comparative infrequency of indulgence in malt liquors by women may account for the smaller incidence of gout on this sex, while the prevalence of the disorder in England as opposed to the Continent may also be due to the nature of our prevailing beverage.

Lead-poisoning.—Chronic lead-poisoning predisposes to gout. This subject will be fully dealt with later on.

Influence of other diseases.—Among these conditions it is interesting to bear in mind the influence of other acute febrile diseases on gout. Many years ago Braun pointed out that gouty patients often remain for a long time free from paroxysms after a febrile malady, of however foreign a nature; and among recent writers Henry M. Lyman shows that various acute febrile diseases and inflammations like tonsillitis, bronchitis, rheumatism, etc., afford great relief from the constitutional symptoms of arthritis.

Hare's view is that these observations go to prove that the relief attained is due to the increase in the rate of combustion associated with pyrexia. Acute gout itself is a pyrexia, and the increase in combustion and carbonic acid evolution has been demonstrated by Magnus Levy. Hence the improvement which succeeds the attack is, as a rule, proportionate to the degree of febrile reaction, and drugs

which cut short the pyrexia tend to prevent the amelioration in general health, and to shorten the ensuing period of freedom from arthritic attacks which commonly follow the uninterrupted attack.

Immediate exciting cause.—An attack of acute gout is frequently induced by unusual indulgence in food or drink, or by some powerful emotion—such as a fit of anger, worry, or anxiety, or by exposure to cold, or by the receipt of some injury.

Clinical features of acute gout.—A slow deposition of sodium biurate within the joints, accompanied by twinges of pain, may occasionally precede the acute attack; but, as a rule, no warning ushers in the first attack of gout, and the individual usually feels in good health just prior to the attack. Subsequent attacks, however, may be preceded by symptoms of dyspepsia, constipation, mental depression, or loss of appetite.

The seizure of acute gout most frequently occurs in the early hours of the morning, but may come on at any hour of the day or night. Usually between the hours of one and four in the morning the patient is awakened by severe pain, generally in the great toe, sometimes in the ankle, instep, heel, or knee. Slight shivering attacks and a little elevation of temperature may follow. The pain increases in intensity, so that the slightest jarring of the affected part may cause extreme torture. After some hours, partial abatement of the pain occurs, and is accompanied by gentle perspiration. In the morning the toe is swollen, and the skin over the affected joint is of an intense red colour, or purple-red, or a livid-red, contrasting with the pale red or rose colour of the skin over the affected joints in cases of acute articular rheumatism. The discoloured skin is tense, shiny, and extremely tender, and the veins are distended. The extreme pain to touch over the joint affected with acute gout is in marked contrast to the much less painful reaction to touch over the joint affected

with acute rheumatism. On the second night the severity of the pain may recur, and such recurrences may, in the absence of suitable treatment, occur for many days. The pain in the joint is excruciating, and is quite out of proportion to the external signs of inflammation. When the attack is subsiding the swelling and redness of the affected part lessen, the skin itches and pits on pressure, and desquamation follows. Sir Willoughby Wade * has pointed out that in an acute attack of gout in the great toe a line of tenderness extends from the base of the great toe across the foot to the outer side. This line is the site of a nerve-trunk, which is distributed to the periphery of the great toe. The cause of the tenderness is probably due to a deposition of sodium biurate in the nerve sheath, or in the nerve itself. The œdema around the joint is characteristic, and is of great assistance in distinguishing the affection from rheumatism. Gouty inflammation of a joint is not followed by suppuration. The temperature most commonly ranges from 99° to 102° F., and the attack is generally accompanied by thirst, anorexia, and constipation, whilst the urine is scanty, high-coloured, and usually deposits amorphous urates on cooling. In very severe attacks of acute gout a temperature as high as 105·8 has been recorded; such an abnormal elevation of temperature is frequently accompanied by severe vomiting. Both conditions point to a profound toxæmia. Temporary albuminuria has been frequently observed during the early stages of an attack of acute gout, and occasionally slight albuminuria lasts throughout the attack. The pulse is generally full and of high tension, but, apart from the acute attacks, my experience is that arterial tension is not much higher in gouty individuals than in other persons of the same age.

An attack of acute gout lasts on an average from eight to fourteen days in persons of strong constitution, but with

* *Brit. Med. Journ.*, 1897, i.

advancing age the duration of the attack becomes prolonged. A first attack of gout may not be followed by another, provided attention be paid to diet and to the general mode of life. On the other hand, frequent recurrences may supervene. At first the attack of gout is most liable to occur towards the end of winter or beginning of spring, but after repeated annual attacks at the period mentioned, autumnal attacks may be added, or even, in exceptional cases, summer attacks. Although the majority of first attacks of gout occur in the great-toe joint, yet the disease may start in other joints, of which those most commonly so affected, placing them in their order of liability to such attacks, are the ankles, the knees, the small hand-joints, the elbows, and, rarely, the shoulders and hips. The selection of any particular joint for a primary attack is no doubt dependent on slight inflammatory or trophic changes in the particular joint from some recent injury or strain.

Cases of typical acute gout are now much less frequent than they were in the days when the disease was so graphically described by Sydenham. This is mainly due to the greater temperance in eating and drinking which prevails in the present age, and in part, no doubt, to the spread of athleticism, and to the development of healthy outdoor exercises. Still, in many cases the faults of the ancestors have transmitted to their descendants a tendency to the minor forms of gout, which frequently require treatment at the hands of the physician.

Transient albuminuria occurs in gout, especially during the acute attacks. The frequency of its occurrence and its amount furnish an index of the degree of renal inadequacy. Transient glycosuria also occurs, and may be regarded as evidence of hepatic inadequacy.

Clinical features of chronic gout.—In the earlier attacks of gout it is not usual for more than one or two joints to be affected, but after repeated seizures a number of joints may become involved. As the recurrence of gout

becomes more frequent the attacks also become more prolonged, and last for weeks or even months unless efficacious treatment is resorted to. In chronic gout the deposits of sodium biurate linger in the joints, leading to deformities and crippling of the parts. Slight recurrences readily occur, and various forms of irregular gout may then become added to the gouty condition.

In the subjects of chronic gout tophi are apt to form in various localities ; these deposits are most frequently seen in the male sex, and constitute the so-called *tophaceous gout*. These tophi consist mainly of deposits of sodium biurate under the skin, and are principally found in the auricles of the ears, in the vicinity of joints, and in bursæ over joints. If excessive accumulation of the biurate occurs, these tophi assume a great size, and may then cause the integument to give way, when a discharge of a thick creamy fluid containing an abundance of crystals of sodium biurate takes place. The swelling in the vicinity of a joint may give rise to fluctuation, but such swelling should never be opened. Tophi may communicate with a joint, or may be situated beneath the skin and remote from a joint. Occasionally they are present in large size in the vicinity of a joint, which otherwise appears free from the disease and whose mobility is unimpaired.

In connection with chronic gout considerable enlargement and deformity of joints may occur to which the deposits of sodium biurate only contribute in small part. In such cases the enlargement is due to thickening of the synovial membrane, and to overgrowth of the cartilages and of the ends of the bones. This form constitutes the so-called *chronic deforming gout*. Permanent deformity of the affected joints may result, and partial dislocations and ankyloses may also occur. On the other hand, the uratic deposits may undergo complete solution, and the joint be left in an apparently normal condition.

The kidneys in chronic gout.—The urine of chronic

gout is somewhat increased in quantity, and is of lower specific gravity and somewhat paler than normal. The amount of uric acid eliminated is diminished. A trace of albumen is frequently present, and permanent albuminuria is a fairly common occurrence in confirmed gout. If the renal condition is allowed to become very aggravated, then cardiac failure follows, with pulmonary congestion, œdema of the lungs, bronchitis, congestive enlargement of the liver, gastric catarrh, dropsy, and symptoms of uræmia. In such cases pneumonia is apt to supervene and to be attended by a fatal issue.

Changes in the heart and circulation, consequent on gouty affections of the kidneys, are indicated by hypertrophy of the left ventricle, a strong cardiac impulse, displacement of the apex beat to the left, loudness and occasional reduplication of the first sound, and accentuation of the aortic second sound. The pulse is of high tension, and the arteries are hard, tortuous, and sometimes atheromatous. Under such conditions a cerebral hæmorrhage may occur. If compensation fails, then dilatation of the heart occurs, the area of dulness is greatly increased, the action of the heart becomes rapid, and the usual signs of back-working of the blood from the left side of the heart follow.

Although granular kidney is fairly common in connection with chronic gout, yet it is not invariably present. Certainly some patients may have gout and never develop granular kidney, and on the other hand some may have granular kidney and never gout; so that, however close the relation may be, it is not constant or essential. As West has pointed out, gout and granular kidney are both of them very common affections, and sufficiently common to be not infrequently associated accidentally without any causal connection. Still, making allowance for this, the association seems altogether more common than mere coincidence could account for.

In men in the fifth and sixth decades albuminuria, apart

from gout, is by no means infrequent and not always serious. It is probably the expression of pre-senile changes in the kidneys. The albuminuria and the number and variety of the casts are not of as much importance in prognosis as are other factors. The facts indicative of serious disease are :—(1) Persistent low specific gravity of the urine (1008 to 1012); (2) marked arterial sclerosis, with the apex beat an inch or two outside the nipple line, and a ringing accentuated aortic second sound; and (3) albuminuric retinitis. A trace of albuminuria and a few casts are the danger signals.

West concludes, with respect to the relationship of both gout and lead to granular kidney, that, though each may produce chronic changes in the kidney, neither causes granular kidney; but the presence of granular kidney greatly increases the liability of the patient to gout on the one hand and lead-poisoning on the other, or to both together, and in each affection alike greatly increases the gravity and risk.

Croftan * states that he has demonstrated that both xanthin and hypoxanthin, when injected hypodermically in the strength of 0.3 to 0.7 per cent. watery solution for a period of several months, produce granular degeneration of the epithelial cells lining the convoluted tubules and a proliferation of the endothelium of the intertubular capillaries. Albuminuria invariably occurred after a period of three months, so that he concludes that the presence of minute quantities of purin bases in the circulation is capable of producing marked kidney changes. He has compared these changes with those of chronic lead poisoning, and finds that they are identical. As he considers that the kidney changes of gout are identical with those of chronic lead-poisoning, he infers that the organic kidney changes in gout may be produced by purin bases. On the other hand, he finds that uric acid injected into the circulation of healthy animals for a period of over three months produces no kidney changes whatever.

* *Journ. of American Med. Association*, 1899.

CHAPTER VII.

THE URINE AND URIC ACID.

The urine in gout—Uric acid excretion—Uric acid and urea elimination—The amorphous urate deposit—Estimation of uric acid—Gowland-Hopkins method—Otto Folin method—Methods of Dimmock and Branson—Plumbism and gout.

The urine in gout.—Considerable difference of opinion exists as to whether the excretion of uric acid is diminished both during the paroxysm of acute gout and in connection with chronic gout.

The uric acid theory was to a great extent based on the view held by Sir Alfred Garrod that the excretion of uric acid is diminished during the paroxysm, this being associated with a retention of uric acid in the system. The results obtained by different observers as to the excretion of uric acid in cases of gout will therefore be considered.

Pfeiffer* compared the quantities of uric acid contained in the urine of gouty patients at various ages, in whom the complaint had not yet become chronic, with the quantities contained in the urines of healthy subjects at the same age. For purposes of comparison the quantities of uric acid found by him were calculated in grammes per 100 kilogrammes of the body-weight. His results were as follows:—

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 „

* *Berlin. klin. Woch.*, 1892.

These results indicate that the amounts of uric acid excreted by gouty subjects were always rather lower than the quantities excreted by healthy persons of the same age.

J. Fawcett* has examined the urine of a series of patients with gout, estimating the uric acid by the Gowland-Hopkins process. He found that the amount of uric acid excreted was very variable, but that in the majority of cases it was distinctly below the average excreted by a healthy man on a similar diet. During acute attacks there was an increased output of uric acid, which was usually most marked towards the end of the attack. The uric acid excretion did not vary inversely to the acidity of the urine, nor was there any definite relationship between the quantity of urine passed and the amount of uric acid excreted.

In the following table are the results of the daily determinations that I made for eight successive days respectively of the total uric acid excretion in the urine of three persons, viz. (a) a male patient suffering from an attack of subacute gout supervening on chronic gout; (b) a male patient suffering from chronic gout and lead-poisoning, with recent pain in the right metatarso-phalangeal joint and in both ankle joints; (c) a healthy man. The quantities of uric acid in the three cases are given in grammes, and are calculated per 100 kilogrammes of the body-weight. All the individuals were between forty and fifty years of age.

TABLE XIV.

Showing the daily elimination of uric acid in (a) a case of subacute gout; (b) a case of chronic gout and plumbism; (c) a healthy person. Quantities of uric acid given in grammes per 100 kilogrammes of the body-weight. All the individuals between forty and fifty years of age.

Subacute gout.	Chronic gout.	Healthy subject.
0.260 gm.	0.578 gm.	1.105 gm.
0.263 „	0.617 „	1.027 „
0.315 „	0.665 „	1.020 „

* *Guy's Hosp. Reports*, 1895, vol. lii.

TABLE XIV. (*continued*).

Subacute gout.	Chronic gout.	Healthy subject.
0.350 grm.	0.715 grm.	1.376 grm
0.442 „	0.443 „	1.175 „
0.556 „	0.372 „	1.030 „
0.506 „	0.593 „	1.252 „
0.494 „	0.594 „	1.203 „
0.398 „ (average)	0.572 „ (average)	1.148 „ (average)

On the other hand, detailed analyses of the urine were made in two cases of typical gout by Chalmers Watson, a daily examination of the urine being made for many weeks. The results of this investigation showed no disturbance in the uric acid elimination either before, during, or after the paroxysm.

Chalmers Watson has also recorded a series of observations, the results showing an actual increase of uric acid excretion during the attack of gout.

From the analyses made by a number of observers Minkowski states that the following conclusions may be drawn:—(1) The daily excretion of uric acid in the intervals between acute attacks ranges within the same limits as does the excretion in healthy individuals. (2) In chronic gout, even in those cases in which there is marked deposition of biurates in the tissues, a constant variation from the normal amount of uric acid excretion in any one direction has not been definitely proved. (3) Immediately preceding an acute attack there is regularly a diminution in the amount of uric acid eliminated in the urine, whereas during and after the attack the uric acid output is increased. Futcher's analyses in a number of cases fully accord with the statement contained in section 3, but they differ materially from those stated in section 2. He almost always found a marked diminution in the uric acid excreted in the intervals between acute attacks in chronic tophaceous gout.

Ratio of uric acid elimination to that of urea.—Haig has advanced the theory that normally there is a constant ratio of 1 to 35 between the uric acid and urea formation, and that if the uric acid excretion falls below this ratio it is due to the retention and storage of uric acid in the liver, spleen, kidneys, joints, and fibrous tissues, whereas an increase in the proportion of uric acid to urea is due to the washing out from its storage places of the deposited uric acid. According to this view, the amount of uric acid produced in relation to urea in each individual is a constant factor, the variations in the amounts eliminated being due on the one hand to excessive storage, and on the other to the discharge of the stored-up supply.

This theory of the existence of a normal ratio of uric acid to urea, and of every departure from it being due to a pathological cause, is disproved by the following experiments:—(1) Bleibtreu and Schultze,* experimenting on themselves, showed that the ratio between uric acid and urea can be considerably altered by means of the diet without the general health being influenced. (2) Herringham and Groves,† as the result of a series of experiments that they made, entirely fail to corroborate Dr. Haig's observations, and think that either what was true for his system was not true for theirs, or that Dr. Haig's results were, to quote their own words, "inaccurate and deceptive owing to his having employed a very uncertain and inaccurate method for the estimation of uric acid." (3) The following results of the determinations which I have made of the total daily eliminations of uric acid and urea in the urine of a healthy adult man, and which consist of observations extending over a period of fifty days, show that the ratio of uric acid to urea varied from 1 : 28 to 1 : 55 (the average being 1 : 42), although throughout the entire period the individual remained in good health.

* *Pflüger's Archiv*, Bd. xlv.

† *Journ. of Physiology*, 1891.

TABLE XV.

Fifty daily eliminations of uric acid and urea of a healthy adult man on a mixed diet.

No. of oz. of urine per diem.	Uric acid excreted per diem (gramme).	Urea excreted per diem (grammes).	Ratio of uric acid to urea.
63	0.654	28.34	1 : 43
68	0.714	31.62	1 : 44
72	0.626	29.82	1 : 47
42	0.532	29.39	1 : 55
61	0.819	30.19	1 : 37
56	0.663	25.22	1 : 38
65	0.616	27.67	1 : 45
59	0.612	24.44	1 : 40
41	0.826	30.32	1 : 37
57	0.705	21.91	1 : 31
49	0.618	31.27	1 : 50
63	0.751	27.57	1 : 37
48	0.722	28.89	1 : 40
64	0.569	23.44	1 : 41
51	0.652	29.89	1 : 46
60	0.608	27.00	1 : 44
56	0.591	27.71	1 : 47
50	0.561	27.54	1 : 49
60	0.630	27.91	1 : 44
45	0.742	26.56	1 : 36
45	0.550	23.60	1 : 40
60	0.640	31.34	1 : 49
61	0.581	28.34	1 : 49
61	0.537	22.35	1 : 41
64	0.572	26.49	1 : 46
53	0.595	21.24	1 : 36
55	0.764	24.73	1 : 32
69	0.637	28.58	1 : 45
63	0.526	23.13	1 : 44
72	0.583	28.88	1 : 49
45	0.620	24.26	1 : 39
45	0.698	28.01	1 : 40
52	0.680	30.04	1 : 44
69	0.705	33.16	1 : 47
40	0.837	25.62	1 : 31
42	0.728	30.54	1 : 42
67	0.665	30.11	1 : 45
44	0.550	29.50	1 : 53
54	0.554	29.88	1 : 54
62	0.582	26.13	1 : 45
55	0.515	22.15	1 : 43
55	0.632	27.14	1 : 43
54	0.585	28.34	1 : 48

TABLE XV. (*continued*).

No. of oz. of urine per diem.	Uric acid excreted per diem (gramme).	Urea excreted per diem (grammes).	Ratio of uric acid to urea.
66	0.776	28.05	1 : 36
49	0.536	25.20	1 : 47
67	0.560	23.56	1 : 42
45	0.550	21.63	1 : 39
35	0.660	23.10	1 : 35
55	0.624	23.09	1 : 37
87	0.691	19.76	1 : 28

TABLE XVI.

	Excretion of uric acid.	Excretion of urea.	Ratio of uric acid to urea.
Daily average in grammes . . .	0.639	26.89	1 : 42
Daily average in grains . . .	9.8	415.0	1 : 42
Average in 24 hours for each lb. of body weight (in grains)	0.07	3.19	—

It is evident from the above results that no constant ratio exists in a given individual between the excretion of uric acid and urea.

Amorphous urate deposit of urine. — Sir William Roberts * has shown that the amorphous urate deposit of human urine is of the same composition as the solid or semi-solid urinary excrement of birds and serpents, the only difference being one of physical form. The deposit from human urine is amorphous, whilst the urinary excrement of birds and serpents consists of minute crystalline spheres. Sir William Roberts shows that this difference in physical form is a mere accident of molecular aggregation, since, under certain conditions, the amorphous urate deposit can be transformed into crystalline spheres, whilst

* Croonian Lectures on "Uric Acid Gravel and Gout," 1892.

the crystalline urinary substance of birds and serpents can be converted into amorphous deposit. Bence Jones * was the first to show that the amorphous urate deposit yielded to water a soluble moiety consisting of true biurate, and left a sediment consisting of pure uric acid, and from the results of his analyses he inferred that the amorphous urate deposit consisted of, or at least often contained, a molecule of biurate in loose combination with a further molecule of uric acid. Sir William Roberts took up and continued the investigation dropped by Bence Jones thirty years before, and has shown that a third order of uric acid salts—the quadriurates—exists, and that the amorphous urate deposit of human urine and the urinary excretion of birds and serpents belong to this order, and consist of a compound of biurate and uric acid in the proportion of one molecule of each. Sir William Roberts concludes that the quadriurates are the physiological combinations of uric acid.

The amorphous urate or quadriurate deposit of urine is generally referred to as consisting of a mixture of the potassium, sodium, ammonium, and calcium urates. As far as I can ascertain, however, no quantitative determination of the bases in the deposit has yet been made. The nearest approach to it is an analysis made by Sir William Roberts † of a sample of amorphous urate deposit prepared by an artificial process with potassium carbonate, which would therefore most probably contain more potassium than the natural deposit. I therefore considered it advisable to determine the actual bases present in the amorphous urate deposit and their relative proportions.

Composition of the amorphous urate deposit of urine.—The deposit was obtained from several gallons of acid urine passed by patients suffering from febrile diseases, and was collected on a filter and allowed to drain.

* *Journ. of the Chemical Society*, 1862, vol. xv.

† Croonian Lectures on "Uric Acid Gravel and Gout," 1892, p. 20.

It was decomposed by boiling with distilled water and excess of hydrochloric acid, the mixture was then allowed to cool, filtered from the deposited uric acid, and the filtrate, which then contained the bases in the form of chlorides, was evaporated to dryness. The residue was taken up with distilled water, filtered from the minute amount of uric acid left in solution after precipitation of the bulk of the acid, and evaporated to dryness. Part of the residue was submitted to qualitative analysis, and found to contain ammonium, sodium, and potassium, with very small traces of calcium and magnesium. The amounts of ammonium, sodium, and potassium were then estimated in the usual manner in the other portion, when their relative quantities were found to be as follows :—

	<i>Parts per 100.</i>
Ammonium	46
Sodium	40
Potassium	14

These amounts, calculated as the respective quadriurates, would approximately give the following composition for the amorphous uratic deposit that naturally forms in acid febrile urines :—

7 molecules $\text{NH}_4\text{HC}_5\text{H}_2\text{N}_4\text{O}_3$, $\text{H}_2\text{C}_5\text{H}_2\text{N}_4\text{O}_3$ —Ammonium quadriurate.

5 molecules $\text{NaHC}_5\text{H}_2\text{N}_4\text{O}_3$, $\text{H}_2\text{C}_5\text{H}_2\text{N}_4\text{O}_3$ —Sodium quadriurate.

1 molecule $\text{KHC}_5\text{H}_2\text{N}_4\text{O}_3$, $\text{H}_2\text{C}_5\text{H}_2\text{N}_4\text{O}_3$ —Potassium quadriurate.

It is possible, however, apart from the quadriurates, that the uric acid is in part excreted in loose combination with some other organic substance. This combination, if it exists, is probably easily broken up, and the uric acid then set free.

Estimation of uric acid in urine.—Various methods have been employed for the estimation of uric acid in the urine, including Heintze's process, Haycraft's process, Fokker's process, Salkowski's process, and Ludwig's modification of Salkowski's process. In connection with all

these processes there are faults or objections from which the following processes are free.

Gowland-Hopkins method.—This process depends upon the fact that when urine is saturated with ammonium chloride all the uric acid is precipitated as an ammonium urate. From the ammonium urate the uric acid is set free, and the amount of it is determined by titration with a standard solution of potassium permanganate. One great advantage of this process is that there is no danger of the reduction of the ammonium urate as there is of the silver urate produced in some of the other processes ; moreover, the ammonium urate is easy to filter, and permits of the liberation of its uric acid with great readiness. Another great advantage of the process is that although xanthin is at first precipitated along with the ammonium urate, yet the subsequent treatment with hydrochloric acid entirely removes it, so that finally it is not estimated along with the uric acid.

The process is worked as follows :—To 100 c.c. of the urine powdered ammonium chloride is added till practical saturation is obtained ; about 30 grammes of ammonium chloride as a rule are required. When a small quantity remains undissolved, after brisk stirring for a few minutes, saturation is sufficiently complete. The urine is then allowed to stand for two hours, during which time, if possible, it is occasionally stirred to promote subsidence, and is then filtered through thin filter-paper, and washed three or four times with a saturated solution of ammonium chloride. The filtrate should remain perfectly clear and bright. The precipitated ammonium urate is then washed off the filter into a small beaker with a jet of hot distilled water, and is heated just to boiling with an excess of hydrochloric acid. The beaker and its contents are allowed to stand in the cold for two hours, when the uric acid separates out completely, and is then collected on a filter and washed with cold distilled water. The filtrate should be measured

before the washing is begun, and 1 milligramme added to the final result for each 15 c.c. of filtrate present—this need never be more than 20–30 c.c. The uric acid is then washed off the filter with hot water, warmed with sodium carbonate till dissolved, and made up with water to 100 c.c. The liquid is now transferred to a flask, 20 c.c. of strong pure sulphuric acid are added, and the mixture is immediately and while warm titrated with one-twentieth normal potassium permanganate solution. The latter should be added slowly towards the end of the reaction, the close of which is marked by the first appearance of a pink colour, which is permanent for an appreciable interval. Previously the disappearance of the colour is instantaneous. The permanganate solution is made by dissolving 1.578 grammes of pure potassium permanganate in a litre of distilled water. 1 c.c. = .00375 gramme of uric acid.

Otto Folin method.—It is contended that the method of Otto Folin is a more accurate method than that of Gowland-Hopkins for the estimation of uric acid in urine. The following is the process:—Take 100 c.c. of urine, add 10 grammes of ammonium sulphate, render it slightly alkaline with ammonia, shake, and set aside for two hours. Collect the precipitated ammonium urate on a filter and wash with 10 per cent. solution of ammonium sulphate. Then dissolve the precipitate on the filter with boiling water made slightly alkaline with ammonia, allow the solution to cool, and make up the volume to 100 c.c. by the addition of water. On adding 15 c.c. of concentrated sulphuric acid the temperature should rise to 55° to 60° C. This temperature is necessary for the final operation, viz. titration with standardised potassium permanganate solution. Add to the result obtained by calculation 1 milligramme, to allow for loss due to the solubility of ammonium urate.

Methods of Dimmock and Branson.—Dimmock and Branson* have recently described three new methods for

* *Lancet*, 1907.

the determination of uric acid :—(a) A measuring process, in which a precipitate of ammonium urate is measured in a tube specially shaped and graduated in parts per cent. of uric acid. (b) A volumetric process in which a precipitate of ammonium urate is collected and washed with a saturated solution of ammonium nitrate until free from chlorides, and decomposed after solution in distilled water by adding in excess a known amount of a volumetric solution of silver nitrate. After filtering off and washing the precipitate of urate of silver, the amount of nitrate of silver in the filtrate is determined by means of a standard solution of thiocyanate of potassium, the filtrate being first rendered acid with a few drops of dilute nitric acid (1 in 3); a few drops of saturated solution of iron alum are used as an indicator. (c) A gasometric process, in which the washed ammonium urate is decomposed by hypobromite of sodium in a specially devised apparatus which can also be used for the determination of urea.

Process (a) is a very convenient method, and gives approximately correct results in a short time. Process (b) is a quick method, and gives very concordant results. Process (c) is suitable for proportions of uric acid ranging from 1 in 1,000 to 1 in 5,000.

General preliminary treatment for all three processes.—The precipitate used in the three foregoing processes consists of ammonium urate, which is obtained by adding ammonium chloride or ammonium nitrate to urine which has previously been rendered slightly alkaline by the addition of 1 per cent. of lithium carbonate, and subsequently boiling, the precipitated phosphates, etc., being removed by filtration. The method employed is as follows :—Take 100 c.c. of clear urine (warm if necessary to dissolve uric acid or urates), and place in a conical flask of about 400 c.c. capacity, add 1 gramme of lithium carbonate, and boil the whole for three minutes. If frothing occurs it can be checked by blowing on the upper portion of the

outside of the flask. Filter the liquid whilst hot, and wash the precipitated earthy salts with a little distilled water until the filtrate measures 100 c.c.

Process (a).—To 50 c.c. of the filtered alkaline urine, which contains the uric acid as lithium urate, add 5 grammes of ammonium chloride, and shake the flask until solution occurs. After three minutes warm the contents of the flask to 50° C. so as to secure a uniform aggregation of the precipitated urate of ammonium. Now pour the whole into a tube graduated in parts of uric acid per 100, allow deposition to take place, and take the reading after twenty-four hours have elapsed. If the urine does not contain a high percentage of uric acid the reading can be taken in four hours. If any ammonium urate adheres to the surface of the glass the tube should be gently rotated.

Process (b).—The ammonium urate is obtained as follows:—To 50 c.c. of the filtered alkaline urine add 15 grammes of ammonium nitrate, and shake the flask until solution occurs. After three minutes warm the contents of the flask to 50° C., as in process (a). Transfer the whole to a beaker, and allow to stand for two hours. Collect the precipitate on a filter paper of 5.5 centimetres diameter, and wash with about 10 c.c. of a saturated solution of ammonium nitrate until no trace of chloride is indicated by the addition of a few drops of a solution of 5 per cent. of nitrate of silver acidulated with nitric acid. After washing the precipitate with about 5 c.c. of distilled water to remove excess of ammonium nitrate, transfer it with the filter paper to a beaker with about 40 c.c. of hot distilled water; solution being effected, pour off from the filter paper and wash the latter with two successive quantities of 5 c.c. of distilled water; to the 50 c.c. of solution thus obtained a measured quantity of the nitrate of silver solution is added—*e.g.* 10 c.c. or 15 c.c. Add about $\frac{1}{2}$ gramme of powdered talc, and stir the whole well, filter into

a flask previously rinsed with a little distilled water, and wash the precipitate with about 10 c.c. of distilled water. Add to the filtrate in the flask a few drops of dilute nitric acid (1 in 3), and a few drops of a saturated solution of iron alum, and titrate with a standard solution of thiocyanate of potassium. The number of cubic centimetres thus obtained is subtracted from the number of cubic centimetres of nitrate of silver solution originally used, and this gives the exact amount of nitrate of silver required for the uric acid in solution. Solutions required

for this process:—Standard silver nitrate solution: $\frac{n}{20}$ solution silver nitrate, 500 c.c.; distilled water, 20 c.c. One c.c. of the above equals uric acid 0.005 gramme. Solution of potassium thiocyanate of equivalent strength to above; dilute nitric acid, 1 in 3.

Process (c).—Dissolve 31 grammes of ammonium chloride in 100 c.c. of urine previously treated with lithium carbonate, decant off the clear portion, and transfer the remainder, with the precipitate, to a narrow cylindrical jar of about 25 c.c. capacity. In a few hours the precipitate will be ready to transfer to a small filter paper, 5.5 centimetres in diameter. Care must be taken that any precipitate adhering to the vessels used is detached and washed out on to the filter paper with some of the clear urine. Wash the precipitate and edges of the filter paper carefully with distilled water, the precipitate being disturbed as little as possible, so that the wash water may percolate through it. The washing of the precipitate may be performed in the following manner. Allow the liquid to drain from the precipitate, then fill the filter paper with distilled water by means of a wash-bottle with a fine jet. Repeat this operation a second and a third time. Test some of the filtrate with a 5 per cent. solution of nitrate of silver, acidulated with nitric acid 5 per cent. Only a very slight precipitate should be given, indicating the absence of any

appreciable amount of ammonium chloride ; but should the filtrate still contain this salt, wash with a small additional amount of distilled water. Place the precipitate with the filter paper in the generating bottle of apparatus, fill the tube up to the mark (25 c.c.) with the hypobromite solution, and lower it into the bottle by means of string. The temperature of the solution should approximate to that of the room in which the operations are carried out. This may be easily attained if the hypobromite solution is immersed for some time in the water vessel in which the generating bottle is placed. Now place the cork in the generating bottle, and plunge the bottle in a vessel of cold water of a similar temperature to that of the hypobromite solution. After two minutes adjust the water level in the measuring burette to zero, and then close the tap and observe if the water level remains constant. In order to test if leakage occurs in any part of the apparatus, alter the water level in the measuring burette ; any defect is then easily seen. Finally, lift the generating bottle and allow the reagent to flow out of the tube, and shake so as to promote the reaction between the sodium hypobromite and the ammonium urate. After ten minutes, during which time the bottle should be shaken at intervals, adjust the level in the two tubes, and read off the percentage of uric acid, as indicated by the nitrogen evolved. The hypobromite solution is prepared as follows :—

Soda solution { Caustic soda, 41 grammes.
 { Distilled water to measure 100 c.c.

Bromine solution { Bromine, 1 c.c.
 { Potassium bromide, 2 grammes.
 { Distilled water to measure 10 c.c.

For use mix equal volumes immediately before being required, and cool.

Plumbism and gout.—Chronic lead-poisoning gives

rise to both chronic kidney disease and gout. A prolonged period of lead intoxication is, as a rule, required to produce true saturnine gout.

The patient suffering from saturnine gout, unlike the majority of sufferers from inherited gout, is pale, thin, and anæmic. The gouty attacks are frequently repeated, and affect many joints, whilst signs of interstitial nephritis make their appearance. If the lead-poisoning has been of short duration the lesions may yield to treatment, but after a prolonged absorption of lead into the system the kidney condition is generally incurable.

In plumbism bluish-black discolorations of the mucous membrane of the intestine occur. These patches, on microscopical examination, exhibit a similar condition to the mucous membrane of the gums affected with the lead line. The dark deposits are on the surface of the membrane, and also in and underneath it. They are not specially associated with the blood vessels, but rather with the lymphatics and the large cells of the mucous membrane. During the attack of lead colic there is heightened arterial tension, which is the cause of the partial suspension of the renal function. In the liver a fatty-granular degeneration of the hepatic cells occurs, together with an intercellular cirrhosis. In the kidneys a very similar change takes place. A parenchymatous nephritis is first produced, and this runs on to an interstitial nephritis.

Sir William Roberts * considered that it was difficult to believe that lead-poisoning produces the same constitutional diathesis as that which exists in true gout, and preferred to think that, while gout and plumbism differ in all other respects, they have one tendency or vice in common, namely the tendency to uratosis—that is, to the deposition of sodium biurate. He regarded this precipitation as a gouty tendency which may be reinforced by lead-poisoning, and the precipitation in connection with plumbism as

* "Transactions of the Medical Society," vol. xiv., p. 88.

one in which lead-poisoning is reinforced by a previously existing gouty tendency.

In the south of England there is an intimate relationship between gout and lead-poisoning ; but, according to the observations of Thomas Oliver, this relationship does not hold good in the north of England. He has observed that workmen from the south who become the subjects of lead-poisoning develop gout in the north of England, whilst the natives of the north, though equally exposed, seldom become gouty, even when the kidneys are affected by the plumbism. At the same time it must be borne in mind that gout, as a disease, is not met with in the north with anything like the frequency that it is in the south of England. This has been ascribed to the difference in the drinking habits of the people, whisky and not malt liquor being the general drink in the north. Oliver, however, does not regard this as a complete explanation, but considers that in some way or other the result is due to external conditions rather than to the use of beverages.

Lorimer * arrived at the following facts and conclusions based on an analysis of 107 cases of gout associated with lead impregnation :—

(1) *Age*.—The first attack of gout in connection with lead impregnation occurs at an earlier age than when independent of it.

(2) *Hereditary tendency*.—In gout associated with plumbism the influence of direct hereditary predisposition is less marked.

(3) *Anæmia*.—In gout the blood corpuscles undergo no change in number and quality, but in gout associated with lead impregnation the red corpuscles are diminished in number, the white sometimes increased, and the red colouring matter is reduced in amount.

(4) *Asthenic type of arthritis*.—From the early age at which saturnine gout occurs, when functional activity is

* *Quarterly Med. Journ.*, 1901.

more vigorous, an acute and asthenic type of arthritis might be expected to prevail. In a number of cases in the first attack, and in a minority of cases in a subsequent attack, the arthritis assumes this type; but in the majority of cases the type of arthritis is asthenic and the accompanying pyrexia slight, with a tendency for the arthritis to pass insidiously into a chronic and adynamic form; the local and constitutional phenomena are less intense, but more persistent, lingering, and obstinate. The asthenic type of arthritis appears to be due to impaired vitality, to the effects of lead on the trophic centres, and to the renal changes.

(5) *The abarticular manifestations of gout* are generally less marked than in ordinary gout, renal affection in lead gout, however, being excepted.

(6) *Arterial thickening and degeneration.*—A sign which was observed to be more or less constantly present, and in two-thirds of the total number of cases pronouncedly marked, was an arterio-capillary fibrosis, along with atheromatous changes, the result of the combined effects of gout and plumbism, leading to premature senile changes in the arterial system. The combined effect of the two toxic influences is to increase and accentuate arterial degeneration and induce cardiac hypertrophy, which is generally present as the disease advances.

(7) *Albuminuria.*—Albuminuria occurs frequently in lead-poisoning; in the 107 cases it was present in 89, either as an intermittent or a permanent condition. In the initial stages it may be absent, or be intermittent; in subsequent stages it is more frequently found, either as an occasional or constant occurrence; but in the later stages it always exists; so that it may be affirmed that albuminuria is one of the most constant, certain, and characteristic symptoms in saturnine gout, and is always present at some time in the progress of the disease.

(8) *Frequency of chronic interstitial nephritis.*—It is,

however, when the combined effects of gout and plumbism are concentrated on the kidney that the distinguishing feature of most serious import arises—namely, chronic interstitial nephritis. Under the influence of lead, there is swelling, degeneration, and shedding of the renal epithelium, glomerulitis, thickening of the vessels, and interstitial nephritis. It is peculiar to the gouty kidney that it is a disease of advancing years; its progress is slow, and its duration long. When, however, the kidneys are assailed by gout and lead, the onset of disease is accelerated and the duration shortened.

CHAPTER VIII.

IRREGULAR GOUT.

Irregular gout affecting the alimentary tract—Irregular gout affecting the air-passages and lungs—Irregular gout affecting the heart and vessels—Irregular gout affecting the nervous system—Irregular gout affecting the genito-urinary system—Irregular gout affecting the skin—Irregular gout affecting the eye and ear—Other irregular gout affections—Retrocedent or metastatic gout.

GOUT appearing in any situation other than a joint is regarded as irregular or abarticular. Different forms of regular gout may accompany arthritic gout, or may take its place, or may alternate with it. Although attacks of irregular gout may occur in persons subject to articular gout, yet they more frequently occur in those who have never suffered from gout in the joints, but who are predisposed to gout either by inheritance or by their mode of life. Metastatic and irregular forms of gout are especially apt to occur in persons of poor physique, and who are broken down in health.

Undoubtedly the terms "irregular gout" and "suppressed gout" have frequently been applied to pathological conditions in no way connected with gout, and it is therefore important that a diagnosis of irregular gout should be based on good and sufficient grounds. The most important points to pay attention to in the diagnosis of irregular gout are the question of heredity, the habits of the patient, the nature of the attack, a careful examination of the urine, and, if possible, of the blood or blood serum, and, lastly, the successful reaction to therapeutic remedies. Cramps

and aching pains in various muscles and tingling sensations in the hands and feet are frequently associated with irregular gout.

It is most probable that the symptoms of irregular gout are not merely dependent on the local deposit of minute crystals of sodium biurate in the affected parts, but are rather due to the selective action of a soluble toxin in the blood on a naturally weak spot. The symptoms vary with the age and constitution of each subject, but in every case they are more liable to develop in that system of tissue which happens to have, from natural or acquired defects, the weakest nutritional activity.

The various forms of irregular gout may be conveniently classified into the following groups:—(1) Irregular gout affecting the alimentary tract; (2) irregular gout affecting the air-passages and lungs; (3) irregular gout affecting the heart and vessels; (4) irregular gout affecting the nervous system; (5) irregular gout affecting the genito-urinary system; (6) irregular gout affecting the skin; (7) irregular gout affecting the eyes and ears; (8) other irregular gout affections.

1. Irregular gout affecting the alimentary tract.—

A gouty tonsillitis is occasionally a precursor of articular gout. It is characterised by intense congestion and œdema of the tonsils and soft palate. It lasts from some hours to three days, but always subsides on the appearance of the gout in the joints.

Acute gouty pharyngitis. — This affection is characterised by a sudden onset, acute course, and sudden disappearance of symptoms. The temperature is generally high, and the local pain is intense and out of proportion to the apparent involvement of the throat. The local condition consists of inflammation of the pillars, soft palate, uvula, and posterior wall of the pharynx, with a general red œdematous appearance, and a tendency for the inflammation to descend to the larynx. The mucous membranes

are free from exudation, and the glands at the angle of the jaw are not involved.

Chronic gouty pharyngitis.—A chronic pharyngitis is a fairly common form of irregular gout, and is also occasionally associated with active gout. As a rule, there is a general irritation and congestion of the whole pharyngeal mucous membrane, with a tendency to lateral thickening. There may be some secretion of tenacious mucus, but not usually to any marked degree. The uvula assumes a dusky-red colour and is œdematous.

Gouty parotitis is an extremely rare form of irregular gout, but when present it seriously interferes with mastication and deglutition. It usually develops suddenly, persists for a few hours, and disappears. Like gouty orchitis, it readily yields to treatment with colchicum, and also rapidly subsides on the appearance of regular gout in one or more of the joints. One case has been reported in which gouty orchitis occurred during an attack of gouty parotitis.

Gouty œsophagismus occasionally occurs, and may be severe.

A sudden gastralgia, with accompanying derangement of the digestive functions, constitutes an occasional form of irregular gout; it may alternate with a true arthritic attack, or with urticaria, or eczema. Acute attacks of *enteralgia* also occur in gouty subjects.

Gouty dyspepsia is a very common form of irregular gout. It is usually accompanied by excessive gastric acidity, flatulence, and heartburn. Gastric pain, dilatation of the stomach, and pyrosis are occasionally associated with this form of dyspepsia, which is frequently of a prolonged and obstinate nature. In other cases slight attacks of gastric catarrh occur characterised by loss of appetite, furred tongue, foul breath, and constipation.

Hyperchlorhydria, or excessive secretion of hydrochloric acid in the gastric juice, occurs in some gouty subjects, and in such should be regarded as a form of irregular gout.

By this, I do not mean that hyperchlorhydria occurs only in gouty subjects, as I have met with many cases of it in individuals who have no tendency to gout, either inherited or acquired ; but I have on several occasions met with it in gouty people, and have not uncommonly seen it alternate with attacks either of regular gout or of some other form of irregular gout. The gastric discomfort does not begin until from one to two and a half hours after a meal, and generally continues up to the next meal, which for a time relieves it. The discomfort may simply be one of distension or oppression, or may amount to severe pain, which is generally described as being of a burning character. The pain is usually referred to the epigastrium, but may also be felt beneath either shoulder blade. The condition is usually accompanied by flatulent distension, acid eructations, and severe heartburn. The eructations give, for the time, considerable relief, as a rule. The effect of this excessive secretion of hydrochloric acid is to cause a too rapid digestion of the proteid elements of the food, with retention in the stomach of the starchy and fatty constituents of the food. In consequence of this retention, the gastric secretion is kept up, while at the same time no constituent is present with which the gastric juice can combine, and, in consequence, an excessive amount of free hydrochloric acid accumulates in the stomach. Undoubtedly, some gouty subjects have the habit of secreting an excessive amount of gastric juice, and especially does this occur as a consequence of the consumption of a diet too rich in nitrogenous substances.

Gastro-intestinal gout.—Attacks of gastro-intestinal gout occasionally alternate with attacks of articular gout. A patient who has been the subject of articular gout may be suddenly seized with epigastric pain, nausea, and vomiting, which recur in bouts. The vomiting is generally repeated in each attack several times, and the attack generally lasts from three to five hours. At other times there

may be intestinal crises, in the form of diarrhœa, lasting from three to four hours, and accompanied by colic and sweating. These gastro-intestinal attacks are accompanied by a marked temporary relief to the joints.

The gastric form of gout manifests itself by the sudden occurrence of abdominal pain, not necessarily associated in any way with the taking of food, and not necessarily referred to any particular spot. The pain may be very severe, so as to cause more or less collapse, and vomiting may occur. This form can only be diagnosed by the absence of other conditions which could cause the pain, and by the complete and immediate disappearance of the pain on the occurrence of an acute attack of regular gout.

2. Irregular gout affecting the air-passages and lungs.

—*Gouty laryngitis*.—Deposits of sodium biurate have been found in the vocal cords, the arytenoids, and the crico-arytenoid ligaments and joints. Congestion and swelling of the mucous membrane occur, and the congestion may extend to the vocal cords. The principal symptoms are hoarseness, irritable cough, and scanty expectoration, which is occasionally streaked with blood.

Gouty tracheitis.—This affection is accompanied by very irritable cough and scanty expectoration.

Acute gouty bronchitis frequently precedes an arthritic attack, and often subsides when the joints become affected. The symptoms of acute gouty bronchitis may be very severe, and the heart's action often becomes irregular and feeble. The expectoration may be blood-stained, and the dyspnœa is frequently severe.

Chronic gouty bronchitis.—This affection is accompanied by an irritable cough and scanty expectoration. It is especially liable to alternate with arthritic attacks.

Gouty asthma.—Attacks may alternate with arthritic attacks, or gouty asthma may occur in early life, and articular gout may develop later, or gouty asthma may

be the only form of gout inherited from a parent who was the subject of articular gout.

Gouty pulmonary congestion.—This is usually at the base of the lungs, but occasionally may be apical. It is accompanied by hæmoptysis, and is a condition that may be mistaken for phthisis.

3. Irregular gout affecting the heart and vessels.—*Cardiac disorders.*—Paroxysmal attacks of cardiac irritability are very apt to occur in gouty subjects. The attacks are nervous in origin, and are evidenced by irregularity, tachycardia, or occasionally bradycardia, and by dyspnœa if organic disease of the heart exist.

Alterations in the cardiac action, from the influence of the toxic agents on the nervous mechanism of the heart, *e.g.* arrhythmia, tachycardia, bradycardia, angina, frequently occur. The liability to these disturbances is increased if myocardial degeneration is also present.

Sansom * states that he has observed a considerable number of cases of gout and gouty manifestations in which there has been a course of severe or of peculiar and perplexing symptoms after an attack or after repeated attacks of influenza. He thinks that the most important association of the post-influenzal irregular heart is with gout and goutiness. In many cases the heart symptoms—pain, distress, and heart failure—have been very severe, and in some fatal.

Mitchell Bruce accepts as evidence of the gouty nature of a cardiac disorder various circumstances, or combinations of circumstances, which may be stated briefly as follows :— (1) a personal history of declared gout, present or previous ; (2) a personal history of free living, and usually of hard work, with occasional explosions suggestive of irregular gout, in the form of hæmorrhage from the bowels, intestinal fluxes, sick headaches, irritability of the bladder, eczema, insomnia, and fits of irritability or depression ;

* *Lancet*, October, 1899.

(3) relief of these symptoms by treatment directed against gout—purgatives, exercise, spare living, and various alkaline salts ; and (4) a family history of gout, megrim, gravel, glycosuria, asthma, and their allies—well marked, direct, and often on both sides.

The first evidence of gouty trouble in connection with the heart frequently comes on after exertion. The following is the description given by Mitchell Bruce of the incidence of such an attack. The patient becomes conscious of a distressing sensation in the præcordia—most likely behind the middle of the sternum. This is pain, or it may be but “oppression,” driving him to unbutton his vest, or to unfasten his jersey, which seems to him to gird him too tightly. If the attack occur during exertion, he has to pause, looks anxious, and clings to the nearest support. In many instances the paroxysm is anginal. There may be no palpitation, unless the attack has come on in bed, when irregular cardiac action—“fluttering”—is common. In either case the mind becomes anxious. A sense of weakness or faintness pervades the chest and head, the extremities become chill, and a cold sweat breaks out on the surface of the body. Presently abundant flatulent eructations occur ; and with these the distressing sensations, and the attack as a whole, pass away.

The pain complained of by the gouty subject appears to be essentially cardiac. When fully developed it occupies the common situations of the pain in structural disease of the heart, particularly such as involves the aortic valves and the root of the aorta. It is referred to mid-sternum ; or it is a “tearing sensation at the heart.” In other instances it is not a pain proper, but a sense of oppression across the chest, or a sense of tightness, or of burning like heartburn. In its full development it is anginal, and may then be accompanied by a variety of disturbances of associated parts, as we have already described. Palpitation occurs in different forms and at different times

in the subjects of gouty heart. Palpitation in these subjects may be readily induced by indigestion, and as readily relieved by eructation. In other instances of the gouty heart it is entirely absent. Faintness may be of different degrees, from simple "giddiness" to complete syncope. Respiratory disturbance and distress are prominent features of some of the acute attacks. In other instances the breathing is entirely unaffected.

In a patient complaining of such symptoms physical examination of the heart generally reveals the absence of any valvular lesion. Usually there are present a feeble impulse, ill-defined limits of præcordial dulness, feeble, dull or indefinite sounds, and no murmur. This indeterminateness of the results of physical examination may be regarded as a characteristic of the gouty heart. The pulse is frequently irregular, sometimes intermittent. Often it is peculiarly indefinite, or indeterminate, like the præcordial signs. The tension is either moderate or actually low. In some instances the wall of the vessel is thickened.

Anginal and pseudo-anginal attacks.—These attacks may occur either in connection with chronic gout, or as an occasional manifestation of irregular gout. True angina pectoris, associated with widespread arterial degeneration and softening of the walls of the heart, occasionally occurs in gouty subjects, the gouty condition no doubt being a powerful factor in the production of the degenerative changes leading up to the anginal attacks. Pseudo-angina pectoris unassociated with any general arterial degeneration also may occur in the gouty, and is accompanied by severe pain in the region of the heart, passing down the left arm, a feeling of suffocation, flatulency, and gastric disturbance.

The toxic agents of gout acting on the walls of the heart may set up chronic myocarditis, with disease of the coronary vessels. Pericarditis is an occasional termination in cases where the gouty form of Bright's disease is developed.

Gouty phlebitis.—This affection is a fairly common complication of chronic gout, but it may also be a phase of irregular gout. It may occur either in the veins of a portion of a limb which is the seat of gouty inflammation, or in veins quite apart from the presence of gouty inflammation in the vicinity. The veins of the lower extremities are most commonly affected, especially the veins of the calf. This affection is not uncommonly of prolonged duration, and is very apt to recur. In consequence of the thrombosis that ensues great care must be exercised to prevent detachment of the clot, and the consequent risk of pulmonary embolism. The œdema of the limb consequent on the thrombosis generally persists for some time.

When the deep veins of the calf are affected, the first symptom is frequently a sudden and acute cramp-like pain, which is soon followed by deeply-seated tenderness to pressure. There is a tendency to frequent recurrences of the attacks, which are especially prone to occur when the patient is fatigued or below the usual standard of health. It is sometimes the only manifestation of gouty inheritance, but is frequently combined with other obviously gouty symptoms.

There is no doubt that persons of gouty habit or ancestry are more than commonly liable to phlebitis, and that in them the affection usually has certain distinguishing characters. To quote Sir James Paget's description: "Gouty phlebitis is far more frequent in the lower limbs than in any other part; but it is not limited to the limb that is, or has been, the seat of ordinary gout. It affects the superficial rather than the deep veins, and often occurs in patches, affecting (for example) on one day a short piece of a saphenous vein, and on the next day another piece of the same or a corresponding piece of the opposite vein, or of a femoral vein. It shows herein an evident disposition towards being metastatic and symmetrical: characters which, I may remark by the way, are strongly

in favour of the belief that the essential and primary disease is not a coagulation of the blood, but an inflammation of portions of the venous wall."

4. Irregular gout affecting the nervous system.—*Migraine and neuralgia.*—Attacks of migraine and of neuralgia not unfrequently occur in persons of gouty habits. Neuralgia is the commonest and also one of the most troublesome of gouty derangements. The fifth nerve, posterior tibial, sciatic, and occipital are the ones most frequently involved, and their derangements are liable to appear and disappear suddenly, or take the place of other manifestations of the disease.

Neuritis.—Neuritis is by no means infrequent, and is probably most encountered in the third and fourth decades of life; the symptoms are numbness, tingling, loss of power in the affected part, muscular wasting occasionally, and sometimes very severe pain. The sciatic nerve and the brachial plexus and its branches are most liable to this form of neuritis. The affection is probably started by a deposit of sodium biurate in the nerve-sheath setting up a perineuritis, with subsequent effusion of lymph within the sheath, and consequent compression of the nerve fibres. When this occurs in the sciatic nerve it is the cause of the severe and prolonged sciatica that some gouty subjects suffer from. In sciatica of gouty origin the affection is not always confined to the sciatic nerve alone; frequently the crural nerve is simultaneously involved, and under certain circumstances the obturator nerve is also affected.

Apart from injury, gout is undoubtedly a prominent ætiological factor in the development of brachial neuritis. The neuritis may be accompanied by any of the ordinary manifestations of gout, or by any of the forms of irregular gout. The prominent symptom in every case is pain, sometimes sudden in onset, but more often slight and occasional at first and only felt on making certain move-

ments, notably those of raising the arm, but it increases and becomes more continuous with paroxysmal exacerbations. The acute forms are probably in most cases at the outset acute inflammations of the fibrous structures of the muscles, or as the condition is aptly termed "fibrositis." The mischief spreads from the muscles to the sheaths of the nerves, and often to other fibrous structures in the vicinity, and when the acute condition subsides a chronic neuritis is often left. The pain is often very severe, and wasting may go on to an extreme degree ; while, on the other hand, cases occur in which the extent of the neuritis is very limited and the symptoms are slight. The duration is seldom less than three or four months, and may extend over a year or more. The older the patient the more chronic the case is likely to be, while much depends on the degree of rest which the parts obtain.

Insomnia is an occasional accompaniment or manifestation of irregular gout. This condition may be due to the ingestion of improper food, giving rise to abnormal gastric fermentation, or to hepatic derangement. In such cases it is frequently accompanied by heartburn and palpitation.

Mental depression is frequently associated with gouty attacks affecting the liver, and, as a rule, is almost immediately relieved by a dose of blue pill at night, followed by a purge of Epsom salts in the morning.

Attacks of *vertigo* and *epilepsy* are occasionally associated with the gouty state. Gouty inflammation of the meninges of the spinal cord occasionally occurs, associated with pain and tenderness over the affected area, and with pain and hyperæsthesia in the lower extremities. Three cases of transient paraplegia supposed to have been due to gouty congestion of the spinal cord have been described.

5. Irregular gout affecting the genito-urinary system.
—*Gouty kidney*.—It is possible that a functional affection of the kidneys may occur in connection with gout. This

functional affection may subside if the exciting cause of it be removed, or it may pass on to a structural lesion, which is then of the contracted granular type. The symptoms associated with the gouty kidney so produced are those usually met with in cases of contracted granular kidney. There is increased frequency of micturition, and more than the normal quantity of urine is passed. The urine may or may not contain a small quantity of albumen. The arterial tension is increased, and this constitutes a point of great importance to be noticed, since cerebral hæmorrhage, hypertrophy and dilatation of the heart, and congestion of the lungs are liable to supervene on this condition.

Uric acid gravel and calculi.—These deposits frequently occur in early life among those with a gouty inheritance, and are not uncommonly followed later in life by true gouty attacks. The presence of uratic deposits in the kidney may produce a referred pain down the back and sometimes the front of the thigh. This pain may be sufficiently severe to interfere with walking, and is apt to be confounded with sciatica or rheumatism. The pain is a referred one and is dependent on the irritation produced within the kidneys, which irritation is caused by uratic deposits, or by the passage of fine uric acid gravel, or occasionally by the passage of an excessive amount of uric acid, as sometimes occurs in cases of gouty diabetes. A careful examination of the urine and palpation of the kidneys will reveal the source of such referred pains.

Irritability of the bladder is associated with the passage of scanty urine of high specific gravity, which yields a copious deposit of amorphous urates on cooling.

Gouty orchitis and *epididymitis* are rare forms of irregular gout, but undoubtedly these affections occasionally occur quite independently of any urethral infection. The gouty origin is frequently shown by the rapid subsidence of the

orchitis and epididymitis if an attack of articular gout supervenes, and also by the successful results following treatment with colchicum.

6. Irregular gout affecting the skin.—Gouty subjects are peculiarly liable to certain affections of the skin, and amongst those who have inherited a gouty tendency the skin affections may constitute the only manifestation of gout. The following are the skin affections liable to be associated with the gouty state.

Eczema.—This disease of the skin more frequently occurs in association with gout than any other. It often precedes arthritic gout, and may even occasionally be the sole manifestation of gout. It may assume either the acute or chronic form, and generally occurs symmetrically on both sides of the body. It is most prone to occur in spring, and is very apt to recur. Gouty eczema occurs most frequently in the following situations, viz. the external ear and around it, the face and forehead, the back of the neck, the flexures of the joints, the scrotum and prepuce, the backs of the hands and feet, the interdigital surfaces, and more rarely the arms, legs, and trunk.

Some authorities have doubted whether there is such a disease as a gouty eczema pure and simple, but it is a common experience, in my practice, to find that eczema is very prone to occur among the gouty. Among the descendants of gouty ancestors, I frequently find that certain members suffer from recurring attacks of eczema, while others suffer from regular gout. Again, with some individuals it is not uncommon to find attacks of eczema alternating with attacks of articular gout, or to find that an attack of eczema subsides with almost startling rapidity when an attack of true gout supervenes, or *vice versa*. It is true that it is impossible to diagnose a gouty eczema at sight, but a careful inquiry into the patient's history, and into the family history, makes the diagnosis, in my opinion, in many cases a certainty.

Herpes is not unfrequently met with in association with gout.

Pruritus and *prurigo* occasionally occur in gouty subjects, especially in connection with gouty glycosuria. Pruritus is generally localised, and especially affects the arms and the vulva; occasionally it is general.

Urticaria sometimes occurs as a result of the gouty state.

For a long time, and by many authorities in this country, psoriasis has been regarded as to a great extent a manifestation of the "gouty diathesis." My experience, however, is that psoriasis is not met with more frequently among gouty individuals than among the non-gouty, and I am strongly of opinion that no such entity as a gouty psoriasis exists.

Pospeloff has observed a macular form of gouty skin eruption. The latter can be seen in three different stages. The first stage consists of disseminated, rusty brown, irregular or dendroid spots, which do not disappear on pressure and are seen chiefly on the shins. Under suitable treatment, and often without it, these spots disappear, but are observed again with each fresh attack of gout. If the original disease persists, owing to the patient's habits, the second stage of the eruption occurs, which consists of bluish-violet spots in addition to those of a rusty brown colour. The spots do not disappear on pressure with the finger, thus indicating an effusion of blood into the skin and cellular tissue. As the blood collects under the horny layer of the epidermis the latter gets soaked and separated, and forms a series of large scales with tooth-like margins of the macerated white horny layer. A microscopical examination of an excised piece of skin by direct and by polarised light shows that the violet-coloured and rusty red spots are due not only to a deposit in the corium of blood pigment, but also of sodium biurate and of crystals of uric acid. If the gout increases a general erythema

of the affected limb occurs ; the reddened skin becomes shiny, sloughs in places, and ulcers are formed ; this constitutes the third stage of these gouty skin lesions.

7. Irregular gout affecting the eye and ear.—Gout certainly plays an important part in eye affections, although in only a few cases have definite deposits of sodium biurate been found in the conjunctiva or elsewhere. Conjunctivitis, episcleritis, sclerotitis, iritis, and iridocyclitis are the most common forms of gouty eye affections, and they are all extremely liable to recur. Gouty subjects are more prone than others to suffer from glaucoma, and cases of hæmorrhagic retinitis and optic neuritis of gouty origin have been described.

Gout may be a cause of ear diseases, especially in causing earache at night and tinnitus aurium. Mirk has recorded deposits in the tympanic membrane, and he is of opinion that some cases with subjective noises are due to gouty deposits in the labyrinth. Gout is also said to exercise considerable influence in the development of exostoses in the external auditory canal. Occasionally a gouty neuritis affecting the terminations of the auditory nerve causes deafness.

8. Other irregular gout affections.—*Glycosuria* and *diabetes*.—The development of glycosuria or diabetes in persons of gouty ancestry is undoubted. The glycosuria is in all probability frequently hepatic in its origin. Glycosuria is generally associated with some form of irregular gout, and but seldom with the ordinary articular gout, but very occasionally it alternates with true gouty attacks, and then, while the glycosuria lasts, the patient is quite free from articular gout, and *vice versâ*. The glycosuria may at first be very slight, but if not checked by proper dietetic treatment it may lapse into true diabetes. With regard to the prognosis in gouty diabetes, much depends on the manner in which the affection responds to dietetic treatment. If the sugar in the urine quickly

disappear, and if several months elapse before its reappearance, then the prognosis is fairly good, and life may continue for many years.

Hepatic congestion.—A condition of congestion of the liver, or possibly of subacute parenchymatous hepatitis, popularly known as “gout in the liver,” is occasionally met with in gouty subjects, or in those who have inherited a gouty tendency.

Pains in the head, chest, abdomen, joints, and other parts, lasting for a few minutes to some hours or even two or three days, are frequently gouty in origin. At times it is difficult to recognise them as forms of irregular gout, but a careful inquiry into the family history and the habits of the patient will often settle the question. Such pains occurring in one who inherits from his family a gouty tendency, or who eats and drinks too much, and at the same time takes too little exercise, are generally indicative of a gouty origin.

During the past few years I have noticed in several cases of so-called “hay-fever” a gouty tendency underlying the local affection. Such cases resisted cure until, in addition to local treatment, attention was paid to the gouty condition, especially with regard to the dietary. These observations confirm those of Karl Grube, who states that in all cases which were treated successfully by him such gouty tendency could be traced to be underlying the local affection. He also points out the fact that hay-fever, like gout, is more common in England than in any other country. Sir Dyce Duckworth, too, has also noticed the connection between gout and hay-fever.

Retrocedent or metastatic gout.—This form of gout occurs when a sudden subsidence of the inflammation in a gouty joint is succeeded by the development of the disease in one or more of the internal viscera, such as the stomach, intestines, heart, or liver. Persons subject to retrocedent gout are generally in a debilitated condition, and of feeble

constitution. The attacks frequently follow an exposure to cold while suffering from an articular attack, and especially after indiscretion in diet. Attacks of retrocedent gout have also not uncommonly followed the extremely baneful practice of suddenly plunging a gouty foot into cold water. If the attacks rapidly shift their position the affection is termed *flying gout*. It is quite possible that attacks of retrocedent gout are caused by a deposition of the crystalline sodium biurate in the affected viscus, and that this crystalline biurate acts as a mechanical irritant, and so produces inflammation of the organ. On the other hand, these attacks may simply be of nervous reflex origin, due to vaso-motor disturbance producing a condition of hyperæmia or congestion of the affected viscus. The following are the principal forms of retrocedent gout, with the symptoms indicative of the sudden transference of the attack to the affected viscus.

Retrocedent gout of the stomach.—The symptoms are severe pain in the stomach, accompanied usually by vomiting and a feeling of general oppression, depression, and faintness. Palpitation may occur.

Retrocedent gout of the intestines.—The usual symptoms are severe abdominal pain, vomiting, tympanites, and constipation.

Retrocedent gout of the heart.—The symptoms are severe palpitation, pain in the region of the heart, a sensation of constriction of the chest, dyspnœa, a small feeble pulse, and great anxiety. Syncopal attacks may occur.

Retrocedent gout of the brain.—Apoplexy is the most frequent symptom. Congestion of the brain or meninges may occur, and may be followed by headache, stupor, convulsions, delirium, and occasionally by maniacal attacks. Transient attacks of aphasia, amnesia, and hemiplegia sometimes occur, and are probably due to congestion of the brain.

Gouty orchitis and parotitis of metastatic origin have occasionally been known to occur.

CHAPTER IX.

DIFFERENTIAL DIAGNOSIS.

Differential diagnosis of chronic diseases of the joints—Forms of rheumatoid arthritis—Distinction of gout from rheumatoid arthritis—Distinction of gout from rheumatism—Distinction of gout from various diseases of the joints—Prognosis in gout.

Differential diagnosis of chronic diseases of the joints.

—The recognition of acute gout is a very easy matter, but the distinction of chronic gout from other chronic diseases of the joints is often a matter of considerable difficulty; a difficulty which is not diminished by the general desire on the part of our patients to have a disease labelled with some distinctive title. There is much looseness in the diagnosis, and consequently in the treatment, of joint affections, due to a great extent to the descriptions of joint diseases in text-books not being up to date with the advances of scientific knowledge as to their mode of origin and pathology. Perhaps the best classification of joint diseases is that of Bannatyne, who divides them into three great classes :—(1) the bacterial or toxic arthropathies; (2) the nerve arthropathies; and (3) the senile degenerative arthropathies. To this division I would add a fourth class—viz. those due to interference with the nutrition of the joints by circulatory changes, such as occur in Raynaud's disease. The term toxic is not meant to be confined to the products of bacterial activity only, but includes those arising from the tissues themselves, or by chemical processes, such as the toxic substance or substances causing gout.

Another classification of arthritic cases is into (1) the essential arthropathies—*i.e.* those in which the joint troubles form the principal or prominent symptom of the disease, such as gout, rheumatism, rheumatoid arthritis, and senile arthritis; and (2) the accidental arthropathies—*i.e.* those which, although they may occur in the course of a disease, yet are not essential symptoms of that disease, such as gonorrhœal, scarlatinal, malarial, tuberculous, syphilitic, pneumococcic, and nerve arthropathies.

With regard to the bacterial arthropathies, considerable discussion has arisen as to whether the bacteria or their products are the cause of the symptoms. I think that the balance of evidence is strongly in favour of the joint troubles being due to the micro-organisms themselves, since the micro-organisms of rheumatism, gonorrhœa, pneumonia, and possibly rheumatoid arthritis, have been found in the joint structures and joint fluids. Moreover, in those cases where operative treatment of the joints has been resorted to, the rapid subsidence of the symptoms points to the joints being the seat of bacterial infection, rather than to their being affected by toxic products elaborated elsewhere. Certainly it may be accepted that infection plays a most important part in the production of joint diseases, while a general defect of nutrition underlies many, if not all, of the chronic forms of arthritis. Unfortunately, the term rheumatism has been applied with too much looseness and too generally. Now that it is known that acute rheumatism is itself an infective disease, it is recognised that many cases of arthritis which have been termed rheumatism certainly belong to the infective class.

I propose first to consider the differential diagnosis of the three forms of chronic joint disease that are most frequently met with, that are most apt to be confounded, and that therefore offer the principal difficulties in diagnosis—*viz.* gout, rheumatoid arthritis, and rheumatism. The differential diagnosis of these diseases is a very important

matter, and it is all the more important to direct attention to such diagnosis, because undoubtedly in the past many cases of rheumatoid arthritis have escaped recognition, and have been diagnosed either as rheumatism or as gout. When it is considered that the treatment of these three diseases is quite different, the necessity for a correct diagnosis is manifest. It is probable that many cases which are diagnosed as chronic rheumatism of the joints are not chronic rheumatism at all; many of them are cases of rheumatoid arthritis, and a fair number are cases of gout. I believe chronic rheumatism of the joints—chronic arthritic rheumatism—to be a comparatively rare affection; at any rate, it is not very frequently met with. Cases are frequently diagnosed as cases of chronic rheumatism, in which there are great deformities of the joints, lipping of the cartilages, osteophytic outgrowths, and grating of the ends of the bones. Those are cases of rheumatoid arthritis. In chronic rheumatism, neither lipping of the cartilages nor the osteophytic outgrowths which are so diagnostic of rheumatoid arthritis ever occur.

Rheumatoid arthritis.—The term “rheumatoid arthritis” is objectionable, as suggesting a causal connection with rheumatism. If, however, it is employed and understood as merely meaning an arthritis somewhat resembling some forms of rheumatism, the term may be retained, although the name “arthritis deformans” is less open to objection. I propose, however, to retain the term “rheumatoid arthritis,” owing to its long usage, as I am afraid that the description of that disease under another and less recognised name may lead to confusion. By rheumatoid arthritis I mean the disease known as “arthritis deformans,” or “polyarthritis deformans,” or “rheumatic gout.” I think that very often the unfortunate name of “rheumatic gout,” as applied to rheumatoid arthritis, is a cause of the two conditions being confused. Certainly it is a name which covers a multitude of sins

and errors in diagnosis, and it is a term which ought to be abandoned.

The cases hitherto grouped together as rheumatoid arthritis undoubtedly include more than one disease. I should define true rheumatoid arthritis as a progressive degeneration of the joints, consisting of changes in the synovial membranes, cartilages, and bones, accompanied by atrophy of some structures and by hypertrophy of others. In chronic cases marked osteophytic outgrowths are peculiar to this disease. Heberden, in 1804, was one of the first to distinguish between this disease and rheumatism. He pointed out that there was swelling of the affected joint, but little or no fever, no great pain, and no redness of the skin; that the disease generally attacked joint after joint, and that it was very crippling; that the fingers and wrists were especially liable to the disease, and that the terminal phalangeal joints of the fingers were liable to become affected with nodosities, which have since become known as "Heberden's nodes."

The disease occurs in acute, subacute, and chronic forms. The chronic form may be chronic from the first, or may be secondary to an acute or subacute attack. The acute and subacute forms are characterised by inflammatory changes in the affected joints, by erosion of cartilages and bones, by nerve and trophic phenomena, and by glandular enlargement. It is polyarticular, and in its acute and subacute forms occurs especially in children and young adults. The disease usually commences in one joint, commonly one of the metacarpo-phalangeal articulations, and then rapidly spreads to most of the other joints. The symmetrical nature of the affection is usually well marked, and the joints are painful, hot, and present a spindle-shaped enlargement, but no outgrowth or thickening of either cartilage or bone during the acute stage. The chronic forms are characterised by progressive thickening and hardening of all the joint structures, by the formation

of osteophytes, by the lipping of cartilages, and by the development of deformities. The disease may affect several joints, or be confined to one or two. It most commonly occurs in middle life, and in females. Comparatively slight injuries of a joint, especially of a small joint, may lead to rheumatoid arthritis, and to an extension of the process to other joints in a symmetrical order. The injuries are frequently the outcome of excessive work and strain, especially in elderly and enfeebled persons with a diminished power of resistance, increasing with years and with imperfect nutrition.

The three divisions of the disease proposed by Charcot constitute the generally adopted classification of the forms of rheumatoid arthritis for a study of their symptoms. They are (1) cases with Heberden's nodes; (2) the general progressive form; and (3) the partial or monarticular form. This last-mentioned monarticular form is, however, in my opinion, an absolutely distinct disease from rheumatoid arthritis, and I shall describe it later among the senile arthropathies.

I. *Cases with Heberden's nodes.*—These cases represent the mildest degree of the disease. The nodes consist of little hard swellings of the finger joints, affecting almost entirely the terminal phalangeal, and are due to a very chronic form of rheumatoid arthritis. This type is more commonly met with in women than in men, and usually at or after the middle period of life. The nodules are due to enlargement of the ends of the bones, which are frequently covered by a pouch of the projecting synovial membrane, which acts somewhat as a bursa. The joints become swollen and tender. The cartilages are softened, and the ends of the bones are eburnated. The enlargements are osseous in character, but there may be a certain amount of increase of the periarticular fibrous tissues. After a time the disease usually becomes arrested, but the swellings remain, and eventually may cause no

discomfort. Treatment cannot produce any diminution in size of the bony growths, but may effect a decrease in size of the periarticular tissues referred to.

Heberden's nodes are frequently associated with some uterine disturbance. Heberden, in his original paper, particularly noted the fact that the thirty-three cases he described occurred only in women, and in women of middle age. This form of rheumatoid arthritis touches a point of age beyond which the influence of the sexual system is likely to be much diminished, and there is undoubtedly a direct connection between it and uterine troubles associated with the climacteric. The affection is not commonly very progressive, and never reaches to much deformity; but, on the other hand, there is no retrocession of the chronic arthritis. The uterine troubles and the active affection of the joints subside together.

Apart from Heberden's nodes, other forms of chronic arthritis are frequently associated with and determined by uterine and ovarian troubles. It has for some time been held that the joint troubles are due to reflex trophic influence, the excessive uterine irritation being reflected from the spinal cord to the joints; but I cannot help thinking that a more probable explanation is that the diseased uterus becomes the channel by which an infective or septic arthritis, generally leucorrhœal in origin, is started in the joints. In a similar way a chronic urethral and prostatic affection in men, quite apart from gonorrhœa, may give rise to a chronic arthritis; such an arthritis may also be started by the use of an imperfectly clean catheter. I have had under me in the course of the past twelve years six cases of severe chronic arthritis, indistinguishable from rheumatoid arthritis, in which the disease followed the removal of both ovaries. Whether in these cases the disease occurred in consequence of the removal of the ovaries, or in association with the diseases requiring their removal, I am unable to say.

2. *The general progressive form.*—Of this there are two varieties—the acute and the chronic. The acute form has been previously referred to. It may resemble, and certainly has been mistaken for, acute articular rheumatism. It generally starts in one joint, and subsequently involves many. There is not much redness of the affected joints, and only moderate fever. It is most common in young adults and young women. Among the last-mentioned it is often connected with recent delivery, rapid child-bearing, or excessive lactation. Rheumatoid arthritis certainly occurs in children, but very rarely, and even more rarely than the joint disease described by Still, to which reference will presently be made.

The chronic form is much commoner than the acute. The joints that have been most especially and actively used, according to the former occupation or employment of the patient, are those which usually show the first signs of the disease. The affection commences with slight swelling and pain on movement. The amount of effusion into the joint is variable, and may be marked or slight. The hands and feet, especially the hands, are most liable to be first affected, and the disease then tends to advance more or less up the limbs towards the trunk, obeying, as Charcot described, “the centripetal law.” In extreme cases every joint in the body may be affected. The temporo-maxillary articulation becomes the seat of rheumatoid arthritis in about 25 per cent. of the total number of cases.

At a later period the articulations of the spine may become involved. The disease usually attacks the cervical vertebræ first, causing pain at the back of the neck, and rendering flexion of the neck and rotation of the head difficult. The dorsal and lumbar vertebræ may be next affected, so that in bad cases the spine may be converted into a rigid column. Pain may be very severe, especially at night; while, on the other hand, the case may proceed to extreme deformity without pain.

Very considerable alterations in the shape of the joints may occur from the formation of osteophytes, thickening of the capsules, and retraction of muscles. The cartilages become worn away at the centres, and the ends of the bones become eburnated by attrition and chronic osteitis. In such joints grating is readily obtained by rubbing the eburnated ends of the bones against each other. The locking of the joints, which sometimes ultimately occurs, is not due to true ankylosis, but to the presence of the projecting osteophytes, and to the thickening of the capsules of the joints. True ankylosis only occurs in the spinal column in cases of rheumatoid arthritis. Atrophy of the muscles from disuse is present in bad cases, with contractures tending to flex the thigh or to bend the knee or elbow. There is usually some increase of myotatic irritability, as shown by some exaggeration, frequently but slight, of the knee-jerks. Most patients finally reach a stage in which the disease becomes arrested, so that they are free from pain, and only are troubled with the associated crippling and consequent inconvenience.

Rheumatoid arthritis is nearly always associated with a certain amount of anæmia, the patients presenting a sallow appearance. Increased rapidity of the heart's action is a not uncommon accompaniment of the disease in its earlier stages, and cold and moist hands and feet are commonly met with. Subcutaneous fibroid nodules and periosteal nodes are occasionally present, especially in those cases which are secondary to rheumatism; and a rheumatoid pigmentation of the skin, somewhat resembling freckles in appearance, is not unfrequently seen, but is especially present in the acute stage. In a small proportion of cases a neuritis is present, but it probably is always secondary to the arthritis, and may be caused, as suggested by Bannatyne, either by the existing joint inflammatory process, or by the action of toxins circulating in the blood. Spender describes the following collateral

symptoms, one or more of which are commonly present, as aids to diagnosis in doubtful cases :—(1) tachycardia ; (2) pigmentation of the face, and perhaps numerous spots or stains on the arms ; (3) cold and moist hands ; (4) neuralgic twinges in the upper and lower limbs ; (5) persistent neuralgic pain over the ball of the thumb and on the ulnar side of the wrist.

Rheumatism.—Rheumatism is a disorder which generally manifests itself as acute rheumatism or rheumatic fever ; but in the chronic condition, although it generally manifests itself as an arthritic disorder—that is to say, a disorder affecting the joints—it may not manifest itself that way at all : it may simply show itself by the production of chorea, or by the production of erythema, or by the production of fibrous nodules, or by the production of endocarditis or pericarditis. Therefore rheumatism is a disorder which does not necessarily show itself as a joint affection ; it may become manifest in some other way. In other words, there is the articular chronic rheumatism and there is the abarticular chronic rheumatism—such as the choreic and erythematous forms.

As an assistance in the diagnosis of a chronic articular affection, there is a rough but fairly sure test which is frequently of assistance in diagnosis : it is treatment with salicylate of soda. If the case responds well to this treatment, it is a case of rheumatism. If it does not respond to this treatment, the existence of rheumatoid arthritis or gout is fairly certain, as neither of these affections responds well to salicylates. When I hear the remark about “an obstinate case of rheumatism which has not done well with salicylates,” I feel fairly sure that it is a case of gout or of rheumatoid arthritis—more probably the latter. Very many of the cases diagnosed as chronic rheumatism are cases of rheumatoid arthritis, or gout, or some form of infective arthritis or arthropathy.

Though much less frequent than is generally supposed,

chronic rheumatic affections of the joints do occur, but they never produce that permanent deformity which the other affections may, especially the lipping of the cartilages and the bony outgrowths already referred to. These chronic rheumatic affections of the joints are generally accompanied by the formation of fibrous nodules over the tendons, by the development of extra-articular fibrous thickening, by the presence of subcutaneous fibres, fibrous nodules (especially on the fingers, elbows, and hand), and not unfrequently by the indication of valvular disease of the heart. There is generally a well-marked history of rheumatism, and the disease is identical with that described as "chronic fibrous rheumatism." It must not be considered that the subcutaneous fibrous nodules occur only in connection with rheumatism. They are fairly frequently seen in cases of rheumatoid arthritis, and less frequently in gout, syphilis, influenza, and other diseases.

It should be carefully remembered that chronic rheumatism is not associated with the formation of bony or cartilaginous deposits in the joints. It shows little symmetry, and is usually associated with rheumatic pains shifting about from one place to another. It never affects the temporo-maxillary joints. As regards the actual diagnosis of rheumatism, it is usually fairly easy. If a patient complains of pains in the joints, which pain flies about from joint to joint, and generally affects some of the muscles at the same time, and if, in connection with these flying pains, there are indications of the presence of the rheumatic erythema—erythema nodosum—then the diagnosis of rheumatism is obvious. As a rule, the fitful way in which the joints are affected, the fairly rapid subsidence of the swellings of the joints, and the association of muscular pains, make the diagnosis a simple matter. Then the response of the disease to treatment by salicylates will settle the diagnosis. The absence of bony thickening and of bony grating distinguishes the

disease from rheumatoid arthritis, and in addition the finger-joints are much less frequently affected.

Differential diagnosis of gout and rheumatoid arthritis.—These are the two chronic joint diseases which are most frequently confounded.

The following distinguishing characters show how very different the two diseases are. In the first place, rheumatoid arthritis occurs most commonly in females; gout occurs mostly in males. Rheumatoid arthritis occurs more commonly amongst the poor and ill-nourished; gout mostly among the well-to-do and well-nourished. Rheumatoid arthritis is a disease which is improved by good dieting; in the case of a gouty person a spare and plain diet is indicated. The onset of rheumatoid arthritis is insidious; that of gout sudden and obvious. As regards the commencement of the attack, gout most commonly begins in one of the feet, especially in the great toe joint; rheumatoid arthritis, although ultimately it frequently affects many joints of both hands, nearly always begins in one joint, most commonly selecting one of the joints of the thumb, either the carpo-metacarpal or metacarpo-phalangeal joint, after which it rapidly spreads to the other joints. Then as regards the appearance: in the case of rheumatoid arthritis there is no obvious swelling at first, and no marked redness. In the case of gout, at its commencement there is very obvious swelling, marked redness, and a shiny condition of the skin around the affected joint.

In rheumatoid arthritis there is very little pain at first. There is some aching in the joint, but it starts in a very insidious manner. It is this insidious character of the disease which is one of its bad features, for the patients do not seek advice until the affection is fairly advanced. Gout, however, begins in the most marked manner with severe pain, the patient as a rule waking up in the early morning with excruciating pain in the great toe. Therefore, if there is doubt as to whether a particular case is

one of rheumatoid arthritis or of gout, the patient should be questioned as to the commencement of the attack, in order to ascertain whether it began with an obvious outburst of pain, and with swelling and redness of the joint, or whether it began very insidiously. Then as to the joint affections: apart from what has been stated as to gout generally beginning in the foot, and rheumatoid arthritis generally in the hand, there is one joint commonly affected in rheumatoid arthritis which is not affected in cases of gout—that is the temporo-maxillary articulation. I have never seen a case of gout in which the temporo-maxillary joint has been affected, whereas in rheumatoid arthritis it is fairly common for that joint to be affected.

In rheumatoid arthritis there is a special liability to the affection of the joints of the cervical vertebræ, as evidenced by pain and stiffness at the back of the neck. This is a most useful distinguishing sign. Another distinction is this—and it is perhaps one of the most important distinctions—that in connection with rheumatoid arthritis there is a remarkable symmetry in the affection of the smaller joints of the hands. In gout that symmetry is wanting. It was this symmetrical affection of the joints which led to the idea—which I believe to be absolutely erroneous—that rheumatoid arthritis is a nervous disease. Lastly, in a case of rheumatoid arthritis sodium biurate is found neither in the joints nor in the blood, whereas in the gouty person sodium biurate exists both in the joints and in the blood.

It is not common to get rheumatoid arthritis and gout associated in the same individual. Undoubtedly rheumatoid arthritis may supervene in joints which have been the seat of any acute infective arthritis. Any affection which impairs the nutrition or weakens the resistance of joints offers a suitable condition for the development of rheumatoid arthritis. Hence rheumatoid arthritis may follow such diseases of the joints as acute rheumatism, gout,

gonorrhœal arthritis, etc. This is the only sense in which such diseases are related to rheumatoid arthritis, in that they have by impairment of the joint structures so lowered the vitality as to render the joints more liable to the invasion of the micro-organism or toxin of rheumatoid arthritis. On the other hand, a person suffering from rheumatoid arthritis, who indulges in rich living for a lengthened period of time, and especially if he takes much wine, may develop gout, and so gouty deposits in the joints of a patient suffering from rheumatoid arthritis may occasionally be met with. This, however, is only a complication; there is no actual relationship between the two conditions, and one disease does not, in the strict sense of the term, predispose to the other.

A form of chronic joint disease in children described by Still.—This is a disease closely resembling the rheumatoid arthritis of adults, and which until recently was always considered to be identical with rheumatoid arthritis, but which, as pointed out by Still, presents such marked differences as to suggest that it has a distinct pathology.

The disease consists of a chronic progressive enlargement of joints associated with enlargement of glands and enlargement of the spleen. The onset, which is usually insidious, almost always occurs before the second dentition, and girls are more commonly affected than boys. The enlargement of the joints is smooth and fusiform, and feels like a general thickening of the tissues around the joint, with none of the bony irregularities of the rheumatoid arthritis of adults. There is no redness, and as a rule no tenderness of the joints; and, although creaking is frequently present, there is never any of the bony grating so commonly present in true rheumatoid arthritis, since in this disease there is a complete absence of the cartilaginous changes so characteristic of the latter disease. Limitation of movement, chiefly of extension, is almost always present.

There is an absence of the extensive deformities of the hands so frequently present in the rheumatoid arthritis of adults. The affection is symmetrical. The joints earliest affected are usually the knees, wrists, and those of the cervical spine; the ankles, elbows, and fingers are subsequently affected. There is no tendency to suppuration nor to bony ankylosis. One of the most distinctive features is the affection of the lymphatic glands. The enlargement is general, but affects primarily and chiefly those related to the joints affected. The enlargement of the spleen is roughly proportionate to that of the glands, but does not extend to more than half-an-inch to one inch below the costal margin. The heart shows no evidence of valvular disease. Sweating is often profuse, and a certain amount of pyrexia, generally recurrent in character, may be present. The disease is usually accompanied by a general arrest of bodily development. The disease is not in itself fatal, but, after running a slow course, the joint disease becomes permanently stationary.

The four important points in the differential diagnosis of this disease from rheumatoid arthritis are (1) the enlargement of the glands; (2) the enlargement of the spleen; (3) the peculiar appearance and feel of the joints, with the absence of bony grating on manipulation, and the absence of osteophytic outgrowths; and (4) the fact that the disease begins nearly always in the knees or wrists, and affects the fingers much later, whereas rheumatoid arthritis in adults affects the small joints of the hands early, and frequently commences in them.

Senile arthropathies.—Senile arthritis in the great majority of cases affects only one joint, usually the hip or shoulder. Occasionally it occurs in the spinal column. This is the form of arthritis frequently known as the monarticular form of rheumatoid arthritis, but it should be regarded as a local degeneration, progressive in its nature. It is, I believe, an entirely different disease from

rheumatoid arthritis, and is probably not microbic in origin. In the hip the disease is known as "morbus coxæ senilis," and in the spine it is known as "spondylitis deformans." It occurs in elderly people, and is in the majority of cases started by some local injury, and is common in old persons who have had to carry heavy weights, or who make excessive use of their lower limbs in the course of their occupation. The arthritis is persistent, and, if not suitably treated, progressive. Grating is nearly always present, with muscular wasting, shortening of the limb, and limitation of movement accompanied by pain. On deep pressure over the affected joint pain is always elicited. The synovial membrane of the joint shows chronic inflammatory changes, along with destruction of cartilages and softening of the articular ends of the bones. The last-mentioned condition is in marked contrast to the eburnation of the ends of the bones in cases of rheumatoid arthritis.

Gonorrhœal arthritis.—This form of arthritis is also known as "gonorrhœal rheumatism," a term which should be abandoned as being misleading in its character. It is always secondary to a gonorrhœal attack elsewhere. This attack is generally in the urethra, but is not necessarily so, as some cases have followed infection of the conjunctiva. The arthritis is due to the presence of the gonococcus in the joints. It usually appears at the decline of the urethritis, or even when this appears to be cured. It is not, therefore, directly proportional to the acuteness of the urethritis. It rarely develops before the third week, and its advent may be postponed for several months after the onset of the gonorrhœa. Time is required for the gonococci to reach the glandular tissues of the prostate, whence they are enabled to enter the circulation. This form of arthritis is most liable to affect the larger joints, especially the knees; the joints that may also be affected are the ankles, elbows, small joints of the feet, shoulders, wrists, small joints of the hands, and the sterno-clavicular joints.

The disease is apt to be mistaken for subacute rheumatism, but it may be differentiated by the comparative absence of temperature, and by the non-reaction of the affection to salicylates. As a rule the diagnosis is rendered easy by the presence of a gonorrhœal discharge, but this is apt to be overlooked in women, on account of the frequency of a leucorrhœal discharge.

The actual condition of gonorrhœal arthritis may be one of synovial effusion, or it may be limited to thickening of the joint capsule and of the periarticular tissues. If neglected, suppuration may occur in the joint.

A form of infective arthritis which is somewhat akin to gonorrhœal arthritis is that accompanying ophthalmia neonatorum. Rapid recovery always follows on fixation of the affected limb and local treatment of the ophthalmia. Two other forms of septic or infective arthritis somewhat resembling gonorrhœal arthritis are those which occasionally occur in connection with profuse leucorrhœal discharges, and in connection with bronchiectasis.

Arthropathies due to infective fevers.—In this chapter I am dealing only with the chronic forms of arthritis, but it is necessary to refer briefly to the forms of arthritis which may occur in connection with any of the infective fevers. As generally seen, these are forms of acute arthritis, but occasionally they persist for a long time, and so become cases of chronic arthritis. These forms of arthritis have been known to occur in connection with scarlet fever, pneumonia, malaria, septicæmia, pyæmia, enteric fever, Maltese fever, measles, influenza, dysentery, glanders, erysipelas, etc. It is, however, only within the last few years that the joint troubles that occasionally occur in the course of the specific diseases have come to be regarded as due to the micro-organisms or poisons of the respective diseases. Formerly they were looked on as manifestations of true rheumatism occurring during the course of the disease. All these forms of arthritis are especially liable

to occur in a joint or joints which have been previously damaged, either by disease or by mechanical injury.

Scarlatinal arthritis.—This is, perhaps, the best known type of arthritis met with in the various infective diseases. The elbows and knees are the joints most frequently affected; the smaller joints of the upper extremities follow next.

Pneumococcic arthritis.—The occurrence of arthritis during an attack of pneumonia has long been known, but until comparatively recently it was generally ascribed to a concurrent attack of rheumatism, and was not directly connected with the attack of pneumonia. A strong tendency to ankylosis is one of the special characteristics of an infective arthritis. Previous damage to a joint, as by injury, rheumatism, or gout, favours the localisation of pneumococcic arthritis. The influence of injuries in predisposing joints to attacks of infective or septic arthritis should be carefully borne in mind, as otherwise cases which are really those of infective arthritis may be considered simply traumatic in origin, and so the possibly necessary operative treatment of the joint may never be considered.

Malarial arthritis.—The parasite, although different in its life history from a bacterium, yet from the point of view of causation of arthritis may be considered as such. Malarial arthritis due to the parasite is a comparatively rare affection, but rheumatoid arthritis coincident with a malarial attack is not by any means uncommon.

Quiet effusion into knee-joints.—This affection was first described by Sir William H. Bennett, and was stated by him to occur only in girls and women, and to be always associated with menstrual irregularity or uterine trouble. It occurs mainly at the time of puberty, and at the climacteric. A similar condition has, however, been observed in males. The affection consists of a passive effusion into the joint, and rarely occurs in any other joint than the knee. It is unattended by pain, and a large number

of the patients are unaware of its existence, unless attention is called to it accidentally. It is best recognised when the patient is standing in the upright position, when the fluid sinks to the lower part of the joint cavity, and sometimes forms a pouch-like overhanging of the synovial membrane at its lower anterior aspect. Attention is generally called to the condition by a slight injury, such as a twist or fall. The joints of the two sides are usually involved at the same time, but the effusion is, as a rule, much more marked on one side than on the other, that on the right side being generally the greater.

Nerve degenerative arthropathies.—These are joint affections that occur in tabes, ataxy, paraplegia, progressive muscular atrophy, etc. The joint troubles are due to abnormal trophic influences started by affections of the central nerve organs, as the result of which inflammatory troubles, generally of a very chronic nature, are set up, characterised by alterations in the ends of the bones, ulceration of cartilages, and formation of fibrous adhesions. Of all the chronic joint affections these are perhaps the easiest of diagnosis, on account of their association with an easily recognisable disease of the nervous system of a degenerative nature.

Tuberculous disease.—The history of the case, both family and personal, is of great assistance in making a diagnosis in this form of joint disease. The swelling is frequently spindle-shaped. When the disease is advanced the joint is in a condition of organised fibrous tuberculosis, and consequently nothing of diagnostic value is to be made out by radiographs.

Syphilitic joint disease.—This is commonly chronic. There is effusion with thickening of the capsules of the medium-sized and larger joints, with occasional bony thickening and lipping of the smaller joints, which may at times closely simulate rheumatoid arthritis. The presence of a gumma, and of old iritis and other indications

of syphilis, will frequently assist in making a correct diagnosis. A form of joint disease occurring in the later stages of syphilis has been described by Whitfield, which presents many resemblances to a joint recovering from acute gout. The joint is considerably swollen, the surface shiny, the skin being of a dark red colour, with distended veins crossing over the joint. As a rule, it is exquisitely tender to the touch. The diagnosis is, as a rule, rendered easy by the discovery of a periosteal gumma over one of the bones. The joint disease itself is undoubtedly gummatous in nature, the gummatous infiltration starting in the ligaments and periarticular tissues.

Pulmonary osteo-arthropathy.—This is a rare disease. It is secondary to some chronic pulmonary disease, such as phthisis, empyema, and chronic bronchitis. The disease may possibly be tuberculous, or be due to some toxic agent. It is characterised by considerable enlargement of the hands, wrists, feet, and ankles. It is apt to be mistaken for acromegaly, but may be distinguished by the clubbing of the finger ends and the enlargement of the wrists, which conditions are absent in acromegaly.

Joint changes in Raynaud's disease.—The joints are much thickened; they present little indication of fluid distension of the cavities; there is a good deal of thickening of the bone, and considerable pain and tenderness. The condition is apt to be mistaken for rheumatoid arthritis, but the diagnosis is rendered easy by the association with the circulatory changes accompanying Raynaud's disease.

Distinction of so-called chronic rheumatism (fibrositis) from gout.—Many cases of so-called chronic rheumatism are frequently confounded with gout. These are cases in which the essential pathological change is an inflammatory hyperplasia of the white fibrous tissue in various parts of the body, to which the term "fibrositis" has been very aptly applied. The articular structures proper—synovial membrane, cartilage, and bone—are not

primarily affected, but the parts implicated are the fibrous tissues of the joints, muscles, and bones, especially the aponeuroses and insertions of the muscles, fasciæ, the fibrous ligaments of the joints, and the periosteum. Such affections cause pain and stiffness in these structures, are especially apt to recur, and are commonly referred to as rheumatic or even gouty in their origin. This inflammatory hyperplasia of the fibrous tissues occurs in patches, and is started by exposure to wet or cold, by injury, or by some irritant, microbic or toxic, conveyed in the blood. The inflamed and swollen fibrous tissue is tender, painful on pressure or on movement, and can frequently be felt on palpation, or is evident by the consequent elevation of the skin. This fibrositis may completely disappear, but recurrences are common, and if not suitably treated the thickened fibrous tissue remains as indurations at various parts.

The indurations may be widespread but generally are well defined, and vary in size from an eighth of an inch to one inch in diameter. They may be situated in the subcutaneous tissue, the muscles, tendons, aponeuroses, and periosteum. The pain is especially aggravated by any sudden movement of the muscles which compresses or stretches the affected fibrous tissues and the sensory nerve filaments. The muscle-spindles, which lie between the bundles of muscular fibres and in the fibrous tissue of the muscle, and each one of which receives one or more narrow muscular fibres, and two or more nerve-fibres, are the only sensory structures in muscle, and it is through them that the pain of so-called muscular rheumatism is felt. Owing to direct pressure of a fibrous nodule on a nerve, or to the involvement of the nerve in the nodule, the pain may be felt over an extensive area, or even be referred to a part of the body which is not the seat of the fibrositis.

Ætiology.—Local fibrositis may result from several causes, of which the following are the commonest :—

(1) *Cold, damp, and wet.*—In a very large number of

cases the only assignable cause of the fibrositis is a history of exposure to cold and wet. Sometimes the attack comes on acutely a few hours after the exposure, as in many cases of lumbago, stiff neck, intercostal "rheumatism," and other forms of so-called muscular "rheumatism." At other times stiffness gradually develops after the exposure, and passes on to the condition of chronic fibrositis generally known as chronic rheumatism.

The exposure may be due to draughts, remaining in wet clothes, lying or sitting on damp ground or some cold substance, or the simple advent of damp or cold weather. Many persons are readily affected by the approach of rain, and by a lowering of the barometric pressure. Longstreth states that the painful symptoms do not correspond to rain, but to the fall of barometric pressure, and Stockman suggests that possibly the atmospheric changes may increase or lessen the lymph-pressure in the body, and so increase or lessen the tension in the affected fibrous tissues. A very common cause of lumbago from exposure to a local draught is sitting on a draughty privy or water-closet; this, no doubt, accounts for the prevalence of that affection in rural districts, combined with the constant strain of the lumbar muscles, amongst so many agricultural labourers.

(2) *Extremes of heat and cold.*—Sudden and considerable variations in temperature constitute by no means an uncommon cause of a generalised fibrositis which takes the form of so-called "muscular rheumatism," following on the resulting chill. One of the severest cases of fibrositis (muscular rheumatism) that I have ever seen was the case of a stoker who after working during very hot weather in the engine-room of a steamer on the Red Sea went straight to the refrigerating chamber of the steamer in order to cool himself. The result was a very severe attack of inflammation of the fibrous tissues over practically the whole of the body, which absolutely prostrated him, and from which he made a very tedious recovery.

(3) *Local injuries*.—These are responsible for a large number of cases of local fibrositis, so-called “local rheumatism.” The injury is generally caused by muscular over-exertion, such as the strain of lifting a heavy weight, the strain exerted in certain muscles in order to save a sudden fall, and the excessive muscular strain that an athlete may put forth. Golf produces a number of such injuries, the fibrous tissue of the muscles of the arms and back and their attachments being specially affected in this game.

If the individual has previously suffered from fibrositis which has not been completely cured, or which has left some fibrous nodules, a comparatively slight wrench may be sufficient to start the aching in the affected part.

(4) *Absorption of irritating toxins from the gastro-intestinal tract*.—It has long been recognised that disorders of the stomach or bowels may give rise to “rheumatic” pains. The aching in the joints and the lumbar region that occasionally occurs the day after a lengthy dinner, especially if several wines have been indulged in, is due to irritation of the fibrous tissues by the toxins absorbed from the intestinal tract, and which have been produced there by abnormal fermentation.

This pain, whether in the joints or the lumbar region, which follows excessive indulgence at the table is generally attributed to gout, and, as a rule, the champagne, claret, or port is blamed for it. I am convinced, however, that this articular or muscular pain has, in the great majority of cases, no relation whatever to gout, and that it is simply an indication of an inability of the gastro-intestinal tract to deal properly with the various articles introduced into it.

(5) *Tonsillitis and pharyngitis*.—The aching pains that occur in various parts of the body in connection with these affections are well known, and are doubtless due to toxic absorption and consequent irritation of the fibrous tissues.

(6) *Influenza*.—The majority of us are probably personally acquainted with the aches and even severe pains in the muscles, joints, and bones which accompany this disease. These are in all probability due to the fibrositis set up by the specific microbe or its toxin. It is not uncommon to find fibrous nodules and thickenings left as sequelæ of this disease.

(7) *Febricula*.—A “feverish cold” is generally accompanied by aching pains in the muscles, joints, and bones. The attack, which is sometimes described as a “rheumatic cold” or an “influenzal cold,” is probably microbic in its origin, and the pains are, no doubt, due to irritation of the fibrous tissues by the microbe or its toxin.

Various forms of fibrositis.—*Muscular rheumatism*.—This affection is always a fibrositis. Any of the muscles may be affected. Affection of the muscles of the lumbar region constitutes one of the forms of lumbago; affection of the muscles of the neck constitutes stiff neck; affection of the deltoid muscle constitutes “deltoid rheumatism;” affection of the intercostal muscles constitutes “intercostal rheumatism.” The pain at first is generally dull, but in anything like severe cases soon becomes sharp and shooting, and is aggravated by damp weather. It is usually worse when the patient becomes warm in bed, and is generally felt severely on waking in the morning and on rising from bed. Brachial fibrositis is especially apt to be of long duration, and interferes with sleep on account of the difficulty of getting the arm into an easy position. To some extent it wears off with exercise or on rubbing the affected parts. It is always accompanied by a feeling of stiffness.

Lumbago.—This is a very typical form of fibrositis. As just mentioned, it may be an affection of the fibrous elements of the lumbar muscles, but more commonly it starts as a localised affection of the insertions of the muscles in the vicinity of one or both of the sacro-iliac joints. It

spreads by continuity of the fibrous tissue, as is manifested by its affecting the tendinous attachments of the neighbouring muscles, by its affecting the sacro-iliac joint itself, and by its often spreading through the joint and reaching the sheath of the sciatic nerve. This explains the very frequent association of some degree of sciatica with an attack of lumbago. It is astonishing to find in a very large number of cases of lumbago that a careful examination of the back reveals no pain or tenderness on pressure over the various muscles, but that as soon as one or both sacro-iliac joints are pressed upon, acute pain is complained of and the patient refers his appreciation of the pain to that region. I am convinced that in the majority of cases of lumbago the affection is not in the *quadratus lumborum*, nor even in the deeper muscles of the back, but is in the fibrous tissues directly over the sacro-iliac joint, and in the joint itself. The production of the pain of lumbago is usually sudden, the patient frequently ascribing it to a sudden strain or rick, especially on rising in the morning, but although the production of the pain is generally sudden, yet the condition on which it depends has been gradually developed.

Rheumatic neuralgia.—This is a fibrositis of the nerve-sheaths, and is a common cause of sciatica, especially accompanying lumbago of the sacro-iliac joints. The affected nerve is painful on pressure or when stretched. The symptoms are numbness, tingling, “pins and needles,” and pain, all of which are due to slight compression of the nerve.

Dupuytren’s contraction.—This is a localised fibrositis caused by habitual postural use of the hand. It is frequently ascribed to gout, but, according to my experience, the condition has no connection with that disease. Certainly I have never seen any gouty deposits in the thickened tissues, nor is the affection commoner amongst gouty subjects.

Prognosis in gout.—If no complications arise, if the attacks are not too frequent, and if no serious amount of albuminuria occurs, the disease is not likely materially to shorten life, especially if the patient is amenable to proper treatment and discipline.

PART III.

INVESTIGATIONS OF CERTAIN POINTS CONNECTED WITH THE TREATMENT OF GOUT.

CHAPTER X.

SOLUBILITY OF SODIUM BIURATE.

Influence exerted by the mineral constituents of meat, milk, and vegetables respectively on the solubility of sodium biurate—Relative effects exerted by the mineral constituents of various vegetables on the solubility of sodium biurate—Influence exerted by the mineral constituents of various vegetables in retarding the conversion of sodium quadriurate into sodium biurate—The vegetables most beneficial to gouty subjects.

It is well known that the excessive consumption of rich nitrogenous food, combined with excesses in wine and malt liquors, both induces and excites gout. The comparative immunity of females and young people from gout is mainly explained by the absence of such determining causes of the gouty attack, combined with, in the case of young people, the absence of predisposing cause, and also the fact that the secreting functions are in full activity. The subjects of gout are generally persons who live well and consume a large amount of animal food. Budd, speaking from a long and extensive professional connection with a large rural district, states that he never knew an instance of gout occurring among agricultural labourers.

Though uric acid is not the primary cause of gout,

yet its deposition as sodium biurate and its subsequent absorption are materially influenced by various conditions. As it is quite possible that the different saline constituents of animal and vegetable foods might very materially affect the solubility of sodium biurate and therefore influence its precipitation, I thought it advisable to ascertain if the saline substances contained in different articles of diet appreciably affected the solvency of sodium biurate at the temperature of the human body, as obviously the subject might have both a pathological and therapeutical bearing. The following experiments were therefore carried out.

Influence of the mineral constituents of meat, milk, and vegetables respectively on the solubility of sodium biurate at 100° F.—A series of experiments was undertaken, operating upon the ash respectively of lean beef, milk, and mixed vegetables (potatoes, spinach, and French beans). The experiments were carried out in the following manner:—The contents of a number of bottles, each containing 100 c.c. of distilled water, were mixed with known quantities of the different ashes and placed in the warm chamber until their contents were at a temperature of 100° F., when an excess of sodium biurate was added to each. The bottles were kept at 100° F. for five hours, during which period they were frequently agitated. At the end of that time the contents of the bottles were filtered and refiltered through double filters until perfectly clear filtrates were obtained. The amount of uric acid in each of the filtrates was then estimated by adding an excess of strong sulphuric acid, and titrating with the standard potassium permanganate solution; the quantity of uric acid found was subsequently calculated into terms of sodium biurate. The results thus obtained are shown in the following tables. The solubility of sodium biurate in distilled water is placed at the head of each table for comparison.

TABLE XVI.

Showing the influence of the mineral constituents of meat (lean beef) on the solubility of sodium biurate at 100° F.

Solvent.	Sodium biurate dissolved.
Water	1.10 per 1,000
Water containing—	
1.0 per cent. of meat ash	0.93 ,,
0.5 " " 	0.76 ,,
0.2 " " 	0.56 ,,
0.1 " " 	0.32 ,,
0.05 " " 	0.15 ,,
0.02 " " 	0.11 ,,
0.01 " " 	0.85 ,,

From the above table it is seen that the mineral constituents of meat, in all proportions between 1.0 and 0.01 per cent., diminish the solvency of sodium biurate. The effect is most marked when the proportions are between 0.1 and 0.02 per cent., which are proportions that may certainly be present in the blood after eating a few ounces of meat. It is therefore quite possible that the well-known influence of excessive meat-eating on the hastening or maturing of an attack of gout may, in part at least, be due to the action of the mineral constituents of the meat.

TABLE XVII.

Showing the influence of the mineral constituents of milk on the solubility of sodium biurate at 100° F.

Solvent.	Sodium biurate dissolved.
Water	1.10 per 1,000
Water containing—	
1.0 per cent. of milk ash	0.62 ,,
0.5 " " 	0.58 ,,
0.2 " " 	0.49 ,,
0.1 " " 	0.44 ,,
0.05 " " 	0.72 ,,
0.02 " " 	0.90 ,,
0.01 " " 	0.94 ,,

The foregoing table shows that the mineral constituents of milk in all proportions diminish the solvency of sodium biurate. The effect is most marked when 0.1 per cent. of milk ash is present. It is extremely unlikely that such a proportion could be present in the blood unless a person were exclusively fed for some time on milk. To introduce 0.1 per cent. of the mineral constituents of milk into the blood would require that all the mineral constituents of about twenty-two ounces of milk should be introduced at one moment into the blood of an adult of average weight. These experiments therefore seem to indicate that the mineral constituents of milk can exercise no appreciable influence in hastening or maturing an attack of gout.

TABLE XVIII.

Showing the influence of the mineral constituents of vegetables (potatoes, spinach, and beans) on the solubility of sodium biurate at 100° F.

Solvent.	Sodium biurate dissolved.
Water	1.10 per 1,000
Water containing—	
1.0 per cent. of vegetable ash	2.15 „
0.5 „ „	1.70 „
0.2 „ „	1.35 „
0.1 „ „	1.15 „
0.05 „ „	1.10 „
0.02 „ „	1.10 „
0.01 „ „	1.10 „

From Table XVIII. it is seen that the mineral constituents of vegetables in quantities of 0.1 per cent. and above very appreciably increase the solvency of sodium biurate. In quantities below 0.1 per cent. the solutions exercise the same solvent power on the biurate as distilled water. These experiments indicate that the mineral constituents of vegetables, if taken in sufficient quantities, would increase the solvency of sodium biurate, and would also exert a solvent effect on gouty deposits.

From the results of these preliminary experiments it appears probable that if the mineral constituents of vegetables were present in sufficient quantities in the fluids of a gouty person, they would not only increase the solubility of the sodium biurate present in these fluids, but would also, by their increased solvent effects on uratic deposits, facilitate the removal of the latter. I have therefore carried out a long series of experiments with the mineral constituents of all the vegetables in ordinary use, in order to elucidate the two following points:—(1) The relative effects exerted by the mineral constituents of various vegetables on the solubility of sodium biurate at the temperature of the human body, and therefore presumably on uratic deposits; and (2) the influence, if any, exerted by these constituents in retarding the conversion of the sodium quadriurate into the sodium biurate. Obviously the elucidation of these points would have a material bearing on the treatment of gout.*

The solvent effects exerted by the mineral constituents of various vegetables on sodium biurate.—The method of carrying out these experiments was similar to that previously described. I operated separately on the mineral constituents of certain vegetables, viz. Spinach, Brussels sprouts, potato, asparagus, Savoy cabbage, French beans, lettuce, beetroot, winter cabbage, celery, turnip tops, turnip, carrot, cauliflower, seakale, and green peas. The results obtained are shown in the following sixteen tables, which are arranged in the order of the average solvent effect exerted by the mineral constituents of the various vegetables, commencing with those exercising the greatest influence. The solubility of sodium biurate in distilled water is placed at the head of each table for comparison.

* The results of these experiments were first communicated to the Royal Medical and Chirurgical Society of London in a paper read on June 14th, 1898.

TABLE XIX.

Showing the influence of the mineral constituents of spinach on the solubility of sodium biurate at 100° F.

Solvent.	Sodium biurate dissolved.
Water	1.10 per 1,000
Water containing—	
1.0 per cent. of spinach ash	3.36 "
0.5 " "	2.76 "
0.2 " "	2.12 "
0.1 " "	1.90 "
0.05 " "	1.52 "
0.02 " "	1.21 "
0.01 " "	1.18 "

TABLE XX.

Showing the influence of the mineral constituents of Brussels sprouts on the solubility of sodium biurate at 100° F.

Solvent.	Sodium biurate dissolved.
Water	1.10 per 1,000
Water containing—	
1.0 per cent. of Brussels sprouts ash	3.06 "
0.5 " " "	2.21 "
0.2 " " "	1.68 "
0.1 " " "	1.62 "
0.05 " " "	1.52 "
0.02 " " "	1.30 "
0.01 " " "	1.23 "

TABLE XXI.

Showing the influence of the mineral constituents of potato on the solubility of sodium biurate at 100° F.

Solvent.	Sodium biurate dissolved.
Water	1.10 per 1,000
Water containing—	
1.0 per cent. of potato ash	2.49 "
0.5 " "	2.17 "
0.2 " "	1.92 "
0.1 " "	1.47 "
0.05 " "	1.36 "
0.02 " "	1.12 "
0.01 " "	1.10 "

TABLE XXII.

Showing the influence of the mineral constituents of asparagus on the solubility of sodium biurate at 100° F.

Solvent.	Sodium biurate dissolved.
Water	1.10 per 1,000
Water containing—	
1.0 per cent. of asparagus ash	2.77 ..
0.5 " " 	2.09 ..
0.2 " " 	1.58 ..
0.1 " " 	1.45 ..
0.05 " " 	1.33 ..
0.02 " " 	1.12 ..
0.01 " " 	1.10 ..

TABLE XXIII.

Showing the influence of the mineral constituents of Savoy cabbage on the solubility of sodium biurate at 100° F.

Solvent.	Sodium biurate dissolved.
Water	1.10 per 1,000
Water containing—	
1.0 per cent. of Savoy cabbage ash	2.32 ..
0.5 " " 	1.92 ..
0.2 " " 	1.77 ..
0.1 " " 	1.57 ..
0.05 " " 	1.34 ..
0.02 " " 	1.13 ..
0.01 " " 	1.10 ..

TABLE XXIV.

Showing the influence of the mineral constituents of French beans on the solubility of sodium biurate at 100° F.

Solvent.	Sodium biurate dissolved.
Water	1.10 per 1,000
Water containing—	
1.0 per cent. of French beans ash	2.48 ..
0.5 " " 	1.87 ..
0.2 " " 	1.68 ..
0.1 " " 	1.56 ..
0.05 " " 	1.28 ..
0.02 " " 	1.16 ..
0.01 " " 	1.10 ..

TABLE XXV.

Showing the influence of the mineral constituents of lettuce on the solubility of sodium biurate at 100° F.

Solvent.	Sodium biurate dissolved.
Water	1.10 per 1,000
Water containing—	
1.0 per cent. of lettuce ash	2.72 "
0.5 " " 	1.92 "
0.2 " " 	1.57 "
0.1 " " 	1.53 "
0.05 " " 	1.21 "
0.02 " " 	1.10 "
0.01 " " 	1.09 "

TABLE XXVI.

Showing the influence of the mineral constituents of beetroot on the solubility of sodium biurate at 100° F.

Solvent.	Sodium biurate dissolved.
Water	1.10 per 1,000
Water containing—	
1.0 per cent. of beetroot ash	2.46 "
0.5 " " 	1.82 "
0.2 " " 	1.60 "
0.1 " " 	1.45 "
0.05 " " 	1.34 "
0.02 " " 	1.15 "
0.01 " " 	1.10 "

TABLE XXVII.

Showing the influence of the mineral constituents of winter cabbage on the solubility of sodium biurate at 100° F.

Solvent.	Sodium biurate dissolved.
Water	1.10 per 1,000
Water containing—	
1.0 per cent. of cabbage ash	2.30 "
0.5 " " 	2.14 "
0.2 " " 	1.63 "
0.1 " " 	1.31 "
0.05 " " 	1.23 "
0.02 " " 	1.10 "
0.01 " " 	1.10 "

TABLE XXVIII.

Showing the influence of the mineral constituents of celery on the solubility of sodium biurate at 100° F.

Solvent.	Sodium biurate dissolved.
Water	1.10 per 1,000
Water containing—	
1.0 per cent. of celery ash	2.20 „
0.5 „ „	1.84 „
0.2 „ „	1.53 „
0.1 „ „	1.44 „
0.05 „ „	1.30 „
0.02 „ „	1.10 „
0.01 „ „	1.06 „

TABLE XXIX.

Showing the influence of the mineral constituents of turnip tops on the solubility of sodium biurate at 100° F.

Solvent.	Sodium biurate dissolved.
Water	1.10 per 1,000
Water containing—	
1.0 per cent. of turnip tops ash	2.16 „
0.5 „ „	1.82 „
0.2 „ „	1.58 „
0.1 „ „	1.42 „
0.05 „ „	1.20 „
0.02 „ „	1.13 „
0.01 „ „	1.11 „

TABLE XXX.

Showing the influence of the mineral constituents of turnips on the solubility of sodium biurate at 100° F.

Solvent.	Sodium biurate dissolved
Water	1.10 per 1,000
Water containing—	
1.0 per cent. of turnip ash	2.04 „
0.5 „ „	1.78 „
0.2 „ „	1.50 „
0.1 „ „	1.42 „
0.05 „ „	1.32 „
0.02 „ „	1.14 „
0.01 „ „	1.10 „

TABLE XXXI.

Showing the influence of the mineral constituents of carrot on the solubility of sodium biurate at 100° F.

Solvent.	Sodium biurate dissolved.
Water	1.10 per 1,000
Water containing—	
1.0 per cent. of carrot ash	1.63 „
0.5 „ „	1.53 „
0.2 „ „	1.47 „
0.1 „ „	1.45 „
0.05 „ „	1.33 „
0.02 „ „	1.13 „
0.01 „ „	1.11 „

TABLE XXXII.

Showing the influence of the mineral constituents of cauliflower on the solubility of sodium biurate at 100° F.

Solvent.	Sodium biurate dissolved.
Water	1.10 per 1,000
Water containing—	
1.0 per cent. of cauliflower ash	1.52 „
0.5 „ „	1.50 „
0.2 „ „	1.42 „
0.1 „ „	1.34 „
0.05 „ „	1.28 „
0.02 „ „	1.09 „
0.01 „ „	1.09 „

TABLE XXXIII.

Showing the influence of the mineral constituents of seakale on the solubility of sodium biurate at 100° F.

Solvent.	Sodium biurate dissolved.
Water	1.10 per 1,000
Water containing—	
1.0 per cent. of seakale ash	1.49 „
0.5 „ „	1.47 „
0.2 „ „	1.35 „
0.1 „ „	1.23 „
0.05 „ „	1.10 „
0.02 „ „	1.10 „
0.01 „ „	1.10 „

TABLE XXXIV.

Showing the influence of the mineral constituents of green peas on the solubility of sodium biurate at 100° F.

Solvent.	Sodium biurate dissolved.
Water	1.10 per 1,000
Water containing—	
1.0 per cent. of green peas ash	0.99 ,,
0.5 " " 	1.01 ,,
0.2 " " 	1.04 ,,
0.1 " " 	1.10 ,,
0.05 " " 	1.10 ,,
0.02 " " 	1.10 ,,
0.01 " " 	1.10 ,,

From the results detailed in these tables it is evident that 0.05 per cent. and over of the mineral constituents of nearly all the vegetables very appreciably increases the solubility of sodium biurate. The solitary exception is in the case of the mineral constituents of green peas, which practically exert no influence whatever on the solubility of the biurate.

As I considered that these solvent effects of the mineral constituents of most vegetables on the biurate might have some bearing on the treatment of gout, I next endeavoured to ascertain whether these effects were due to the alkalinity of the vegetables ashes, or whether they could be referred to any one saline constituent of the vegetables.

Experimental proof that the solvent effects of the mineral constituents of vegetables on sodium biurate are not due to their degree of alkalinity.—That the solvent effect exerted respectively by the mineral constituents of each vegetable on the sodium biurate was not proportional to the alkalinity of the ash was very easily determined. I made estimations of the alkalinities of the different vegetable ashes, and calculated the percentages of alkalinity in terms of sodium carbonate. The alkalinity

of the ashes was due to potassium and sodium carbonates ; none of the ashes contained either potassium or sodium hydrate. The following table shows a comparison of the solubility exerted by the mineral constituents of vegetables on sodium biurate, and the alkalinity of those constituents :—

TABLE XXXV.

Showing that the solvent effect on sodium biurate of the mineral constituents of vegetables is not dependent on the alkalinity of those constituents.

Vegetables arranged in order of solvent effect of their mineral constituents on sodium biurate. Commencing with those exerting the greatest effect.	Vegetables arranged in order of the alkalinity of their ashes, and showing percentages of alkalinity reckoned as sodium carbonate. Commencing with the most alkaline.
Spinach	Spinach 26.00
Brussels sprouts	Celery 20.80
Potato	Turnip 20.80
Asparagus	Potato 17.55
Savoy cabbage	Beetroot 15.60
French beans	Cauliflower 13.20
Lettuce	Carrot 13.00
Beetroot	Brussels sprouts 12.35
Cabbage	French beans 12.35
Celery	Turnip tops 11.70
Turnip tops	Lettuce 11.05
Turnip	Asparagus 8.45
Carrot	Cabbage 5.85
Cauliflower	Green peas 5.20
Seakale	Savoy cabbage 4.55
Green peas	Seakale 1.95

It is evident from a glance at this table that the solvent effect of a vegetable ash on sodium biurate, with the exception of spinach ash, bears no relationship, either of a direct or an inverse ratio, to the alkalinity of the ash. For instance, it can be seen that the solvent effect on the biurate of the ash of Brussels sprouts is high, while its

alkalinity is low; on the other hand, the solvent effect on the biurate of the ash of celery is low, while its alkalinity is high. In other words, it is evident that the order in which the vegetables are arranged as regards the solvent effect of the mineral constituents on the biurate is neither the order nor the inverse order of their relative alkalinities. These results support the conclusions I arrived at from some experiments made with blood serum, and described in the "Goulstonian Lectures" of 1897. I then showed that a diminution in the alkalinity of blood serum did not cause a diminution in the solvent power of the serum for biurate, and, conversely, that an increase in the alkalinity of the serum did not increase its solvent power for the biurate.

Experimental proof that the solvent effects of the mineral constituents of vegetables on sodium biurate are not due to any single constituent.—The next problem to solve was whether the effect exerted by the mineral constituents of vegetables in increasing the solubility of sodium biurate is due to any one constituent. With regard to this point, it appeared probable beforehand that such would not prove to be the case, since Sir William Roberts had shown that sodium, calcium, and magnesium salts diminish the solvent power of water on sodium biurate, and that potassium salts exercise no influence, one way or the other, on the solubility of the biurate.

Now it can easily be demonstrated that the solvent effect is not due to the potassium salts. The next table contains a comparison of the solvent powers exerted by the mineral constituents of vegetables on sodium biurate, and the proportions of potassium salts present.

TABLE XXXVI.

Showing that the solvent effect on sodium biurate of the mineral constituents of vegetables is not dependent on the amounts of potassium salts present.

Vegetables arranged in order of solvent effect of their mineral constituents on sodium biurate. Commencing with those exerting the greatest effect.	Vegetables arranged in order of the proportions of potassium salts present, and showing the percentages of potassium salts present in the ashes, reckoned as potassium oxide. Commencing with those richest in potassium salts.
Spinach	Potato 56.03
Brussels sprouts	Turnip 54.05
Potato	Carrot 53.36
Asparagus	Lettuce 48.01
Savoy cabbage	French beans 46.50
French beans	Asparagus 39.21
Lettuce	Green peas 38.96
Beetroot	Beetroot 38.33
Cabbage	Cabbage 37.71
Celery	Brussels sprouts 35.00
Turnip tops	Celery 33.14
Turnip	Turnip tops 30.55
Carrot	Savoy cabbage 26.82
Cauliflower	Cauliflower 23.46
Seakale	Spinach 23.43
Green peas	Seakale 2.59

It is evident from this table that the solvent effect of the mineral constituents of vegetables on sodium biurate bears no relationship, either of a direct or an inverse ratio, to the proportions of potassium salts present. For instance, it can be seen that the solvent effect on the biurate of the ash of spinach is high, while the proportion of potassium salts is low; on the other hand, the solvent effect on the biurate of the ash of turnips is low, while the proportion of potassium salts is high.

It can also be demonstrated that the increased solubility of the biurate effected by the mineral constituents of vegetables is not due to the sodium salts. Table XXXVII. contains a comparison of the solvent powers exerted by

the mineral constituents of vegetables on sodium biurate, and the proportions of sodium salts present.

TABLE XXXVII.

Showing that the solvent effect on sodium biurate of the mineral constituents of vegetables is not dependent on the amounts of sodium salts present.

Vegetables arranged in order of solvent effect of their mineral constituents on sodium biurate. Commencing with those exerting the greatest effect.	Vegetables arranged in order of the proportions of sodium salts present, and showing the percentages of sodium salts present in the ashes, reckoned as sodium oxide. Commencing with those richest in sodium salts.
Spinach	Seakale 33.84
Brussels sprouts	Spinach 31.42
Potato	Beetroot 31.17
Asparagus	French beans 30.50
Savoy cabbage	Celery 19.33
French beans	Asparagus 16.79
Lettuce	Carrot 14.17
Beetroot	Savoy cabbage 13.86
Cabbage	Brussels sprouts 12.60
Celery	Lettuce 11.80
Turnip tops	Cauliflower 10.87
Turnip	Turnip 6.37
Carrot	Green peas 5.20
Cauliflower	Turnip tops 4.19
Seakale	Cabbage 2.39
Green peas	Potato 2.18

This table shows that the solvent effect of the mineral constituents of vegetables on sodium biurate bears no relationship, either of a direct or an inverse ratio, to the proportions of sodium salts present. For instance, it can be seen that the solvent effect on the biurate of the ash of potato is high, while the proportion of sodium salts is low; on the other hand, the solvent effect on the biurate of the ash of seakale is low, while the proportion of sodium salts is high.

In like manner it can be demonstrated that the increased solubility of the biurate effected by the mineral constituents

of vegetables is not due to the calcium salts. The following table contains a comparison of the solvent powers exerted by the mineral constituents of vegetables on sodium biurate, and the proportions of calcium salts present :—

TABLE XXXVIII.

Showing that the solvent effect on sodium biurate of the mineral constituents of vegetables is not dependent on the amounts of calcium salts present.

Vegetables arranged in order of solvent effect of their mineral constituents on sodium biurate. Commencing with those exerting the greatest effect.	Vegetables arranged in order of the proportions of calcium salts present, and showing the percentages of calcium salts present in the ashes, reckoned as calcium oxide. Commencing with those richest in calcium salts.
Spinach	Turnip tops 37.15
Brussels sprouts	Seakale 27.56
Potato	Cauliflower 23.33
Asparagus	French beans 17.48
Savoy cabbage	Cabbage 17.14
French beans	Lettuce 15.02
Lettuce	Savoy cabbage 14.83
Beetroot	Turnip 13.38
Cabbage	Celery 13.06
Celery	Spinach 10.64
Turnip tops	Carrot 6.88
Turnip	Brussels sprouts 6.16
Carrot	Potato 5.46
Cauliflower	Asparagus 5.05
Seakale	Green peas 4.98
Green peas	Beetroot 2.58

It is clear from this table that the solvent effect of the mineral constituents of vegetables on sodium biurate bears no relationship, either of a direct or an inverse ratio, to the proportions of calcium salts present. For instance, it can be seen that the solvent effect on the biurate of the ash of potato is high, while the proportion of calcium salts is low ; on the other hand, the solvent effect on the biurate of the ash of seakale is low, while the proportion of calcium salts is high.

Similarly it can be shown that the increased solvent

effect on the biurate exerted by the mineral constituents of vegetables is not due to either the magnesium or iron salts present.

It can also be demonstrated that the increased solubility of the biurate is not due to the phosphates present in the vegetables. The following table contains a comparison of the solvent powers exerted by the mineral constituents of vegetables on sodium biurate, and the proportions of phosphates present:—

TABLE XXXIX.

Showing that the solvent effect on sodium biurate of the mineral constituents of vegetables is not dependent on the amounts of phosphates present.

Vegetables arranged in order of solvent effect of their mineral constituents on sodium biurate. Commencing with those exerting the greatest effect.	Vegetables arranged in order of the proportions of phosphates present, and showing the percentages of phosphates present in the ashes, reckoned as phosphoric anhydride. Commencing with those richest in phosphates.
Spinach	Green peas 35.62
Brussels sprouts	Cauliflower 22.14
Potato	Asparagus 21.93
Asparagus	Potato 15.99
Savoy cabbage	Carrot 15.02
French beans	Celery 14.39
Lettuce	Brussels sprouts 14.20
Beetroot	Savoy cabbage 13.19
Cabbage	French beans 12.21
Celery	Cabbage 11.99
Turnip tops	Lettuce 9.62
Turnip	Turnip 9.26
Carrot	Spinach 8.56
Cauliflower	Beetroot 8.25
Seakale	Seakale 8.00
Green peas	Turnip tops 6.15

It is manifest from this table that the solvent effect of the mineral constituents of vegetables on sodium biurate bears no relationship, either of a direct or an inverse ratio, to the proportions of phosphates present. For instance, it can be seen that the solvent effect on the biurate of the

ash of spinach is high, while the proportion of phosphates is low; on the other hand, the solvent effect on the biurate of the ash of green peas is low, while the proportion of phosphates is high.

It can also be demonstrated that the increased solubility of the biurate is not due to the sulphates present in the vegetables. The following table contains a comparison of the solvent powers exerted by the mineral constituents of vegetables on sodium biurate, and the proportions of sulphates present:—

TABLE XL.

Showing that the solvent effect on sodium biurate of the mineral constituents of vegetables is not dependent on the amounts of sulphates present.

Vegetables arranged in order of solvent effect of their mineral constituents on sodium biurate. Commencing with those exerting the greatest effect.	Vegetables arranged in order of the proportions of sulphates present, and showing the percentages of sulphates present in the ashes, reckoned as sulphuric anhydride. Commencing with those richest in sulphates.
Spinach	Seakale 19.78
Brussels sprouts	Turnip tops 15.27
Potato	Cauliflower 14.16
Asparagus	Savoy cabbage 12.85
Savoy cabbage	Turnip 12.47
French beans	Brussels sprouts 8.31
Lettuce	Cabbage 7.28
Beetroot	French beans 6.82
Cabbage	Potato 5.60
Celery	Asparagus 5.40
Turnip tops	Carrot 5.20
Turnip	Spinach 4.44
Carrot	Green peas 4.36
Cauliflower	Lettuce 3.92
Seakale	Beetroot 2.41
Green peas	Celery 1.10

This table makes it evident that the solvent effect of the mineral constituents of vegetables on sodium biurate bears no relationship, either of a direct or an inverse ratio, to the proportions of sulphates present. For instance, it

can be seen that the solvent effect on the biurate of the ash of spinach is high, while the proportion of sulphates is low ; on the other hand, the solvent effect on the biurate of the ash of seakale is low, while the proportion of sulphates is high.

Finally, as disposing of all the mineral constituents of any importance in vegetables, it can be demonstrated that the increased solubility of the biurate is not due to the chlorides present in the vegetables, as seen in the following table :—

TABLE XLI.

Showing that the solvent effect on sodium biurate of the mineral constituents of vegetables is not dependent on the amounts of chlorides present.

Vegetables arranged in order of solvent effect of their mineral constituents on sodium biurate. Commencing with those exerting the greatest effect.	Vegetables arranged in order of the proportions of chlorides present, and showing the percentages of chlorides present in the ashes, reckoned as chlorine. Commencing with those richest in chlorides.
Spinach	Celery 22.14
Brussels sprouts	Beetroot 18.13
Potato	Seakale 15.46
Asparagus	Cabbage 9.09
Savoy cabbage	Lettuce 8.80
French beans	Spinach 7.78
Lettuce	Savoy cabbage 7.53
Beetroot	Turnip tops 7.33
Cabbage	Asparagus 6.62
Celery	Turnip 5.06
Turnip tops	Cauliflower 4.83
Turnip	Carrot 3.70
Carrot	Brussels sprouts 3.00
Cauliflower	Potato 2.50
Seakale	French beans 2.50
Green peas	Green peas 2.10

From this table it is clear that the solvent effect of the mineral constituents of vegetables on sodium biurate bears no relationship, either of a direct or an inverse ratio, to the proportions of chlorides present. For instance, it can be seen that the solvent effect on the biurate of the

ash of Brussels sprouts is high, while the proportion of chlorides is low; on the other hand, the solvent effect on the biurate of the ash of seakale is low, while the proportion of chlorides is high.

These results collectively show that the solvent effect exerted on sodium biurate by the mineral constituents of vegetables is not due to any one constituent.

Experimental proof that an artificially prepared ash does not react to sodium biurate in the same manner as a natural vegetable ash.—I next endeavoured to ascertain whether an artificially prepared ash of the same composition as the natural ash of one of the vegetables would exercise a similar effect in increasing the solubility of the sodium biurate to that possessed by the natural ash. For this purpose I selected the spinach ash, which has the greatest solvent effect on the biurate. An artificial ash was prepared, which was made with the same proportions of potassium, sodium, calcium, sulphates, phosphates and chlorides as those present in the natural spinach ash, and also of precisely the same degree of alkalinity. Experiments were carried out with this artificial ash and the biurate in a similar manner to that employed in working with the natural vegetable ashes. The following table shows the results of these experiments:—

TABLE XLII.

Showing the influence of artificial spinach ash on the solubility of sodium biurate at 100° F.

Solvent.	Sodium biurate dissolved.
Water	1.10 per 1,000
Water containing—	
1.0 per cent. of artificial spinach ash .	0.20 "
0.5 " " " "	0.34 "
0.2 " " " "	0.62 "
0.1 " " " "	0.86 "
0.05 " " " "	0.96 "
0.02 " " " "	1.04 "
0.01 " " " "	1.06 "

These results are very remarkable, as they indicate that the artificial ash exercises in all proportions a deterrent effect on the solubility of the biurate. This deterrent effect is well seen by contrasting the results with those of the natural ash, which show the marked solvent effect exerted by the latter on the biurate.

TABLE XLIII.

Showing the different influences exerted by artificial and by natural spinach ashes on the solvency of the biurate at 100° F.

Solvent.	Sodium biurate dissolved in 1,000 parts.	
Water	1.10	
	Artificial spinach ash.	Natural spinach ash.
Water containing—		
1.0 per cent. of ash	0.20	3.36
0.5 " " "	0.34	2.76
0.2 " " "	0.62	2.12
0.1 " " "	0.86	1.90
0.05 " " "	0.96	1.52
0.02 " " "	1.04	1.21
0.01 " " "	1.06	1.18

The only explanation that I can offer of these remarkable results is that in the natural ash there is some combination of the mineral constituents which cannot be artificially imitated, and that upon this natural combination of the salts is dependent the increased solvent effect exerted on the biurate by the mineral constituents of most vegetables. If this view be correct, then modern science is but confirming the correctness of the practice of those ancients who employed vegetable ashes in the treatment of gout.

It is well to make here a brief reference to the experiments previously described, which show that the mineral constituents of meat exercise a marked deterrent effect on the solubility of sodium biurate; and that this effect

is most marked by proportions of the mineral constituents which may certainly be present in the blood after eating a few ounces of meat. The following table shows in contrast the effects exercised respectively by the mineral constituents of lean beef and spinach on the solubility of the biurate.

TABLE XLIV.

Showing the respective effects exercised by the mineral constituents of beef and spinach on the solubility of sodium biurate at 100° F.

Solvent.	Sodium biurate dissolved in 1,000 parts.	
Water	1.10	
	Beef ash.	Spinach ash.
Water containing—		
1.0 per cent. of ash .	0.93	3.36
0.5 " " "	0.76	2.76
0.2 " " "	0.56	2.12
0.1 " " "	0.32	1.90
0.05 " " "	0.15	1.52
0.02 " " "	0.11	1.21
0.01 " " "	0.85	1.18

Experimental inquiry to ascertain the effect exerted by the mineral constituents of various vegetables on the conversion of sodium quadriurate into sodium biurate.—It is well known from the researches of Bence Jones and of Sir William Roberts that sodium quadriurate is an unstable body, and is gradually converted by combination with the sodium carbonate of the blood into sodium biurate, which latter body, on account of its comparative insolubility, deposits in the tissues and thus constitutes the gouty uratic deposit. This gradual conversion of the quadriurate into biurate is known as the *maturation process*.

It is obviously of therapeutical importance to know whether the mineral constituents of any of the vegetables,

in addition to exerting an increased solvent effect on the biurate, possess the power of delaying this maturation process; or, in other words, of inhibiting the conversion of the quadriurate into the biurate. In order to ascertain this, I conducted a series of experiments. In all these experiments I employed Sir William Roberts's standard solution, as being a more convenient medium to work with than blood serum. This standard solution contains 0.5 per cent. of sodium chloride and 0.2 per cent. of sodium bicarbonate dissolved in distilled water. Sir William Roberts found that this solution is a fairly exact representation of blood serum, in so far as its saline ingredients are concerned, and that it reacted with uric acid and the urates in the same manner as blood serum itself, and in the same manner as a solution comprising all the salines of the serum in their due proportions.

The experiments were conducted in the following way. Pure sodium quadriurate was prepared by shaking for one minute ten grammes of uric acid with a litre of a boiling-hot 5 per cent. solution of sodium acetate. This was filtered hot, and the filtrate was then rapidly cooled on ice. The quadriurate, which falls down, was at once collected on a filter, washed with absolute alcohol, and dried at 100° F. Ten milligrammes of pure sodium quadriurate were well rubbed with ten drops of the standard solution, and the mixture was placed in a small corked bottle in the warm chamber and kept at 100° F. Every half-hour a small quantity of the mixture was examined under a high power of the microscope, and the time at which crystals of sodium biurate first appeared was noted. This represented the time occupied by the maturation process when the standard solution was saturated with sodium quadriurate. Similar experiments were conducted with the same amount of sodium quadriurate in the same quantity of standard solution containing respectively 0.1 per cent. of the mineral constituents of each of the vegetables

in ordinary use. The results are shown in the following table:—

TABLE XLV.

Showing the effects exerted by the mineral constituents of vegetables on the conversion of sodium quadriurate into sodium biurate.

Solvent.	Crystals of sodium biurate first appeared in—
Standard solution	2 hours
Standard solution containing—	
0.1 per cent. of potato ash	2 „
„ „ cauliflower ash	2 „
„ „ lettuce „	2 „
„ „ carrot „	2 „
„ „ asparagus „	2½ „
„ „ beetroot „	3 „
„ „ green peas „	3½ „
„ „ celery „	3½ „
„ „ Brussels sprouts ash	4 „
„ „ cabbage „	4 „
„ „ turnip tops „	4 „
„ „ turnip „	4 „
„ „ Savoy cabbage „	4 „
„ „ seakale „	4 „
„ „ French beans „	4½ „
„ „ spinach „	5 „

These results show that the mineral constituents of some of the vegetables—notably spinach, Brussels sprouts, French beans, cabbage, turnip tops, and turnips—very considerably delay the conversion of sodium quadriurate into sodium biurate. The inference is that if such mineral constituents were present in suitable proportions in the blood of gouty subjects, the elimination of that body might be secured without the occurrence of any precipitation of the biurate in the tissues. Moreover, it must be borne in mind that these experiments were conducted under very stringent conditions, in that they were all carried out with a saturated solution of the quadriurate, and it is extremely unlikely that the fluids of the body are ever, in gouty subjects, saturated with so soluble a

compound as the sodium quadriurate; therefore, it is but fair to infer that, with smaller proportions of the quadriurate in solution, the inhibitory effects of the mineral constituents of vegetables would extend over much longer periods than actually occurred in the carrying out of these experiments.

Results of the experimental inquiry.—The net results of all the experiments described indicate that the mineral constituents of most vegetables increase the solubility of sodium biurate, and also, in several cases, delay for considerable periods the conversion of the sodium quadriurate into the biurate. On the other hand, the mineral constituents of meat diminish the solubility of sodium biurate, and exercise but little effect in delaying the conversion of the quadriurate into the biurate.

I wish it to be clearly understood that I do not attribute the different effects of animal and vegetable diets on gouty subjects to the saline constituents alone. I think, however, that the results of these experiments clearly show that it is to the different mineral constituents of animal and vegetable foods, and to the different physical effects they exercise on the quadriurate and biurate, that we must look for a partial explanation of the known facts that an excessive diet of the one tends to produce gout and of the other tends to retard it.

A reference to some of the tables previously given will show that certain vegetables stand out prominently with regard to the effect exercised by their mineral constituents both in retarding the conversion of the sodium quadriurate into the biurate, and in increasing the solubility of the latter. These vegetables are spinach, Brussels sprouts, French beans, winter cabbage, Savoy cabbage, turnip tops, turnips, and celery. These are the vegetables which I consider are likely to prove most beneficial to gouty subjects. Of these, in so far as the effects produced by their mineral constituents are concerned, spinach occupies

the first place, both as regards inhibiting the decomposition of the quadriurate and increasing the solubility of the biurate. Spinach has the further advantage of being extremely rich in mineral constituents, since it contains 16.27 per cent. of mineral matter as compared with 8.50, which is the average percentage of the mineral constituents of all the vegetables experimented with. It may be urged that a drawback to the employment of spinach is that it cannot be obtained fresh throughout the year. Very excellent spinach is, however, now obtainable in the desiccated and compressed state, and when cooked makes a dish which is practically indistinguishable from the fresh vegetable.

General conclusions drawn from the investigations.

1. The solubility of sodium biurate is markedly increased by the presence of the mineral constituents of most vegetables.
2. The mineral constituents of certain vegetables delay the conversion of sodium quadriurate into the biurate.
3. The vegetables most useful to gouty subjects are spinach, Brussels sprouts, French beans, winter cabbage, Savoy cabbage, turnip tops, turnips, and celery.

CHAPTER XI.

SOLUTION OF GOUTY DEPOSITS.

Reasons for believing that the removal of gouty deposits by alkalies is erroneous—Experimental investigation of the value of the various alkalies, piperazine, and lysidine as solvents of gouty deposits—Experimental investigation of the value of salicylates as solvents of gouty deposits.

FOR a considerable period of time two methods of treatment which have for their professed object the elimination of uric acid from the system have been more or less employed by medical men. They are the treatment of gout by means of alkalies, and by means of salicylates. These two methods of treatment I consider owe their popularity to the entirely erroneous supposition that uric acid is present as such in the fluids and deposits of gouty patients, whereas the uric acid is always present as sodium quadriurate or biurate, and the chemical and physical behaviour of these substances is entirely different from that of uric acid.

The plea for the treatment of gout by means of alkalies is mainly based on the following assumptions:—(1) That uric acid is present in the blood and tissues, and is rendered soluble by the administration of alkalies; (2) that the biurate deposited in joints is rendered soluble by means of alkalies; and (3) that there is a general acidity of the system which is neutralised and removed by alkalies. It will be seen that these assumptions do not stand the test of experimental inquiry. With regard to the first assumption, it is now well known that in gouty subjects uric acid is never present as such in the blood and tissues, but is always combined with sodium as the quadriurate or biurate,

and possibly in some organic combination as well. The only way in which alkalies could beneficially affect the quadriurate would be to delay its conversion into the biurate. In order to test this point, I conducted a series of experiments so as to ascertain the effect of artificial blood serum, to which different alkalies had been added, on the decomposition of sodium quadriurate. In all the experiments the artificial blood serum employed was Sir William Roberts's standard solution. This was employed instead of blood serum in order to obviate the objections that have been raised to the use of blood serum in such experiments, viz. the tendency to variation in its alkalinity. Moreover, as shown by Sir William Roberts, this standard solution reacts with uric acid and with the quadriurates and biurates in the same manner as blood serum itself.

Objects of conducting the experiments with sodium quadriurate.—These experiments were undertaken in order to ascertain whether any of the drugs ordinarily employed in the alkaline treatment of gout possess any power, when introduced into the circulation, of restraining the precipitation of sodium biurate from the quadriurate contained in the blood. Such experiments would show whether any such drugs would be of use in lessening the formation of gouty deposits.

When sodium quadriurate is mixed with water it is decomposed into a uric acid moiety and a sodium biurate moiety, the uric acid appearing, immediately it is set free, in the form of ovoid or spindle-shaped crystals. These crystals appear in a very short time after the contact of the quadriurate with water—generally in from one to five minutes—whilst the sodium biurate passes into the gelatinous form, which, if sufficient water be present, is dissolved. If, instead of water, an alkaline medium be employed to decompose the quadriurate, such as blood serum or artificial blood serum, at the temperature of the human body, then as long as free alkaline carbonate is present

the uric acid moiety of the quadriurate, instead of crystallising out as uric acid, unites with the sodium carbonate to form sodium biurate, which first assumes the amorphous form. After a time this amorphous biurate becomes gradually converted into the needles of the crystalline biurate. The time, therefore, that elapses between the saturation of the blood serum with sodium quadriurate, and the first appearance of needle-shaped crystals of sodium biurate, represents the inhibitory influence of the medium on the crystalline precipitation of sodium biurate. The next paragraph describes how the experiments to ascertain the effect of drugs employed in the alkaline treatment of gout were conducted.

Method of conducting the experiments with sodium quadriurate.—Ten milligrammes of sodium quadriurate were well rubbed with ten drops of a 0.1 per cent. solution of the drug in artificial blood serum, and the mixture was then placed in a small corked tube and kept at 100° F. Every half-hour a small quantity of the mixture was removed and examined under a high power of the microscope, and the time at which crystals of the sodium biurate first appeared was noted. A similar experiment, for purposes of comparison, was made with the quadriurate and artificial blood serum alone. I experimented separately in this way with potassium bicarbonate, potassium citrate, lithium carbonate, lithium citrate, sodium bicarbonate, sodium phosphate, piperazine, and lysidine. The results are set out in Table XLVI. They show that none of the drugs mentioned in the table exercises the slightest effect in delaying the conversion of the quadriurate into the biurate, even when present in far larger proportions than could possibly be introduced into the blood by the medicinal administration of the drugs. Therefore it appears that the treatment of gout by alkalies and salts of the alkalies does not delay the conversion of the quadriurate into the biurate.

TABLE XLVI.

Showing the influence exerted on the decomposition of sodium quadriurate by artificial blood serum alone, and by artificial blood serum containing 0.1 per cent. of various drugs in solution.

Solvent.	Sodium biurate crystals appeared after the lapse of—
Artificial blood serum	2 hours
„ „ containing 0.1 per cent. of potassium bicarbonate	„
„ „ containing 0.1 per cent. of potassium citrate . .	„
„ „ containing 0.1 per cent. of lithium carbonate .	„
„ „ containing 0.1 per cent. of lithium citrate . .	„
„ „ containing 0.1 per cent. of sodium bicarbonate .	„
„ „ containing 0.1 per cent. of sodium phosphate .	„
„ „ containing 0.1 per cent. of piperazine	„
„ „ containing 0.1 per cent. of lysidine	„

Does the treatment of gout by alkalies increase the solubility of sodium biurate?—With regard to the second assumption, that the administration of alkalies increases the solubility of the biurate deposited in the joints and tissues, Sir William Roberts * has shown that sodium bicarbonate and sodium phosphate diminish the solubility of sodium biurate, while potassium bicarbonate exercises no influence whatever on its solubility. That the administration of alkalies might increase the solubility of the biurate appeared at one time to be probable from the results of some experiments performed by Sir Alfred Garrod. He immersed small pieces of cartilage infiltrated with sodium biurate for forty-eight hours in aqueous solutions of the carbonates of lithium, potassium, and sodium respectively. At the end of that time he found

* Croonian Lectures, 1892.

that the cartilage immersed in the lithium solution was restored to its natural condition ; that in the potassium solution was much acted upon, while that in the sodium solution appeared to be unaltered. These results are somewhat in opposition to those of Sir William Roberts, and as neither the experiments of Sir Alfred Garrod nor those of Sir William Roberts represent the conditions under which alkalies, when introduced into the circulation, would act on sodium biurate, I thought it desirable to re-investigate the subject, as far as possible under such conditions.

Investigation of the effects of various alkaline drugs on the solubility of sodium biurate.—These experiments were undertaken in order to compare the solubility at 100° F. of sodium biurate in artificial blood serum, and in artificial blood serum containing different proportions of the various drugs. The experiments were carried out in a similar manner to those previously described. I experimented separately with the following drugs, viz. potassium bicarbonate, potassium citrate, lithium carbonate, lithium citrate, sodium bicarbonate, sodium phosphate, piperazine, and lysidine. Much greater proportions of the drugs were employed than could possibly be introduced into the blood by medicinal administration. The results are shown in the following tables :—

TABLE XLVII.

Showing the solubility at 100° F. of sodium biurate in artificial blood serum alone, and in artificial blood serum containing different proportions of potassium bicarbonate.

Solvent.	Sodium biurate dissolved.
Artificial blood serum	0.11 per 1,000
Artificial blood serum containing 0.01 per cent. of potassium bicarbonate	0.10 ,,
Artificial blood serum containing 0.10 per cent. of potassium bicarbonate	0.10 ,,
Artificial blood serum containing 0.20 per cent. of potassium bicarbonate	0.11 ,,

These results show that potassium bicarbonate would not in the slightest degree increase the solvent power of the blood for gouty deposits.

TABLE XLVIII.

Showing the solubility at 100° F. of sodium biurate in artificial blood serum alone, and in artificial blood serum containing different proportions of potassium citrate.

Solvent.	Sodium biurate dissolved.
Artificial blood serum	0.11 per 1,000
Artificial blood serum containing 0.01 per cent. of potassium citrate	0.10 ,,
Artificial blood serum containing 0.10 per cent. of potassium citrate	0.10 ,,
Artificial blood serum containing 0.20 per cent. of potassium citrate	0.11 ,,

These results show that potassium citrate would not in the slightest degree increase the solvent power of the blood for gouty deposits.

TABLE XLIX.

Showing the solubility at 100° F. of sodium biurate in artificial blood serum alone, and in artificial blood serum containing different proportions of lithium carbonate.

Solvent.	Sodium biurate dissolved.
Artificial blood serum	0.11 per 1,000
Artificial blood serum containing 0.005 per cent. of lithium carbonate	0.11 ,,
Artificial blood serum containing 0.01 per cent. of lithium carbonate	0.11 ,,
Artificial blood serum containing 0.10 per cent. of lithium carbonate	0.15 ,,

These results show that lithium carbonate would not in the slightest degree increase the solvent power of the blood for gouty deposits, even when present in far larger proportions than could be introduced into the blood by medicinal administration. Lithium salts are usually given

in doses of one to five grains three times a day, whereas to get 0.01 per cent. of a lithium salt into the blood it would be necessary to introduce 10 grains of the salt at once into the circulation of an adult man of average weight.

TABLE L.

Showing the solubility at 100° F. of sodium biurate in artificial blood serum alone, and in artificial blood serum containing different proportions of lithium citrate.

Solvent.	Sodium biurate dissolved.
Artificial blood serum	0.11 per 1,000
Artificial blood serum containing 0.005 per cent. of lithium citrate	0.11 ,,
Artificial blood serum containing 0.01 per cent. of lithium citrate	0.11 ,,
Artificial blood serum containing 0.10 per cent. of lithium citrate	0.11 ,,

These results show that lithium citrate would not in the slightest degree increase the solvent power of the blood for gouty deposits.

TABLE LI.

Showing the solubility at 100° F. of sodium biurate in artificial blood serum alone, and in artificial blood serum containing different proportions of sodium bicarbonate.

Solvent.	Sodium biurate dissolved.
Artificial blood serum	0.11 per 1,000
Artificial blood serum containing 0.01 per cent. of sodium bicarbonate	0.10 ,,
Artificial blood serum containing 0.10 per cent. of sodium bicarbonate	0.09 ,,
Artificial blood serum containing 0.20 per cent. of sodium bicarbonate	0.08 ,,

These results show that sodium bicarbonate would slightly decrease the solvent power of the blood for gouty deposits.

TABLE LII.

Showing the solubility at 100° F. of sodium biurate in artificial blood serum alone, and in artificial blood serum containing different proportions of sodium phosphate.

Solvent.	Sodium biurate dissolved.
Artificial blood serum	0.11 per 1,000
Artificial blood serum containing 0.01 per cent. of sodium phosphate	0.11 ,,
Artificial blood serum containing 0.10 per cent. of sodium phosphate	0.11 ,,
Artificial blood serum containing 0.20 per cent. of sodium phosphate	0.11 ,,

These results show that sodium phosphate would not in the slightest degree increase the solvent power of the blood for gouty deposits.

TABLE LIII.

Showing the solubility at 100° F. of sodium biurate in artificial blood serum alone, and in artificial blood serum containing different proportions of piperazine.

Solvent.	Sodium biurate dissolved.
Artificial blood serum	0.11 per 1,000
Artificial blood serum containing 0.01 per cent. of piperazine	0.09 ,,
Artificial blood serum containing 0.10 per cent. of piperazine	0.11 ,,
Artificial blood serum containing 0.20 per cent. of piperazine	0.13 ,,

These results show that piperazine would not in the slightest degree increase the solvent power of the blood for gouty deposits, even when present in far larger proportions than could be introduced into the blood by medicinal administration. Piperazine is usually given in doses of five grains three times a day, whereas to get 0.10 per cent. of piperazine into the blood it would be necessary to

introduce 100 grains of the drug at once into the circulation of an adult man of average weight.

TABLE LIV.

Showing the solubility at 100° F. of sodium biurate in artificial blood serum alone, and in artificial blood serum containing different proportions of lysidine.

Solvent.	Sodium biurate dissolved.
Artificial blood serum	0.11 per 1,000
Artificial blood serum containing 0.01 per cent. of lysidine	0.09 „
Artificial blood serum containing 0.10 per cent. of lysidine	0.10 „
Artificial blood serum containing 0.20 per cent. of lysidine	0.10 „

These results show that lysidine would not in the slightest degree increase the solvent power of the blood for gouty deposits, even when present in far larger proportions than could be introduced into the blood by medicinal administration. Lysidine is given in doses of from 30 to 120 grains three times a day, whereas to get 0.20 per cent. of lysidine into the blood it would be necessary to introduce 200 grains of the drug at once into the circulation of an adult man of average weight.

Further experiments as to the influence of potassium and lithium salts on the solvency of gouty deposits.—As it appeared to me that the experiments of Sir Alfred Garrod, previously referred to, as to the solvent effect of potassium bicarbonate and lithium carbonate on gouty deposits, were scarcely comparable with what occurs when those drugs are acting *viá* the blood and other fluids of the body, I thought it desirable to repeat the experiments under different conditions. I therefore investigated the solvent action on gouty deposits of artificial blood serum impregnated with quantities of potassium bicarbonate and lithium carbonate respectively ;

the quantities of the drugs used were as nearly as possible equal to those which would be present in the fluids of the human body when full doses are being administered. The artificial blood serum impregnated with potassium bicarbonate contained 0.01 per cent. of that drug. The artificial blood serum impregnated with lithium carbonate contained 0.0015 per cent. of that drug. The experiments were carried out in the following manner.

Method of ascertaining the solvent effects of potassium bicarbonate and lithium carbonate on gouty deposits.—A piece of cartilage well and uniformly infiltrated with sodium biurate, which had been removed from a gouty joint at a post-mortem examination, was divided into three equal pieces. One piece was suspended in a bottle containing 100 c.c. of artificial blood serum, the second piece in a bottle containing 100 c.c. of artificial blood serum impregnated with potassium bicarbonate, and the third piece in a bottle containing 100 c.c. of artificial blood serum impregnated with lithium carbonate. The bottles with their contents were kept throughout the experiments at the blood heat, and every twenty-four hours fresh supplies of fluid were introduced, so that the first piece of cartilage was constantly bathed in artificial blood serum at the blood heat, the second piece in artificial blood serum impregnated with potassium bicarbonate, and the third piece in artificial blood serum impregnated with lithium carbonate. By this method of procedure it was considered, as regards any solvent effect that the drugs might exert on the gouty deposit, that the results would be fairly comparable with what occurs when potassium or lithium salts are medically administered. The pieces of cartilage were removed every twenty-four hours and examined by means of a lens, and the experiments were continued until all the sodium biurate was dissolved out of the cartilage. The solution of the sodium biurate from the cartilage proceeded

at the same pace in the three pieces, and was in no way accelerated by the presence of the potassium bicarbonate or the lithium carbonate. The sodium biurate was completely dissolved from the three pieces of cartilage on the fifteenth day.

These experiments indicate that the quantities of potassium bicarbonate and lithium carbonate that could, by ordinary dosage, be introduced into the fluids of the body can exercise no influence on the solvency of gouty deposits, and the results obtained support the view of Sir William Roberts that potassium bicarbonate and lithium carbonate exercise no influence on the solubility of sodium biurate. The net result of all these experiments is that the treatment of gout by alkalies or by piperazine or lysidine does not increase the solubility of the biurate deposited in the joints and tissues. Levison * holds very similar opinions with regard to the alkaline treatment of gout. He considers that the administration of the ordinary alkalies, of lithium salts, or of piperazine with the object of either dissolving sodium biurate or of preventing its deposition is decidedly useless. He also found that the administration of piperazine exerts no influence upon the amount of uric acid excreted.

J. Fawcett, † as the result of his investigations on the treatment of gout by piperazine, arrives at an unfavourable conclusion as to its efficacy in gout. He found that in acute cases it did not relieve the pain, nor was there any constant increase in the excretion of uric acid under its use. Mordhorst ‡ also considers that piperazine and lysidine are useless in the treatment of gout.

A general acidity of the system not associated with gout.—The third assumption, that in connection with gout there is a general acidity of the system which

* "The Uric Acid Diathesis," 1894.

† *Guy's Hosp. Reports*, 1895.

‡ *Therap. Monats.*, x., 1896.

causes a diminished alkalinity of the blood, is opposed to the results of recent investigations on the subject. The experiments of Klemperer and my own experiments show that the alkalinity of the blood of gout is not diminished, and that variations in the alkalinity of the blood may frequently be met with in healthy individuals. Moreover, the experiments previously described demonstrate that a diminution in the alkalinity of blood serum containing uric acid in solution does not facilitate the deposition of sodium biurate from it, nor does a diminution in the alkalinity of blood serum diminish its solvent power for sodium biurate. It appears therefore that there is no ground whatever for the assumption that the treatment of gout by alkalies tends to neutralise a so-called general acidity of the system, and so renders the blood a better solvent of gouty deposits.

No relationship between the acidity of the urine and the alkalinity of the blood.—The idea that a general acidity of the system is associated with gout has, in my opinion, arisen from observations of the fact that the urine of gouty patients is acid. These observations are generally made on small samples of the urine, although when the total acidity of the urine for the twenty-four hours is determined, it is frequently found to be below that of the normal acid output in the urine for that period of time. It is certain that the erroneous assumption has been made by some writers that variations in the acidity of the urine can be taken as a gauge of corresponding variations in the alkalinity of the blood, and that therefore a fall of acidity in the urine means an increased alkalinity of the blood, and *vice versa*. That this assumption is quite wrong is shown by reference to the next table (Table LV.), in which are arranged side by side the determinations that I made on the same days of the alkalinity of the blood and of the total acidity of the urine for each twenty-four hours of an adult patient suffering from subacute

gout. The total acidity of the urine was determined by collecting the whole of the urine for the twenty-four hours, and then titrating a portion of the urine by the process described by Lépinos.* The estimations were made mostly on alternate days throughout the duration of the attack.

TABLE LV.

Showing the absence of any constant relationship between the alkalinity of the blood and the acidity of the urine of a patient during an attack of subacute gout.

Dates of determinations.	Alkalinity represented as percentage of anhydrous sodium carbonate present in the blood.	Acidity of total urine for the 24 hours, reckoned as grammes of hydrochloric acid.
Feb. 4th.	0.167	1.392
„ 6th.	0.167	0.953
„ 8th.	0.167	1.096
„ 10th.	0.156	1.374
„ 12th.	0.167	1.583
„ 15th.	0.158	1.529
„ 17th.	0.158	1.629
„ 19th.	0.167	1.581
„ 22nd.	0.180	1.602
„ 24th.	0.173	Alkaline
„ 26th.	0.161	Alkaline
„ 28th.	0.179	0.608
Mar. 2nd.	0.167	0.622

This table shows that no constant relationship existed in this case of gout between the alkalinity of the blood and the acidity of the urine, and moreover that on those days when, owing to treatment with citrate of potassium, which was administered from February 19th to 28th, the urine remained alkaline, there was no corresponding rise in the alkalinity of the blood.

These determinations of the alkalinity of the blood and the acidity of the urine of this case of subacute gout are shown in curves in the following diagram, a glance at

* *Journ. Pharm.*, 1896 (6), iii., 8-16.

which at once demonstrates that no constant relationship existed between the alkalinity of the blood and the acidity of the urine.

Reasons for believing the treatment of gout by salicylates to be erroneous. — Just as the treatment of gout by means of alkalies is based on the entirely erroneous supposition that uric acid is present as such in the fluids and deposits of gouty patients; so the main reason for

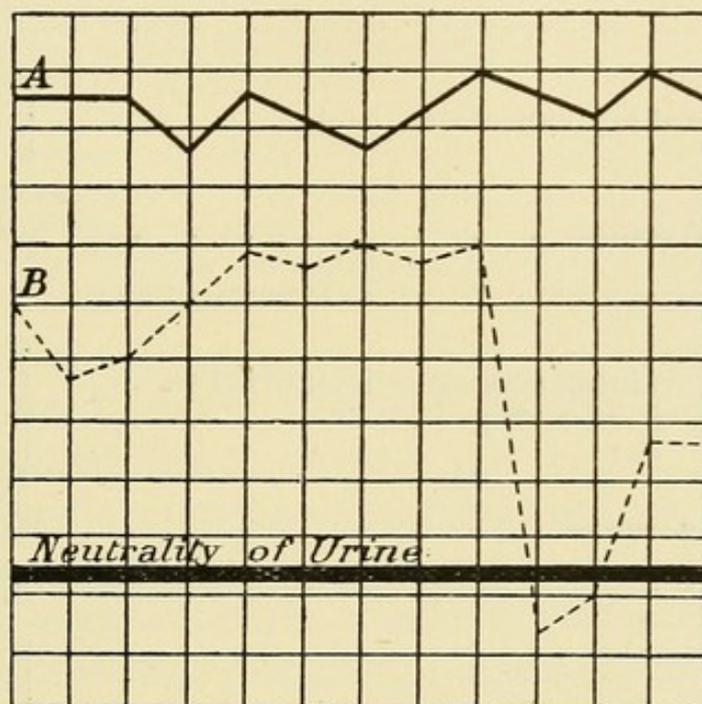


Diagram showing the absence of any constant relationship between the alkalinity of the blood and the acidity of the urine of a patient during an attack of subacute gout.

A, Alkalinity of blood. B, Acidity of urine.

giving a salicylate in gout is based on the assumption that it unites with uric acid throughout the system, and so effects its removal from the system and its elimination in the urine. That sodium salicylate does cause an increased elimination of uric acid in the urine, at all events in the early stages of its administration, is undoubted. This is shown by the following daily determinations that I made of the total uric acid excretion of a healthy man before, during, and after treatment with sodium

salicylate. The diet was of the same nature throughout the experiment.

TABLE LVI.

Showing the daily excretion on successive days of uric acid by a healthy man before, during, and after treatment with sodium salicylate.

	Daily excretion of uric acid in grammes.
Before taking salicylate	{ 0.547 0.589 0.731
Average	0.622
Fifteen grains of sodium salicylate taken . three times a day	{ 0.852 0.942 0.826 0.784
Average	0.851
Salicylate left off	{ 0.340 0.581 0.543 0.677 0.686
Average	0.565

That this increased elimination of uric acid is due, however, to the removal of ready-formed uric acid stored in the system is, in my opinion, incorrect. In the first place it must be remembered that any uric acid deposited in any of the organs or tissues of gouty subjects is deposited in the form of sodium biurate, and the results of the following experiments show that artificial blood serum containing sodium salicylate, in much greater proportions than could be introduced into the blood by the medicinal

administration of the drug, has not the slightest increased solvent effect on the biurate.

TABLE LVII.

Showing the solubility at 100° F. of sodium biurate in artificial blood serum alone, and in artificial blood serum containing different proportions of sodium salicylate.

Solvent.	Sodium biurate dissolved.
Artificial blood serum	0.11 per 1,000
Artificial blood serum containing 0.003 per cent. of sodium salicylate	0.11 „
Artificial blood serum containing 0.006 per cent. of sodium salicylate	0.11 „
Artificial blood serum containing 0.01 per cent. of sodium salicylate	0.11 „
Artificial blood serum containing 0.10 per cent. of sodium salicylate	0.11 „

These results show that sodium salicylate would not in the slightest degree increase the solvent power of the blood for gouty deposits, even when present in far larger proportions than could be introduced into the blood by medicinal administration. Sodium salicylate is usually given, in the treatment of gout, in doses of fifteen to twenty grains three times a day, whereas to get 0.1 per cent. of sodium salicylate into the blood it would be necessary to introduce 100 grains of the drug at once into the circulation of an adult man of average weight. J. Fawcett,* who likewise finds that sodium salicylate produces an increased uric acid excretion, considers it improbable that the increase can be explained by a mere clearing out of retained uric acid.

I also find that artificial blood serum containing sodium salicylate in far larger proportions than could be introduced into the blood by medicinal administration has no effect whatever in delaying the conversion of sodium quadriurate into the biurate, as is shown in the following table:—

* *Guy's Hosp. Reports*, 1895.

TABLE LVIII.

Showing the influence exerted on the decomposition of sodium quadriurate by artificial blood serum, and by artificial blood serum containing 0.1 per cent. of sodium salicylate in solution.

Solvent.	Sodium biurate crystals appeared after the lapse of—
Artificial blood serum	2 hours.
Artificial blood serum containing 0.1 per cent. of sodium salicylate	2 hours.

It therefore appears from the results of the experiments given in Tables LVII. and LVIII. that sodium salicylate has no direct action either in delaying the decomposition of sodium quadriurate or in effecting a solvent action on deposits of sodium biurate. The erroneous supposition as to salicylates possessing a solvent power on gouty deposits probably arose from the faulty deduction that increased elimination of uric acid in the urine after the administration of a salicylate was necessarily due to the solvent effect of the salicylate on uratic deposits. The correct explanation of this increased elimination of uric acid is, I believe, to be found in the known fact that salicylic acid unites readily with glycocine to form salicyluric acid, and that it thus brings an increased amount of glycocine to the kidneys, where by the combination of that body with urea an increased amount of uric acid may be formed.

General conclusions drawn from the investigations.

1. The administration of the ordinary alkalies, of lithium salts, of piperazine, and of lysidine, with the object of removing gouty deposits, appears to be useless.
2. No general acidity of the system is associated with gout.
3. No relationship exists between the acidity of the urine and the alkalinity of the blood.
4. The administration of salicylates with the object of removing gouty deposits appears to be useless.

PART IV.

THE TREATMENT OF GOUT AND OF GOUTY CONDITIONS.

CHAPTER XII.

ACUTE AND CHRONIC GOUT: TREATMENT AND DIET.

General principles of treatment—Examination of the urine—Treatment of acute gout—The action of colchicum—Diet in acute gout—Treatment of subacute and chronic gout—Preventive treatment of gout—Local treatment of gouty joints — Electric light and superheated-air baths—Cataphoresis.

General principles on which the treatment of gout is based.—In the first place it should be borne in mind that no routine treatment can be adopted which is suitable to all cases. The nutritional condition of the patient, his habits, surroundings, and mode of life constitute factors that must necessarily modify the treatment of individual cases, and with gout, as with so many other diseases, it will be found that each individual case requires separate study, and frequently special treatment. Quite apart from the treatment of an attack of gout, which is a comparatively simple and easy matter, must be considered the treatment of the condition or conditions which led up to the attack. In connection with this point it must be remembered that the gouty individual is one whose general metabolism is unstable, and that this instability may be present in one or more of the great physiological systems — the digestive, the nervous, the

circulatory, etc. The question which of these systems is primarily and mainly at fault should always be a matter for patient investigation, and one must then endeavour to improve the metabolism of that system by suitable medicinal, dietetic, and hygienic treatment.

The treatment of gout should have for its aim the following objects:—(1) The treatment of the gouty paroxysm in cases of acute gout, and the relief of the pain as speedily as possible; (2) the treatment of the subacute or the chronic condition, and prevention of the recurrence of an attack; (3) the treatment of the affected joint, or joints, with the object of removing the uratic deposits, and of preventing permanent deformity; and (4) the treatment of the various forms of irregular or abarticular gout.

Examination of the urine.—In all cases of gout a very careful examination of the urine should be made. The indications that the kidneys are not performing their proper functions are the existence of a certain amount of polyuria, a low specific gravity of the urine—usually from 1007 to 1016—the presence of a small quantity of albumen, which, however, may disappear for some time and then reappear, the presence of a few granular casts if a careful microscopical examination is made after centrifuging the urine, and a diminished daily excretion of uric acid and generally of urea. It is most important carefully to examine the urine for traces of albumen, and for the presence of casts. For the latter purpose the centrifugal machine should be used, as the casts, when present, are usually present in but small numbers, and are otherwise very slow to settle. This examination for casts should always be made in those cases where there is a suspicion of organic renal disease, even though there may be a complete absence of albuminuria. It is a common occurrence to find gouty individuals with marked signs of renal inadequacy passing urine of fairly low specific

gravity and quite free from albumen, but in such cases a careful examination of the urine will always reveal the presence of granular and frequently hyaline casts.

It is desirable before commencing treatment, and from time to time during treatment, to know the amount of uric acid that is being daily eliminated in proportion to the body-weight of the patient. This determination of the amount of uric acid eliminated must be made on a sample of the mixed urines of twenty-four hours. The mere determination of the percentage of uric acid in a sample of the urine is useless, as it constitutes no guide to the actual amount of uric acid that is being excreted. It is absolutely necessary to determine the total uric acid elimination for the twenty-four hours, and that can only be done by examining a sample of the mixed urines of that period. Similarly the determination of the percentage of urea in a sample of the urine is no guide to the amount of nitrogenous elimination that is taking place from the kidneys. To ascertain that factor the total output of urea for the twenty-four hours must also be determined.

Treatment of acute gout.—In order to arrest the abnormal intestinal fermentation, to remove the excessive numbers of intestinal bacteria, and to relieve the catarrh of the intestinal mucosa, all factors in the development of abnormal intestinal toxins, the bowels should be freely opened with four grains of calomel or “blue pill,” followed by a saline aperient. For the first twenty-four hours it is preferable that no food should be taken, but water should be drunk freely.

For the treatment of the gouty paroxysm the limb should be placed in the horizontal position, or slightly elevated above the level of the body, and a cradle should be arranged so as to take the weight of the bed-clothes from the affected part. To alleviate the severe pain felt in the affected joint, warm packs should be arranged round it, consisting of cotton-wool saturated with a soothing

lotion, and then lightly covered with oil-silk. I have found the following lotion most useful in relieving the local pain :—

Sodii Carb.	℥	iiij.
Linim. Belladonnæ	℥	ij.
Tinct. Opii	℥	ij.
Aq. ad	℥	viiij.

A small portion of the lotion should be mixed with an equal quantity of hot water, and then poured on cotton-wool previously arranged round the joint. The pack should be changed every four hours. In connection with the acute paroxysm, no attempt at local depletion, such as the application of leeches to the inflamed joint, blistering, or incisions, should on any account be made, owing to the great liability of thereby extending the inflammatory condition, and so producing subsequent ankylosis or deformity.

For the internal treatment of acute gout, colchicum is one of the most valuable drugs that we possess. It should be especially used for acute gout, and for subacute attacks supervening on chronic gout. If it is used continuously, tolerance is apt to be acquired, and then the drug ceases to act. At the commencement, a large dose of thirty to forty minims of colchicum wine should be given, followed by a mixture containing in each dose fifteen to twenty minims of the wine, with from forty to sixty grains of citrate of potassium, which should be administered three times a day. The citrate of potassium, which is given for its combined properties of acting as a diuretic and of diminishing the acidity of the urine, may, if desired, be given as an effervescing mixture, using thirty grains of potassium bicarbonate to twenty grains of citric acid. Colchicum reduces the gouty inflammation, relieves the pain, and shortens the attack. It should only be taken under medical advice, and should never be given in such doses as to produce extreme depression; after the

inflammation of an acute attack has subsided, the doses of colchicum should be gradually diminished until the drug is left off. A very useful method of administering colchicum is in the form of its active principle, colchicine, which may be given in doses of one-fiftieth to one-eightieth of a grain three or four times a day immediately after food. Only a few patients will tolerate doses of one-fiftieth of a grain, the contra-indication of such a dose being the production of diarrhœa and intestinal griping. The following constitutes a very useful pill :—

Colchicinæ	gr. $\frac{1}{60}$
Ext. Nucis Vom.	gr. $\frac{1}{4}$
Ext. Hyoscyami	gr. $\frac{1}{2}$
Ext. Gentianæ	gr. j.

After the initial free purgation, as previously mentioned, it is not desirable to produce too free an action of the bowels. All that is necessary is to have a sufficient action to relieve portal congestion and intestinal catarrh. The following pill effects this purpose, in most cases, very well. It is administered at night, and is followed up, when necessary, by a dose of saline in the morning.

Leptandrin	gr. j.
Iridin	gr. j.
Ext. Hyoscyami	gr. j.
Ext. Colocynth Co.	gr. ij.

If the pain of an acute attack of gout is so severe as to prevent sleep, seven grains of veronal, or ten grains of trional may be given, or a full dose of extract of hyoscyamus will, in some cases, act as a very useful anodyne. The administration of opium or morphine should, if possible, be avoided owing to the risk of its deficient elimination, and also on account of its diminishing the amount of urine, and its tendency to derange digestion and to check hepatic metabolism.

Action of colchicum.—For the past few years my thoughts have been directed with increasing intensity

to the view that the intestinal tract is a very powerful factor, if not the primary factor, in the development of gout. My attention was first directed to this view as the result of some clinical observations which I was making in an attempt to explain the action of colchicum in cases of gout. I happened at that time to see some cases of acute colchicum poisoning, which in many respects resembled acute arsenical poisoning.

In toxic doses, colchicum is first a gastro-intestinal irritant ; it produces nausea, vomiting, choleraic diarrhœa, and rice-water stools, just as arsenical poisoning does. It also, in sufficient toxic doses, produces cardiac depression, and a bilateral neuritis, similar to that produced by arsenic. If, then, in therapeutic doses, the main action of colchicum is upon the gastro-intestinal canal, its rapid efficacy, in cases of gout, is possibly due to its effect upon those abnormal intestinal changes which constitute the primary factor in that disease. Colchicum increases the secretion from the intestinal mucous membrane, and so either prevents the formation, or effects the destruction, of the intestinal toxin which, when absorbed into the circulation, is responsible for the development of gout.

It is probable that the drugs that are of most value in the treatment of gout owe their efficacy chiefly to their power of checking intestinal putrefaction, as well as to preventing the absorption or promoting the elimination of the products of such intestinal putrefaction.

Diet in acute gout.—As previously mentioned, it is preferable that no food be taken for the first twenty-four hours of an acute attack of gout, but water should be drunk freely. During the acute attack the patient should be restricted to a milk diet, which may consist of milk, bread and milk, and tea made with boiling milk instead of with water. Weak tea with cold toast thinly buttered may also be taken. The free drinking of hot or cold water, of salutaris water, or of some simple mineral water, should

be encouraged. The milk diet should be continued until the acute inflammation is subsiding, which stage is indicated by the lessening of the pain, and by the pitting on pressure of the affected parts. No alcohol in any form should be given during this stage, unless there are strong reasons for its administration, such as a weak action of the heart and a feeble, irregular pulse, when a little well-matured whisky diluted with salutaris water will prove the best form of alcohol. Beef tea and any of the meat extracts or essences should be avoided at all times by gouty patients, owing to the tendency they have to irritate the kidneys, and to the fact that they are loaded with waste nitrogenous products. With the subsidence of the acute attack the patient may return to a more liberal diet, but care should be taken to avoid anything indigestible. The dietary suitable for gouty subjects after the acute attack has subsided is fully dealt with in the chapter on diet in gout.

Treatment of subacute and chronic gout. — In addition to colchicum, which may be given in small doses, guaiacum may very usefully be administered as an alterative which stimulates the metabolism of the liver, and also affords relief to the portal system. From five to ten grains of guaiacum resin should be given in cachets two or three times a day, according to the effect on the bowels, since guaiacum sometimes acts as a laxative. The method of administering the powdered guaiacum resin in cachets is far preferable to giving the tincture of guaiacum in a mixture, as, in the latter form, a nauseous medicine is produced, and the precipitated resin tends to cling obstinately to the tongue and fauces. In cases of chronic gout, the colchicum may be very conveniently administered in the form of the colchicine pill, given three times a day. In order to encourage the elimination by the kidneys of the toxic agents of gout, citrate or bicarbonate of potassium should be employed as a diuretic, which increases the volume

of the urine, and, at the same time, diminishes its acidity. The use of the potassium salt may with advantage be pushed until moderate alkalinity of the urine is produced, as, by such means, the tendency to the deposition of uric acid, or sodium biurate, in the kidney-tissues is removed. Free diuresis should also be encouraged by the drinking of sufficient quantities of water. Of the beneficial effects of employing a potassium salt in conjunction with colchicum in the treatment of acute and subacute gout I am fully assured, and my experience is that, of the various potassium salts, the citrate is the most useful. If given in sufficiently large doses, it tends, by its conversion in the kidneys into the carbonate, to diminish the acidity of the urine, which is generally high in connection with the gouty paroxysm, while, at the same time, it increases the solvent power of the urine for the uric acid salts, and so assists their elimination. In cases of sluggish action of the liver, of gastro-intestinal catarrh and torpor, of gouty dyspepsia, and of other forms of irregular gout, in which there are no appreciable uratic deposits in the joints, mineral waters containing sodium salts are undoubtedly beneficial, owing to the action of those salts as hepatic and gastro-intestinal stimulants.

As regards the use of lithium salts in the treatment of gout, my opinion is that they are not so useful as the potassium and sodium salts. The principal objection to their use is their greater toxicity, and depressing action on the heart, as compared with the potassium salts. They consequently have to be given in such small doses that I am very doubtful whether, in such doses, they possess any remedial effect at all. On the other hand, I constantly meet with patients suffering from cardiac depression, and even dilatation, as the result of the excessive and continued consumption of lithia tablets, which are so persistently, so speciously, and so wrongly vaunted as curative of gout.

The enlargement and tenderness of the gouty joints is

due to two causes, the deposition of sodium biurate in the cartilages and fibrous structures, and a chronic inflammatory thickening of the fibrous tissues. For the reduction of this thickening, as well as for painful gout of the sole of the foot, and for gouty neuralgic affections, iodide of potassium, given internally, is a useful remedy. In cases of gout associated with the contracted granular kidney, as evidenced by slight albuminuria and high arterial tension, the administration of iodide of potassium is also most beneficial. I usually prescribe it in doses of ten grains three times a day, and continue its use over a period of six or eight weeks. My experience is that it seems to act more beneficially when given in combination with the compound decoction of sarsaparilla.

In the treatment of the gouty state associated with disturbance of the functions of the liver, the most important consideration is the restoration of that organ to its normal state of activity, and here the alkaline sodium salts are especially useful. There is no better treatment at the outset than a dose of blue pill or calomel at night, followed by a dose of Epsom salts or Carlsbad salts in the morning. Subsequently a pill containing a small dose of "blue pill" or calomel combined with euonymin and colocynth will be found most useful. In such cases of gouty hepatic inadequacy a mixture which I have found most beneficial as regards its stimulating effect on the metabolism of the liver, and also of the gastro-intestinal tract, is one containing sodium bicarbonate, gentian, and nux vomica, taken a quarter of an hour before meals.

The indulgence in high living by gouty subjects induces arterial plethora and a rise of blood pressure. The consequent strain on the arterial walls produces arterial disease if continued long enough, but in the early stages of such rise in blood pressure the administration of "blue pill" and careful attention to diet will always prevent the incidence of arterial disease. Gouty subjects are more prone to the injurious

effects of constipation of even a slight degree than non-gouty individuals.

So-called "Solvents of uric acid."—Uric acid cannot be "washed out" of the system. Substances that dissolve uric acid in the test tube are of little or no use in increasing the output of uric acid in the body. When drugs do increase or diminish the uric acid excretion, they act by directly affecting the cellular processes of the body, and not by dissolving out the uric acid deposits. In no case is there a possibility of converting the uric acid in the deposits into a more soluble condition by the addition of potassium or lithium salts. The only possibility of converting a sparingly soluble primary urate into a more soluble compound is to remove the primary uric acid ions from the solution. That can be done by addition of strong alkaline solutions which convert the primary uric acid ions into secondary ions ; but that is obviously a method inapplicable in therapeutical practice.

Some years ago a solvent of uric acid seemed to have been found in urea. It was apparently shown by Rudel that a water solution of urea, as well as urine, would dissolve very considerable quantities of uric acid or urates. One litre of a 2 per cent. urea solution was said to dissolve at the normal temperature about 0.5 gramme of uric acid, and a 10 per cent. solution more than 2 grammes, while a litre of water dissolves only 0.0253 gramme. Moreover, compounds of the urea with uric acid were said to have been isolated, and these observations excited much interest in regard to the treatment of gout and stone formation. Careful repetition of Rudel's experiments has, however, led to directly opposite conclusions, and it may be confidently stated that urea does not affect the solubility of uric acid in water. Neither does its presence in a water solution sensibly counteract the separation of uric acid from its salts. Nor could any compounds of uric acid and urea be obtained. Consequently, since urea has no influence upon the relations

of solubility and equilibrium of uric acid or its salts, the proposed treatment with urea is destitute of any scientific foundation.

I have deemed it advisable to make no reference to the employment of any of the numerous preparations which are so constantly being introduced to our notice as infallible solvents of uric acid, and as specifics for gout. It is not that I have not made trial of them, but such trials have always led to disappointment, and have sent me back with renewed confidence to the drugs of our Pharmacopœia. I have witnessed, and doubtless shall again witness, the rise and fall in popularity of many a so-called solvent of uric acid, which has been introduced with exaggerated praise, and with the usual undeserved laudation born of insufficient experience.

Preventive treatment of gout.—After convalescence, as much exercise as possible, short of fatigue and discomfort, should be taken in the open air. Cycling is an excellent exercise for the gouty, since it furnishes good muscular movement in the open air without the gouty joints having to bear the weight of the body.

I have now had a considerable experience of the prophylactic effects of guaiacum resin, and I must confess that I know of no drug which is more useful in the preventive treatment of gout. Its action is probably due to its stimulating effect on intestinal and hepatic metabolism. The form in which I prefer to give it is that of the powdered resin in cachets, commencing with doses of 5 grains three times a day after meals, and gradually increasing the dose to one of 10 or 12 grains. In this form it can be taken without any discomfort to the patient, whereas if administered in the form of the tincture in a mixture a most nauseous medicine results.

To prevent, as far as possible, the recurrence of gout the patient should also give careful attention to diet on the lines laid down in the chapter on diet. Regular habits

of life, with even and sufficient exercise, should be encouraged, and constipation should be zealously avoided.

Briefly stated, the individual who is subject to gout, and who wishes to prevent a recurrence of the disease, should lead an active and an abstemious life.

Local treatment of gouty joints.—If much swelling of a joint persists, the limb should be elevated as much as possible, and a light flannel bandage applied to the joint. If the œdema persists, the hot douche followed by sponging with a cold strong solution of common salt will be found serviceable. The application of the so-called solvents of uric acid externally to affected joints is useless, as they are not solvents of sodium biurate. Careful massage and gentle exercise of the stiffened joints should be employed, but only when convalescence is fairly established; massage and muscular movement increase the flow of lymph in the lymph channels, and so tend to promote the removal of uratic deposits, and to increase general metabolism.

A free movement of the lymph in the lymph channels is essential to oxidation and metabolism, and therefore massage and muscular movements exercise an important influence on account of the pumping action produced in the lymph-spaces by both forms of exercise. Muscular movements and respiration are almost the only means by which the circulation is ordinarily carried on in this system, as it has no motor mechanism with the exception of the *vis-à-tergo* of the heart and arteries, and, if these latter are in default, delay and defective metabolism must result if muscular exercise is not taken. This is an argument, from the physiological side, in proof of the fact that a sedentary life and deficient exercise conduce to gout. Massage should never be resorted to in cases of acute gout, as it not only aggravates the disease at that stage, but also causes severe pain; it should be reserved for the more chronic cases. Massage produces an increase in the amount of blood and lymph passing through the tissues concerned,

at the time and afterwards. This improves the nutrition of the affected tissues, promotes absorption of deposits, and restores physiological activity. In subacute or chronic cases, where the joints remain swollen and œdematous, and are the seat of considerable deposits, much benefit is frequently derived from massage and galvanism. Each of the affected joints should be massaged for a few minutes, and then galvanism (5 to 10 milliampères) applied for a few minutes with the negative pole over the affected region, to be again followed by massage. Under this combined treatment the œdema and deposits frequently disappear rapidly. Probably the beneficial effects are due mainly to the increased circulation of blood and lymph induced, and the consequent absorption that takes place.

The Scotch douche is very useful in the treatment of chronically affected joints. A good-sized stream is thrown with considerable force upon the affected joint, cold water being first employed for half a minute, and then hot; the latter should be as hot as the patient can bear, and should be continued for one minute. This process is repeated for fifteen or twenty minutes. The repeated alternations of temperature produce a stimulating effect upon the circulation about the joint, and so increase tissue change, and favour absorption. Massage of the joint should be resorted to immediately after the douching, as the tissues are then in a relaxed condition. In many cases of chronic articular gout the salt pack is efficacious. It consists of flannel soaked in a warm saturated solution of common salt, which is wrapped round the affected joint, covered with oiled silk and a bandage, and kept on all night. It should be repeated nightly as necessary.

For the stiffness and thickening of joints, careful rubbing with iodide of potassium and soap liniment or with the compound camphor liniment may be resorted to. The thermal baths of Bath, Buxton, Harrogate, Strathpeffer, Llandrindod Wells, Aix-les-Bains, and other spas and

mud-baths, are useful in the treatment of cases of chronic articular gout. Treatment by means of baths should, however, be avoided by patients suffering from acute gout, by elderly patients, and by those suffering from any serious cardiac affection.

Electric light and superheated-air baths.—I have found in many cases that a decidedly beneficial influence on gouty joints is produced by electric light baths, followed by electrical treatment in the form of cataphoresis to the affected joints.

Electric light and superheated-air baths promote the oxidative processes within the body, as is shown by the increased elimination of carbon dioxide from the lungs, and also by the increased metabolism of the body in general. They also stimulate the circulation of both the blood and the lymph in the affected joints and so lead to improved nutrition of the parts. This curative action undoubtedly continues after the treatment has been left off. Such treatment therefore is better given intermittently—say, six baths on alternate days ; then intermit for two or three weeks and so on. These baths improve the atrophic condition of the muscles. They cause a temporary elevation of the body-temperature, marked reddening of the skin of the part treated, profuse local or even general perspiration, quickened pulse, lowered arterial tension, and generally considerable amelioration of the pain, and in some cases complete disappearance of it for a time. Radiant heat has a greater penetrative effect than other forms of heat, and, in my opinion, the effect is more stimulating. In cases of acute or subacute gout the pain, as a rule, recurs at varying intervals after a bath, but usually with diminished severity ; and in favourable cases a progressive reduction of the pain occurs after the use of subsequent baths.

Undoubtedly many cases of chronic gout do not show much improvement after the use of electric light or superheated-air baths, and I have frequently experienced great

difficulty in selecting the cases most likely to be benefited by it. As a general rule my experience has been that cases of chronic gout of long standing, with considerable deposits in the joints, do not derive much benefit from these baths. For such cases undoubtedly much more good can be done by the employment of vapour baths, followed by massage of the affected joints, a method of treatment which is frequently most useful in producing softening and absorption of the deposits. It should, however, be borne in mind that electric light baths seem to set up improved circulatory and trophic changes in the joints, which apparently are maintained for a prolonged period after the baths have been discontinued. Certainly I have seen in several cases, after a course of twelve to eighteen electric light baths had resulted in but slight improvement, and the baths had been abandoned in despair, a progressive improvement maintained for weeks and even months after the discontinuance of the baths, an improvement which in some cases has issued in more or less complete cure.

If only one limb is the seat of gout, the question arises as to whether that limb should be locally treated by being placed in a small specially-constructed bath, or whether the "entire body" bath should be used. My experience is that the "whole body" bath is in all cases the most useful, with, in the case of the electric light bath, an extra localisation of the heat and light rays on the affected part. That means, according to my experience, that the more extensive the surface to which the heat and light rays are applied the better is the result. When the ordinary electric light or superheated-air baths are not obtainable, very good results may be obtained at home by the use of an ordinary blanket-tent with a small opening at the top to let out the hot air saturated with moisture. The hot air is supplied by a ring bunsen gas-burner, or by a large spirit-lamp with a flue passing through an opening in the blanket at the foot of the tent.

In the acute or subacute stage of gout, or when a slight attack of gout has just started, I consider the use of the Turkish bath most undesirable. I have known of its employment in such cases being followed by an exacerbation of the attack and extension to joints not at the time affected. This is a point which should be borne in mind by medical men, as many patients on the first appearance of an attack of gout are apt to have immediate recourse to the Turkish bath, and it is well that they should be warned of the danger they thereby incur.

Cataphoresis.—Cataphoresis is useful in many cases of chronic gout with considerable deposits in the joints. By cataphoresis is meant electric osmosis, or the transfer through porous partitions from anode to cathode. The joint may be treated either by immersion in a local bath of the fluid which is to be introduced, the positive electrode being placed in the bath and the negative on the back, or the positive electrode may be kept thoroughly wet by frequent applications of the fluid. The negative electrode should be a large one, about eight inches by five inches, made of zinc and protected by a flannel cover. It is well moistened with warm water, and applied to the lumbar or dorsal region. At the positive pole either potassium bicarbonate or lithium iodide may be introduced into the affected joint. In the former instance the positive electrode is kept thoroughly wet with a saturated solution of potassium bicarbonate ; in the latter the joint is painted over with iodine liniment, and a pad of lint soaked in a saturated solution of lithium carbonate is laid over the iodine surface ; on the lint the positive electrode, which should be a large flat one, is placed, and closely applied to it. Care must be taken to have everything *in situ* before turning on the current, so as to avoid any shock, and to give an easy, steady flow of current.

Although it is not possible to absorb gouty deposits through the skin by means of alkaline baths, yet it seems

probable that such a result can be effected by means of electrolysis. Edison, in 1890, suggested electrolysis for the introduction of lithium into gouty tissues, and since his time several medical experimenters have noted the good effect of this form of treatment. More recently Bordier repeated these experiments, also using as electrode a bath containing a solution of lithium, and made a series of applications to a patient with large gouty deposits in the hands. He was not only able to demonstrate the presence of lithium in the patient's urine, as had been done before by others, but, and this is even more striking, he detected the presence of uric acid in the liquid of the arm baths, thus proving both the introduction of the cation lithium and the extraction of the anion uric acid at one operation. There was also a marked change for the better in the condition of the patient's gouty deposits as a result of the experiments.

CHAPTER XIII.

TREATMENT OF IRREGULAR GOUT.

The treatment of the various forms of irregular gout—Gouty dyspepsia—Hyperchlorhydria—The gouty heart—Neuritis—Insomnia—Gouty eczema—Gouty glycosuria and diabetes—Retrocedent or Metastatic Gout.

Gouty dyspepsia and acidity.—In addition to the usual remedies, such as bismuth subcarbonate, sodium bicarbonate, bitters, etc., taka-diastrase is a most useful drug in the treatment of gouty dyspepsia. It is made up in the form of tablets containing two and a half grains in each tablet, and one of these should be taken immediately before each meal. The taka-diastrase encourages the digestion of the carbohydrate elements of the food, and so prevents the development of fatty acids, which, by their irritating effects, are so common a factor in the development of gouty dyspepsia.

Hyperchlorhydria.—The treatment of this condition consists in a proper regulation of the diet by cutting off any excess of the proteid articles of diet, and by neutralising the superfluous acid by the administration of some alkali. A drug that I have found most useful in the treatment of this hyperchlorhydria is hopogan (the magnesium peroxide). It not only gives immediate relief of the pain and discomfort by its neutralising effect on the excess of acid, but it also parts with one-half of its oxygen, and acts as an internal antiseptic. It is a most valuable drug in many abnormal gastric and intestinal fermentations. It is a white tasteless powder, and is best given in a little milk in doses of twenty to thirty grains three or four times a day taken one hour

after meals. If it exerts too great a purgative effect, the dose should be diminished. It is also very useful in allaying the irritation in many cases of gouty pruritus, which are probably due to absorption of a toxin or toxins from the intestinal tract. In cases of ordinary neurotic dyspepsia, associated with flatulence, the drug is, in my experience, of no value whatever.

Hepatic torpor.—A very common form of irregular gout is due to defective metabolism of the liver, and is known as hepatic torpor, or hepatic inadequacy. In this form, the fæces are pale, generally very offensive, and, as a rule, constipation occurs. Slight jaundice is usually present, as evidenced by a yellowish conjunctiva and muddy complexion, and the urine is highly coloured, of high specific gravity, and very acid. In the treatment of this form of irregular gout the most important consideration is the restoration of the liver to its normal state of activity, and here the alkaline sodium salts are especially useful. There is no better treatment at the outset than a dose of “blue pill” or calomel at night, followed by a dose of Epsom salts or Carlsbad salts in the morning. Subsequently, a pill containing a small dose of “blue pill” or calomel, combined with euonymin and colocynth, will be found most useful. In such cases of gouty hepatic inadequacy a mixture which I have found most beneficial as regards its stimulating effect on the metabolism of the liver, and also of the gastro-intestinal tract, is the following, which should be taken a quarter of an hour before meals :—

Sodæ Bicarb.	gr. xij.
Tinct. Nucis. Vom.	ʒ x.
Tinct. Gentian Co.	ʒ ss.
Sp. Chloroformi	ʒ xij.
Aq. Menth. Pip.	ad ʒj.

Gouty heart is associated with fatty degeneration of the cardiac walls. The treatment should be rest in the recumbent position, and a small dose of “blue pill” or calomel,

followed by a purge of Epsom salts, should be administered. If the pulse is of low tension a mixture containing convallaria and strychnine will be suitable. If anginal attacks occur, nitroglycerine or erythrol tetra-nitrate may be given by the mouth, or inhalations of nitrite of amyl employed. Iodide of potassium is also a very useful drug when there is much pain. The patient must be carefully dieted, and graduated exercise, at first of a passive nature, such as the Schott treatment, and later of an active nature, may be very beneficial. The action of the bowels should be properly regulated, and entire abstinence from tobacco smoking, or extreme moderation in its use, should be advised.

The anginal and syncopal attacks that occur in connection with the gouty heart do not prove fatal, but care must be taken not to overtax the heart, and, at first, only gentle outdoor exercise on the level should be allowed.

Angina pectoris.—In anginal attacks in gouty subjects the pulse is generally one of high tension without the existence of any necessary association of atheroma of the vessels. For the immediate relief of the actual attacks nitroglycerine is the best drug to employ, although in rare cases nitrite of amyl may be found more efficacious. Stimulants and morphine administered hypodermically should also be employed if necessary. For some days after an attack nitroglycerine in doses of one-hundredth of a grain should be given two or three times a day. If organic cardiac mischief exist, the condition must be suitably treated on general principles. In cases of anginal attacks occurring in gouty subjects, as soon as the severe pain has been relieved by the administration of nitroglycerine, a pill containing one grain of the acetic extract of colchicum and three grains of "blue pill" should be given at night and should be followed by a dose of Epsom salts in the morning. When the administration of nitroglycerine is discontinued citrate of potassium and iodide of potassium should be given for some time thrice a day.

Pseudo-angina pectoris.—For the treatment of this affection a dose of hot brandy and water should be given at once, and a mustard leaf should be applied to the epigastrium. On the subsidence of the severe symptoms a pill containing one grain of the acetic extract of colchicum and three grains of “blue pill” should be given at night, and should be followed by a dose of Epsom salts in the morning.

Gouty phlebitis.—For the treatment of this fairly common form of irregular gout the patient should be kept in the recumbent position, and any sudden movement of the affected limb must be prevented, on account of the danger of detaching a portion of thrombus and the occurrence of consequent embolism of the pulmonary artery. Equal parts of glycerine and extract of belladonna should be smeared over the affected part, and a linseed poultice with some of the glycerine and extract of belladonna spread on the surface should be applied and renewed every six hours. In addition to this the ordinary treatment of the gouty state must be resorted to.

Gouty sciatica.—For the treatment of this painful affection the patient must be kept in the recumbent position, and in severe cases the pain should be relieved by a hypodermic injection of morphine. Ammonium chloride, given in doses of thirty to forty grains three or four times a day, is a very useful drug in the treatment of this form of irregular gout. Two grains of salicylate of quinine should also be given in a pill two or three times a day. These measures should be supplemented by the ordinary treatment of the gouty state.

Gouty neuritis.—Blistering along the course of the affected nerve-trunk is the most rapid way of relieving this painful affection. If such a mode of treatment should not be considered desirable, then iodine liniment may be painted along the course of the nerve-trunk, and hot linseed poultices applied as soon as the iodine is dry, and kept in position by a bandage loosely applied. Internally, iodide of potassium

combined with small doses of perchloride of mercury should be given.

Insomnia in gouty subjects.—Many gouty persons complain of insomnia or restlessness when in bed. This is frequently either toxic in its origin, or is due to a state of high tension in the cerebral arteries. As a rule, the insomnia is not complete, but consists of restlessness, interspersed with varying intervals of light or broken slumber. In such cases, careful attention should be given to the state of the pulse, the heart, and the condition of the urine. In many cases it will be found that the pulse is of high tension, and is associated with accentuation of the aortic second sound, perhaps reduplication of the first sound in the vicinity of the apex of the heart, and a slight degree of albuminuria. In such cases the insomnia is best relieved by the administration at night of small doses of "blue pill" or calomel, combined with full doses of the extract of hyoscyamus. Bromide of ammonium may also be given as a sedative, and as a drug which reduces arterial tension, but, with such patients, it is most undesirable to resort to the use of the ordinary hypnotic drugs.

Irritable temper.—For the treatment of the irritable temper of gout, Sir Lauder Brunton recommends the administration of twenty grains of bicarbonate of potassium and ten to twenty grains of bromide of potassium.

Renal calculi.—For the treatment of uric acid renal calculi citrate of potassium should be given in full doses, so as to produce a moderate alkalinity of the urine. By this means the further deposition of free uric acid in the kidneys is prevented, and the alkaline urine, moreover, gradually carries into solution the uric acid already deposited. The free drinking of ordinary water or of one of the mineral waters of the simple kind should be advised.

Gouty eczema.—Of the purely internal causes of eczema, disorder of the gastro-intestinal tract should, in my opinion, be placed first. The gouty person is one who

is not only liable to such disorder and to faulty assimilation of food, but is also particularly vulnerable to inflammations of the synovial and mucous membranes, and of the skin.

In the treatment of this form of irregular gout special attention should be given to two details. One is to see that the bowels are freely opened, which at the outset may be secured by the administration of "blue pill" or calomel followed by a saline; the other point is that entire abstention from alcohol is most desirable, at all events during the treatment and persistence of the eczema. It is best that any form of alcohol should be abstained from, but the prohibition applies more especially, in my experience, to the red wines. I have met with several cases occurring among gouty individuals past the middle age of life in whom two or three glasses of claret or burgundy will in the course of a few hours cause the development of an eczema. During the irritative stage of dry gouty eczema I have found the application of a lotion consisting of liquor plumbi subacetatis ʒj, liquor carbonis detergens ʒj, aqua sambuci ad Oj, most soothing, especially if followed by the use of a simple dusting-powder, such as cimolite powder. For the acute moist type of eczema a similar lotion, but with a preparation of opium replacing the tar-solution, is advisable.

When the eczema is in a chronic condition much benefit is usually experienced from immersion in sulphur-baths, such as those of Harrogate, Strathpeffer, Aix-les-Bains, etc. After the bath the skin should be carefully dried, and a dusting-powder such as cimolite powder freely applied. In cases of gouty eczema and gouty pruritus a careful dietary must be enforced, care being taken to forbid all articles which the experience of the patient in the past has shown to produce dyspepsia. Persons who are subject to attacks of gouty eczema should avoid such acid fruits as strawberries, gooseberries, apples and pineapples; rhubarb also should be excluded from the dietary. As

regards the medicinal treatment of gouty eczema, my experience is that it is not necessary to give the ordinary anti-gout remedies, such as colchicum, etc. It is much more important to treat the dyspepsia and the catarrhal condition of the gastro-intestinal tract, which are generally present as associated or causative conditions, by the administration of subcarbonate of bismuth with the bicarbonate of sodium or the bicarbonate of potassium.

In cases of gouty pruritus, or, as it is sometimes termed, latent gouty eczema, the severe itching is frequently relieved by the use of carbolic-acid lotion, or the itching attending pruritus and urticaria may be relieved by the application of the following lotion :—

Liq. Plumbi Subacet.	ʒij.
Tinct. Opii	ʒiv.
Aq. Rosæ ad	ʒviij.

Rubbing the skin with a menthol cone moistened with water is frequently useful in relieving the irritation. For the treatment of dry skin eruptions Sir William Roberts recommends the skin to be rubbed with a piece of smooth hard paraffin night and morning, so as to leave on the skin a delicate coating, which then probably acts by protecting the cutaneous surface from the air.

Treatment of gouty glycosuria and gouty diabetes.
 —*Dietetic treatment.*—Careful dietetic treatment should be resorted to, without, however, restricting the diet too much. An excessively nitrogenous diet is to be avoided as tending to accentuate the gouty condition, but no hard and fast rules as to the amount of diet can be laid down. Each case must be treated by ascertaining what amount of proteids, fats, and carbohydrates is best borne by the individual. Toasted bread, milk, and milk puddings made with rice, sago, and tapioca are generally permissible in this form of glycosuria. The best test of the suitability of the diet is the fact that the weight of the patient is not diminishing, while, at the same time, the excretion of sugar

is becoming less. The patient should, therefore, be weighed once a week, and the whole of the urine for twenty-four hours should be collected once a week, measured, and the quantity of sugar determined in a sample of the mixed urines, so that the total output of sugar for the twenty-four hours may be known.

Medicinal treatment.—A pill containing one grain of “blue pill,” one grain of acetic extract of colchicum, and two grains of euonymin should be given every other night. A mixture containing thirty grains of ammonium chloride and fifteen minims of dilute nitro-hydrochloric acid in each dose should be taken three times a day; this mixture acts as a stimulant to hepatic metabolism. Opium and its alkaloids are best avoided. A list of the mineral waters best suited for the treatment of gouty glycosuria and gouty diabetes is given later on.

Treatment of retrocedent or metastatic gout.—

Immediate treatment.—If the symptoms are urgent some brandy should be immediately given, and, if necessary, a hypodermic injection of morphine should be administered, provided marked albuminuria does not exist. If the metastatic seizure is a severe one, and especially if it affects either the heart or brain, it may be desirable to reinduce an attack of articular gout by placing the feet in a hot mustard-and-water bath, containing a full tablespoonful of flour of mustard to a gallon of water.

Treatment of the gastro-intestinal form.—A mustard leaf should be applied to the epigastrium, and a mixture containing bismuth subcarbonate, sodium bicarbonate, and hydrocyanic acid should be given. If there is much depression suitable stimulants must be employed.

Treatment of the cardiac form.—Heart tonics, such as digitalis, convallaria, or strophanthus, and brandy, should be administered. A mustard leaf may be applied to the epigastrium. If an anginal attack occurs, then, in addition to this treatment, a dose of nitroglycerine should be given

at once, or an inhalation of nitrite of amyl employed, and, if necessary, a mustard leaf should be placed over the præcordial region. For the treatment of syncopal attacks the patient should be immediately placed in the recumbent position, with the foot of the sofa or bed raised ; some hot brandy and water should be given, warmth and friction applied to the extremities, and a mustard leaf placed over the epigastrium.

Treatment of the cerebral form.—If the patient is plethoric, and if the pulse is hard, and stupor or coma supervenes, venesection should be performed, and from eight to sixteen ounces of blood withdrawn ; in less urgent cases six leeches may be applied to the mastoid region. Five grains of calomel should afterwards be administered by the mouth, and a turpentine enema given.

CHAPTER XIV.

DIET IN GOUT.

General principles of dieting—Digestibility of food—Chittenden's views—Animal food—Purin-free diet—Vegetable food—Starchy and saccharine foods—Fruits—Beverages—Simplicity of meals—The Salisbury diet—Plan of diet for gouty subjects.

General principles of dieting. — No hard-and-fast lines as to dietary can be laid down in the treatment of gout. Each individual must be carefully considered as regards his habit of body, his capacity for the digestion of different articles of food, the amount of exercise he is able to take, and the nature of his work. Derangements of the gastro-intestinal tract constitute a most important factor in the development of acute, chronic and irregular gout; in all forms of gout, whether regular or irregular, there is one invariable symptom, viz., digestive disturbance. It is, therefore, of the utmost importance to secure and maintain a healthy condition of the gastro-intestinal mucous membrane, and a normal daily evacuation, in order to guard against auto-intoxication, which is undoubtedly an early factor in the development of the gouty condition. The individual who is subject to gouty attacks can certainly diminish the number and severity of the attacks, and in many cases can prevent their recurrence, by careful attention to diet, to the quality and the quantity of fluid taken, to exercise, and to a sufficient daily action of the bowels.

Gouty people may for the purposes of the consideration of diet be roughly grouped into three classes:

(1) those who suffer from more or less frequent attacks of acute gout; (2) those who have never suffered from an acute attack, but who are constantly subject to some chronic form of regular or irregular gout, especially after slight indiscretion in diet; and (3) those who are only affected with gouty symptoms (generally of the irregular kind) when they eat or drink certain articles, and who therefore in order to avoid these gouty symptoms have to be specially watchful over their diet. As Mouillot has observed, it will usually be found that patients in classes 2 and 3 are the offspring of those who have suffered from acute gout.

In advising as to the diet of any particular gouty individual the personal factor is a most important one to consider, and it is wise to gain some knowledge as to the likes and dislikes of the individual with regard to food. In this connection it is well to remember the saying of Sydenham, that "more importance is to be attached to the desires and feelings of the patient, provided they are not excessive, than to doubtful and fallacious rules of medical art."

It is well known that the excessive consumption of rich nitrogenous food, combined with excesses in wine and malt liquors, both induces and excites gout. The comparative immunity of females and young people from gout is mainly explained by the absence of such determining causes of the gouty attack, combined, in the case of young people, with the absence of predisposing cause, and also with the fact that the secreting functions are in full activity. The subjects of gout are generally persons who live well and consume a large amount of animal food. Budd, speaking from a long and extensive professional connection with a large rural district, states that he never knew an instance of gout occurring in an agricultural labourer.

Digestibility of food.—Gout, which is a toxæmia originating to a great extent in the alimentary tract, derives its toxic products from the improper digestion of food-stuffs.

Whatever articles of food can be properly digested by the gouty are therefore suitable articles for their dietary. The physical condition of an article of food to a very great extent determines its digestibility. By digestibility is meant not necessarily the extent to which it is absorbed into the blood, but the power of disposing of the food by the stomach, without the production of discomfort or pain. The digestibility of the various kinds of fish, and of the flesh of birds and animals, depends on the length of the muscular fibres, and on the amount of fat deposited between the fibres. The shorter the fibres, and the smaller the amount of fat deposited between them, the more digestible will the article of food be. If an article of food tends to be swallowed in a solid lump, such for instance as new bread or new potatoes, so as to prevent the ready permeation of the substance by the digestive juices, it tends to be indigestible purely by virtue of its physical condition. If such articles were first reduced to minute subdivision by thorough mastication and insalivation, their indigestibility, as far as ordinary individuals are concerned, would disappear.

It is not so much a matter of importance to know whether or not any particular article of food contains uric acid or its antecedents, as to know what are its properties as regards digestibility and as regards its influence on the processes which are concerned in the conversion of food-stuffs into body-stuffs. The researches of Pawlow have shown that the food value of any particular article of diet must depend to a large extent upon the amount of energy necessary for its digestion.

If gouty persons partake of meals of too complex a character, then, owing to the abnormal intestinal and hepatic metabolism of such subjects, excessive production and imperfect elimination of toxic products may result. Although both excessive production and imperfect elimination of these abnormal products of digestion go more or less

together, yet it is a matter of fairly frequent observation that some gouty persons seem to be especially the victims of excessive production of toxic products, and others to be mainly affected by defective elimination.

In regulating diet it is very important to bear in mind that it is in many cases not advisable to change too suddenly the diet to which the patient is accustomed. The composition of the various digestive secretions is adapted to the food they have to digest, so that the individual who habitually eats an excess of proteid comes in time to have gastric and pancreatic secretions which will digest proteid well, and if the carbohydrates of the food have been limited he will also have a limited capacity for their digestion ; so that if a sudden change of diet is ordered, it takes a little time for the constituents of the digestive secretions to adapt themselves to the altered food, and in the meantime the patient may feel worse for the change of diet which will ultimately benefit him. The diet suitable to any patient will depend on the digestive capability of that patient, and should be regulated accordingly ; it is important to remember to treat the individual as well as the disease.

Maintenance of a healthy alimentary tract.—

If, as is probably the case, the toxin or toxins of gout are produced in the intestinal tract, it is obvious that the first efforts at treatment should be directed to obtaining a healthy alimentary tract, and to modifying those habits of living which have caused gastro-intestinal derangement.

Before deciding how these objects can be attained, it is first necessary shortly to consider some points in the digestive processes which take place in the small intestine. Under normal conditions bacterial decomposition does not take place in the upper part of the small intestine, as the duodenum and upper portion of the jejunum are practically sterile. The conditions which favour increased bacterial growth in the intestine are (1) increase in the amount of proteid food (the number of bacteria in the intestine varying

directly with the amount of proteid food), and (2) the reaction of the intestinal contents. As long as the contents are acid, bacterial growth is inhibited, but when, owing to gastric or intestinal dyspepsia, the intestinal secretion is changed, the reaction of the intestinal contents changes, and great increase in the number of intestinal bacteria takes place, while at the same time their pathogenicity is increased. Therefore, the growth of bacteria in the intestinal tract and their pathogenicity will vary directly with the amount of proteid food and the amount of catarrh present.

These facts obviously have a great bearing on the treatment of gout, and explain how it is that excess of proteid food, and those forms of alcohol which tend to produce intestinal catarrh, have such a strong influence on the production of gout.

As regards the amounts of proteid, fat, and carbohydrate that the ordinary individual of average body weight needs during the twenty-four hours to satisfy the normal nutritive requirements of the body, it may be answered in a general way that he requires enough of these foodstuffs to establish physiological and nitrogenous equilibrium, sufficient, that is, to keep up the strength of body and mind that is essential to good health, to maintain the highest degree of physical and mental activity with the smallest amount of friction and the least expenditure of energy, and to preserve and heighten if possible the ordinary resistance of the body to disease germs. Chittenden's opinion is that the smallest amount of food that will accomplish these ends is the ideal diet. There must be enough to supply the true needs of the body, but any great surplus over and above what is really called for may in the long run prove an undesirable addition. It is therefore necessary to have definite and precise knowledge of the amount of proteid, and of the total calorific value, needed to maintain the body in the highest state of efficiency, before any very

exact estimate of what constitutes over-nutrition or under-nutrition can be formed.

It must be understood that no diet contains an adequate amount of proteid food that does not keep up a condition of nitrogenous equilibrium. If the nitrogen output persistently exceeds the nitrogen intake, it is obvious that the body is feeding on its own tissue, which means that the proteid of the food is insufficient in amount. On the other hand, a diet that suffices to maintain body weight, with establishment of nitrogen equilibrium, should, so far as our present knowledge goes, be quite adequate to meet all the wants of the body for proteid matter.

Chittenden considers that the daily consumption of proteid food far beyond the amount required to maintain health, strength, mental and physical vigour, body weight, and nitrogen equilibrium, constitutes a form of over-nutrition as serious in its menace to the health and welfare of the human race as many other evils more striking in character. He believes that there are more people suffering to-day from over-eating and over-nutrition than from the effects of alcoholic drink. He maintains that if people, as shown by experiments, can maintain nitrogen equilibrium and body weight, gain in strength, show greater freedom from muscular fatigue, lose their rheumatic and gouty symptoms, regain a smooth and soft skin, exhibit greater freedom from colds, retain the normal hæmoglobin content of their blood, and in every recognisable way manifest a good condition of health on a low proteid diet, there should be no hesitation in accepting the teaching which the scientific data point to. Chittenden's experiments show that it is quite possible to maintain body weight, and keep up nitrogen equilibrium, and preserve strength, vigour, and good health on from 34 grammes to 56 grammes of proteid matter per day. My own experience is that, on a diet containing this amount of proteid, gouty persons maintain their nitrogen equilibrium and body weight, become free

from most of their gouty symptoms, and generally enjoy a good condition of health.

Animal food.—As regards the question of meat, it must be remembered on the one hand that animal foods constitute to the majority of people the most attractive and appetising forms of diet, and are therefore likely to be taken in excess ; hence the necessity for limiting the amount to be taken. But, on the other hand, it must be borne in mind that it is most desirable to increase the combustion and the oxidative powers within the tissues. In my opinion it is absolutely erroneous to exclude from the dietary of the gouty such articles as meat, fish, and tea, because they are assumed to contain uric acid.

The so-called estimations of uric acid in those articles of diet are not, as I have elsewhere pointed out, estimations of uric acid at all. Moreover, the deduction is an erroneous one that because uric acid is a nitrogenous body, it must therefore be directly derived from nitrogenous constituents of the food, the consumption of which must consequently be avoided.

The contention that a meat diet is poisonous to the human body, on account of the uric acid that it contains, or produces, is preposterous, in view of the facts that many races have maintained robust health on such a diet, and that, for centuries, the beef-eating Englishmen have managed to spread and advance knowledge and civilisation, and to acquire territory in all parts of the world. Surely, if meat is the poison which a certain class of enthusiasts and fanatics maintains it to be, we as a nation should have ceased to exist long ere this. Harry Campbell, in his interesting series of articles on "The Evolution of Man's Diet," has shown that man has evolved from the ape on a highly animalised diet, and that it was on such a diet that the intellectual faculties, and the faculty of language, which distinguish him from the beast, were developed. It is interesting to note that the recent remarkable advance

of the Japanese to the position of a first-class Power amongst the nations is concurrent with the adoption of a more animalised diet by them. The fact that many races in the past have been largely carnivorous as regards their diet, and that some are so even at the present time (Esquimaux, Andamanese, etc.), shows that the assumption that animal foods are necessarily poisonous to man is an entirely erroneous one. No class of food-stuff gives so great an amount of energy and produces so much heat as animal food, and none is more easily digested by the majority of gouty people. On the other hand, the tendency with most people in this country, as I shall have occasion to remark later on, is to eat too much, and to masticate too little, and this applies to the consumption not only of meat but of all other solid articles of diet.

On the whole, it may be stated that animal food, such as fish, chicken, game and meat, is best suited to the majority of gouty cases, whilst foods of the farinaceous class are most likely to disagree. White meats, such as chicken and fish, are more digestible than red meats. The quantity of meat, and especially of red meat, must be restricted in those cases in which the kidneys are imperfectly performing their eliminating functions, as evidenced by a pale urine, of low specific gravity, and deficient in urea and purin-bases.

Purin-free diet.—A purin-free diet is one selected from milk, cheese, butter, white bread, cereal foods, nuts, and fruit. Milk suits gouty people very well, and milk has a special effect in reducing the number of intestinal bacteria, their number being less with a milk diet than with any other.

It is true that a purin-free diet has proved of benefit in certain cases of disease, but there is every reason to believe that in such cases an equal benefit would be obtained by a mixed diet, in which the proteid consumption is kept down to a minimum. So long as temperance in the ingestion

of proteid is observed, it matters but little from what source the proteid is derived.

From Walker Hall's experiments it would appear reasonable to administer sweetbread to gouty patients, since its nuclein portion is only slightly absorbed, for thymus sweetbread contains principally adenin, which is rapidly excreted, and pancreas sweetbread contains mainly guanin, an amino-purin incapable of increasing the urinary purin output and of exerting any injurious effects upon the tissues.

Vegetable food.—A fair proportion of vegetable food should be taken with two meals each day. The choice of vegetables will depend upon the digestive capacity of the patient ; but, excepting the potato, as a rule those vegetables that grow above ground are preferable to root vegetables. Whereas the mineral constituents of meat exercise a marked effect in diminishing the solubility of a gouty deposit, the mineral constituents of most vegetables exercise a marked power in increasing its solubility. The vegetables, the mineral constituents of which I find are most efficacious in this respect, are spinach, Brussels sprouts, potatoes, cabbage, and French beans. At the same time, it must be borne in mind that with certain patients some of these vegetables may tend to produce some form of dyspepsia ; and I must again insist that in the dieting of the gouty no hard-and-fast rules can be laid down, but the idiosyncrasy of each patient to various articles of diet must be made the subject of careful observation and study. Due consideration should also be given to the patient's experience of what articles of diet disagree or agree with him.

Starchy and saccharine foods.—A diet that too largely consists of bread and starchy material leads to gravel in a number of cases. The frequency of uric acid gravel and stone among the rice-fed Hindoos is well known.

Starchy articles of food should be especially limited in

amount in those gouty individuals who are subject to gastric hyperacidity (hyperchlorhydria). This condition is not due to gastric fermentation, but to an excessive secretion of hydrochloric acid by the gastric glands, and is a common cause of dyspepsia, and ultimately of gastric dilatation. It is due to an acid dyscrasia, as the result of which the secretion of gastric juice does not cease with the digestion of the proteid materials of the food, but continues after they have been disposed of. The result is that a considerable portion of the starchy materials is kept back in the stomach, and this retained starch keeps up the gastric secretion, without at the same time giving it any work to do.

When intestinal fermentation and putrefaction occur, as evidenced by a sense of discomfort after a meal, I attach great importance to the reduction of the starchy articles of food, but not to the total exclusion of what I believe to be comparatively harmless, the potato. It is remarkable how frequently one hears from gouty patients the emphatic statement, "I never eat potatoes." I must confess that I do not know of any good and sufficient reason for a wholesale condemnation of this common article of diet. Undoubtedly amongst those gouty patients who suffer from an inability to digest starchy articles of diet—in other words, who suffer from amylaceous dyspepsia—a reduction for the time in the amount of starchy foods taken, including potatoes, is desirable ; but the recognition of the existence of amylaceous dyspepsia is a fairly easy matter, and when present it can be suitably treated. Certainly those who are gouty and fat should be very sparing in the use of potatoes, as of other carbohydrate forms of food. I wish, however, to protest against the too general exclusion from the food of the gouty of so popular and useful an article of diet as the potato. The best form in which potatoes can be taken by the gouty is the crisp form, which requires thorough mastication and insalivation. Boiled new potatoes should be absolutely interdicted to the gouty.

Equally wrong, in my opinion, is the total exclusion of sugar from the dietary of all gouty individuals. Undoubtedly in certain individuals sugar may do harm, as in the cases of gouty persons who are fat, or who suffer from glycosuria, or who are prone to attacks of eczema ; and in such it should be cut off ; but that is no reason for the exclusion of it from the dietary of all gouty patients. I know of many gouty individuals who take sugar with absolute impunity. Some gouty subjects undoubtedly digest very badly all starchy articles of diet, and in such fats may well take the place of starches. Fat bacon, properly cooked, is generally well digested by gouty individuals.

Subjects who are both gouty and fat should avoid sugar, but undoubtedly sugar may be taken with advantage by those who are gouty and thin, and such subjects may also take in moderation marmalade and wholesome jams. Bread may advantageously be given as crisp toast, or in the form of rusks, or in the "Zwieback" or twice-baked form, as in these conditions it requires thorough mastication and insalivation.

In those cases in which it is desirable to reduce the carbohydrate intake, such restriction may be achieved (1) by cutting off sugar, and all articles containing any form of sugar ; (2) by carefully graduating (by weight) the daily intake of starch-containing foods, so as to attain the minimum consistent with adequate nutrition in each individual case ; (3) by similarly graduating the intake of fats if necessary ; and (4) by throwing the onus of nutrition to a considerably greater extent than previously upon fish, lean meat, green non-starchy vegetables, and gelatinous soups.

Fruits.—Any fruit which from experience is known to agree with the individual may be taken by gouty subjects. Apples and oranges generally agree best. Uncooked fruit should never be taken at a meat meal, and is best consumed fasting fairly early in the day, as between breakfast and lunch.

It should always be thoroughly masticated. Strawberries are frequently avoided by the gouty owing to their producing in some subjects a certain amount of temporary irritation of the skin, but such irritation generally passes off in a short time. In a few subjects strawberries produce eczema or some other rash, but such cases merely represent idiosyncrasy to the special fruit, and necessarily such individuals, whether gouty or not, should not eat strawberries. I am, however, strongly of opinion that the indiscriminate banishment of strawberries from the dietary of the gouty is unnecessary. Except in those cases in which there is an idiosyncrasy to their use they constitute a good article of diet for the gouty, on account of their delicious flavour, their antiscorbutic properties, and their richness in potassium salts. It is, however, very necessary that they should be ripe and fresh. They are soon prone to decomposition, and in such a state they aid in the development of those intestinal fermentations which are so inimical to the gouty.

Beverages.—It is my custom to question closely each gouty patient that I see, not only as to the nature of the beverages taken, but also as to their amount; and my general experience is that the great majority of people suffering from gout take an insufficient quantity of water to drink. Consequently there is an inadequate flushing of the liver, kidneys, and other organs and tissues, and therefore imperfect removal of waste and toxic products. More especially does one find this insufficient consumption of fluid among female patients, in many cases due to the absurd and erroneous belief that a diminution in the amount of fluid taken tends to keep down the body-weight and to prevent the occurrence of obesity. Taking from my case-books ten consecutive cases of gout occurring in ladies whom I carefully questioned as to the amount of fluid consumed per diem, I find that amongst these ten the amount averaged only 26 fluid ounces; this included all fluid,

whether taken as water, tea, coffee, soup, wine, ale, etc. The amount is obviously insufficient for the proper flushing of the system. For the treatment, as well as for the prevention, of the gouty condition the free consumption of water apart from meals is most desirable.

Only a small quantity of fluid should be taken during meals, but during the day from two to three pints of some pure water should be taken. In many cases the ordinary tap-water answers perfectly well; but if it should happen to be too hard a water, or of doubtful purity, then some simple water such as still Salutaris, Contrexéville, etc., may be taken.

“Imperial drink” constitutes an excellent febrile drink for the gouty, and in cases of chronic gout may advantageously be taken when the urine is high-coloured and when it deposits amorphous urates on cooling. It is made by dissolving a teaspoonful of powdered cream of tartar (potassium bitartrate) in an imperial pint of water or barley-water, and then sweetening to taste with loaf-sugar which has been flavoured by rubbing against the rind of a fresh lemon. In place of the sugar, an ounce and a half of syrup of lemon may be added to the pint of liquid. In cases of obese individuals the drink should be sweetened with saccharin or saxin in place of the sugar.

The question of alcohol is fully dealt with in the next chapter.

Simplicity of meals.—The diet of gouty patients should be simple, that is, the meals should not be made up of too many articles. Simplicity of food means facility of digestion. Moderation in both eating and drinking is perhaps one of the most essential points to insist on in the dietary of the gouty. Certainly meat, even red meat, should not be excluded from the diet. No class of food-stuff, as I have said, is so productive of energy as animal food; and as most cases of chronic gout are suffering from lowered vitality and want of tone, animal food, at all events in moderate quantity,

is distinctly indicated. My experience supports the truth of this view, as I advise, in the great majority of cases of chronic gout, the taking of one meat-meal a day. The exclusion of any article of diet or of any class of food, without taking into account the surroundings of the case and the peculiarities of the individual, is unscientific. Those articles of diet that are known in the individual to favour intestinal fermentation and putrefaction should be avoided, and, speaking generally, a sense of discomfort after a meal indicates that some article or articles of food have been taken which are not beneficial to the individual in his present condition.

If the gouty symptoms are due to over-production of toxic material from faulty intestinal and hepatic metabolism, and if at the same time the kidneys are sound, then a diet which mainly consists of animal food is indicated, and in extreme cases of this class even the so-called "Salisbury diet" may be useful. If, on the other hand, the symptoms are due to defective elimination on account of diseased kidneys, then a diet which is more vegetarian will be best. The value of the so-called "Salisbury diet" consists in the small amount of energy necessary for the digestion of so simple a diet, and in the fact that it contains little which can set up intestinal fermentation or putrefaction. On the other hand, a strictly vegetarian diet requires more digestive energy than a purely animal one, and a much larger quantity of vegetable food must be taken to produce an equal nutritive effect.

In connection with the question of the amount of food necessary for the maintenance of the most perfect health, it is very important to bear in mind the necessity of adopting the habit of thorough mastication and insalivation of food. This applies not only to the gouty, but to everyone. The thorough mastication and insalivation of food has a very striking effect upon the appetite, leading to the choice of a more simple dietary and enabling

it to be satisfied with a diet which is considerably less in amount than the ordinary habit of incomplete mastication demands.

If, during the treatment of gout, an attack of gouty dyspepsia should at any time intervene, then a milk diet should be employed until the dyspeptic symptoms have abated.

The "Salisbury diet."—As previously stated, as little complexity as is possible in the meals is the main desideratum in the dietary of the gouty, and in a few intractable cases of chronic gout it may even become necessary to reduce the dietary for a time to the simplest possible form, namely, to two articles of food—lean meat and water. There are a few cases of *chronic* gout which undoubtedly improve, and even recover, on an exclusive diet of red meat and hot water. These are generally cases of chronic gouty arthritis which have failed to yield to the ordinary methods of treatment, and which are accompanied by dyspepsia, flatulence, acid eructations, pyrosis, and offensive stools. I have successfully treated a few such carefully-selected cases of chronic gout by the employment of this, the so-called "Salisbury" treatment. It is essential, before placing a patient on such diet, that the urine should be carefully examined, as any advanced condition of kidney disease contra-indicates the employment of such a dietary. If the evidence of kidney derangement is only slight, the adoption of the dietary is not contra-indicated; but the urine must be carefully examined every two or three days, as any considerable increase in the albuminuria would at once be an indication for the discontinuance of this special diet. Gouty patients suffering from organic heart-disease with any failure of compensation should never be placed on this dietary. The dietary consists in the patient drinking from three to five pints of hot water daily, the water being taken from one hour to one hour and a half before each meal, and half an

hour before retiring to rest, and eating from two to four pounds of beefsteak daily. The meat should be freed from fat, gristle, and connective tissue, thoroughly minced, mixed with a little water, and then warmed through with gentle heat until it becomes brown in colour. A little salt and pepper may be added, and the meat eaten in this form or made up into cakes and cooked on the grill. Later on in the treatment, part of the steak may be taken grilled, or a grilled lean mutton-chop may be substituted for one of the daily meals. The course of treatment should last for from four to twelve weeks, after which a gradual return to ordinary diet should be made.

Articles of diet to be avoided by the gouty.—

Rich meat-soups — ox-tail, turtle, mock turtle, kidney, mulligatawny, hare, giblet.

Salmon, mackerel, eels, lobster, crab, mussel, salted fish, smoked fish, preserved fish, tinned fish.

Duck, goose, pigeon, high game.

Meats cooked a second time. Hare, venison, pork, lean ham, liver, kidney; salted, corned, or cured meats, pickled meats, preserved and potted meats; sausages; all articles of food pickled in vinegar; all highly-seasoned dishes and rich sauces.

Tomatoes, beetroot, cucumber, rhubarb, mushrooms, truffles.

Rich pastry, rich sweets, new bread, cakes, nuts, dried fruits, ices, ice-cream.

Diet in chronic gout and for gouty subjects.—

The following plan gives an indication of the diet to be recommended to gouty subjects:—

Morning.—Half a pint to a pint of hot water, flavoured with a slice of lemon-peel, should be slowly sipped immediately on rising.

Breakfast.—A selection may be made from the following articles of diet, according to the taste of the patient:—Porridge and milk, whiting, sole, or plaice, fat bacon,

eggs cooked in various ways, dry toast or "Zwieback bread," thinly buttered, and tea infused for three minutes and then strained from the leaves. Fat bacon is digestible when grilled, but less so when boiled. Eggs should not be taken hard-boiled.

Lunch and Dinner.—Soups suitable for the gouty are vegetable *purées*, and soups made by boiling beef or mutton bones with vegetables, and subsequently removing the fat which separates on cooling. These soups should not be thickened with farinaceous substances.

The varieties of fish most suitable to the gouty are whiting, sole, turbot, plaice, smelt, flounder, grey mullet, and fresh haddock.

The birds that are admissible as articles of diet are chicken, pheasant, turkey, and game (not high).

Butcher's meat, mutton, lamb, and beef should be taken at only one meal in the day, and then in moderate quantity. Two vegetables may be taken at both lunch and dinner. Any of the ordinary vegetables may be taken, except those previously mentioned as best avoided; but those that I consider most likely to prove beneficial to gouty subjects are spinach, Brussels sprouts, French beans, winter cabbage, Savoy cabbage, turnip tops, turnips, and celery. Potatoes may also be taken in moderate quantities. Stewed fruits, or baked apples or pears, may be taken every day at one meal.

Green vegetables as salads may be taken, provided oily dressings are avoided. A simple savoury may, if desired, be taken at the end of dinner, or a small quantity of cheese, if well masticated, and if free from the *penicillium* fungus or mould.

Night.—Half a pint to a pint of hot water, flavoured with a slice of lemon-peel, should be slowly sipped before retiring to bed.

With regard to persons who are disposed to gout, but are not actually suffering from it, the usual mixed diet

may be taken, but they should limit the starchy articles of food, and should avoid all rich sweets, rice, tapioca, and sago. Thin and ill-nourished subjects require modifications in their diet as compared with people who are stout, while those who take plenty of exercise can take food forbidden to the sedentary.

Individuals who especially benefit by a reduction of diet, both as regards quantity and quality, are those overfed people who are past middle life.

CHAPTER XV.

ALCOHOL IN GOUT.

Alcoholic drinks — Acidity and gout-inducing power of wines and beers—Cause of the inducement of gout by wines and beers—Wines least injurious to the gouty—Cider—Perry.

Alcoholic drinks. — Stated as a general principle, a person who is subject to gout is better without alcohol in any form. There are, however, some who require a little alcohol, either to aid digestion or to enable them to get through their work; and here I am entirely in accord with the advice given by Goodhart, that, if a man requires any stimulant at all, it is a matter he must decide by experiment for himself, for no medical man can tell him. If alcohol is necessary or desirable, the form in which it is to be taken is frequently a matter which the patient can decide better than the medical man; but I would insist upon the importance of definitely limiting the amount to be taken, and of restricting its consumption absolutely to meals. Some patients find that a little whisky or brandy suits them best; others find a light still Moselle preferable; a few, but in my opinion only a very limited number, find a light claret agrees best with them. Champagne is a wine which is seldom suited to the gouty, especially if taken daily. In elderly people or in the feeble, a moderate amount of pure whisky undoubtedly does good; but the indiscriminate ordering of whisky to gouty subjects is, I am sure, wrong.

It is well known that certain alcoholic drinks injuriously affect the gouty process, whilst others exert a less injurious

influence. Alcoholic drinks which have been obtained by fermentation, but which have not been submitted to distillation, such as wines and beers, appear to exercise a more harmful influence than if the same amount of alcohol be consumed in the form of one of the distilled spirits, such as whisky, brandy, etc. Sir Alfred Garrod considers that the reason for the prevalence of gout in the south of England and its rarity in Scotland is chiefly to be found in the difference between the beverages drunk in the two countries.

Acidity of wines and beers.—Distilled spirits contain little or no acid, whilst wines and beers are distinctly acid ; and to the acids contained in these drinks many physicians have attributed, and still do attribute, their gout-producing properties. The acids present are tartaric, succinic, malic, acetic, formic, propionic, butyric and œnanthic. The acidity of wines is mainly due to tartaric, malic, and succinic acids. The amount of free acid in sound wine, reckoned as tartaric acid, varies between 0.3 and 0.7 per cent. I found the acidity of some 1847 port, reckoned as tartaric acid, to be 0.6 per cent. Cider owes its acidity mainly to malic acid. Its total acidity is usually 0.1 per cent. If we arrange the various wines in (*a*) their order of acidity and (*b*) the order of their gout-inducing power, we find that the most acid wines are not those which most predispose to gout (Table LIX.). The arrangement of wines and beers in the order of acidity, beginning with the most acid, is that given by Bence Jones, while the arrangement in order of their gout-inducing power is that given by Sir Alfred Garrod.

Hock, Moselle, and the weaker kinds of ales have comparatively little gout-inducing power.

The acidity of alcoholic liquors cannot have much influence in determining an attack of gout, as port, sherry and malt liquors, which are the most powerful predisposing agents, are amongst the least acid, whilst the more acid

wines are comparatively harmless in this respect; moreover, it must be remembered that the organic acids and their salts contained in wines are converted in the body into alkaline compounds, and are excreted in the urine as such.

TABLE LIX.

Wines and beers arranged in order of acidity and gout-inducing power.

(a) Acidity (beginning with the most acid).	(b) Gout-inducing power (beginning with the most powerful).
Moselle Rhine wines Burgundy Madeira Claret Champagne Port Sherry Malt liquors	Port Sherry Other stronger wines Champagne Stout and porter Strong ales Claret Hock Moselle Weaker kinds of ales

Gout-inducing properties of alcoholic drinks. —

The question is—To what constituent or constituents of wines and beers are their gout-inducing properties due? They are not due to the alcohol alone, for in countries such as Scotland, Norway, Sweden and Poland, where distilled spirits are, or were, freely consumed, gout is almost unknown. Moreover, several experiments that I have made indicate that alcohol, in such quantities as are ever likely to be present in the blood, has no effect either upon the conversion of sodium quadriurate into biurate or on the solubility of the latter. The gout-inducing properties are most probably not due to the acids of the wines and beers, for the reasons which have already been given. It is also very doubtful whether the sugar present in wines is *per se* harmful; but as a rule the sweet wines are fortified wines, while the natural wines are generally dry. It is very probable that the sweet fortified wines are prone to produce

fermentative and catarrhal changes in the gastro-intestinal tract, and are on that account harmful to the gouty.

The gout-inducing properties are certainly not directly due to the œnanthic ether and other ethereal salts of wines exerting any effect either on the rate of decomposition of the sodium quadriurate or on the solubility of the biurate. To demonstrate these points, I have extracted from old port wines the ethereal salts to which the bouquet of the wines is due, and have experimented with these ethereal compounds on the quadriurates and biurates. Using quantities far in excess of those likely to be present in the blood after the moderate, or even immoderate, consumption of such wine, I find that none of these volatile constituents exercises the slightest effect either in hastening the decomposition of the sodium quadriurate or in diminishing the solubility or hastening the precipitation of sodium biurate. As to the *modus operandi* of certain wines, such as port, etc., in hastening an attack of gout, I incline to the opinion that the influence of wines on the development of gout is in great part due to the effect they exercise in producing fermentative and catarrhal changes in the gastro-intestinal tract, and in also injuriously affecting hepatic metabolism. At the same time, it must be remembered that those accustomed to drink wine are also able to indulge in other luxuries of the table which greatly favour the development of gout.

As Woods Hutchinson has pointed out, the experiments of Boix appear to have shown that, in the case of alcohol, it is not the direct toxic effect of the drug, so much as the catarrhal and other irritative changes set up by it in the intestines, which produce the poisonous products that are carried to the liver and cause the irritation and degeneration of that organ. In other words, unless alcohol is taken in sufficient amounts to disturb gastric and intestinal digestion, it will not produce the hob-nail liver.

Another consideration to be borne in mind is the rapidly fermentable fruit and malt sugars, esters, and higher alcohols,

which are also present in wines and beers, and which experience in gout shows are more closely concerned with fermentative changes in the stomach and intestines than is the alcohol itself.

Port is a wine which is especially unsuited to the majority of gouty subjects. The gout-inducing properties of the wine are, I believe, mainly dependent upon the ethereal compounds which give the aroma or bouquet to the wine, although these bodies do not act directly on either the quadriurate or biurate of sodium. If this view is correct it would explain the well-known fact that old and matured ports are much more provocative of gout than comparatively new ports taken direct from the wood. The development of the ethereal compounds in the wine extends over many years, and especially progresses after the wine is laid by in bottles. In a few cases of asthenic gout, especially in old people, a moderate amount of comparatively new port taken direct from the wood undoubtedly does good.

In my opinion the wines which are least injurious as a rule to gouty subjects to whom it is found necessary to order a small amount of wine are the light still white wines, such as Moselle, certain French wines, certain Austrian wines, hock, and a few of the lighter Australian and Californian wines. These last, owing to their greater alcoholic strength, should be taken diluted with water or some mineral water.

Gouty subjects suffering from glycosuria or diabetes should entirely abstain from alcoholic drinks, unless marked debility and loss of appetite necessitates the restricted administration of them. Gouty persons subject to attacks of eczema are also much better without alcohol in any form.

“ Rough ” cider, that is the completely fermented apple-juice, taken in moderation, agrees well with most gouty subjects. It contains but a small percentage of alcohol, is free from sugar, and its acidity is chiefly due to malic acid, which passes into the circulation in the form of alkaline malates, which in their turn are converted in the kidneys

into alkaline carbonates and excreted as such, thereby increasing the elimination of urates. The bottled or "champagne" cider, which is imperfectly fermented, should never be used by gouty individuals, owing to its undoubted liability to set up gastro-intestinal fermentations. Dry or "rough" cider mixed with an equal quantity of an aerated water is an excellent beverage for the gouty. Dry perry is also a suitable drink for the subjects of gout.

CHAPTER XVI.

SPA, BALNEOLOGICAL, AND CLIMATIC TREATMENT.

Spa treatment—Ionic theory and Radio-activity—The uses of mineral waters in the treatment of gout—Classification of mineral waters—The simple waters—Simple alkaline waters—Alkaline sulphated waters—Alkaline muriated waters—Common salt or muriated waters—Sulphur waters—Hot and cold mineral waters—Choice of a spa—Balneology—Climatic Treatment.

Spa treatment.—The free employment of water in the treatment of gout dates from ancient times. At the Temples of Asklepios at Epidaurus and Athens water was used extensively both internally and externally, and active gymnastic exercise, riding, friction of the skin, massage, and counter-irritation were prescribed.

Spa treatment is a complex treatment made up of several factors, and on the correct apportionment of these different factors depends much of the successful issue of the treatment. These several factors are (1) hydrotherapy, which includes the taking of, and the bathing in, the waters; (2) diet; (3) exercise; and (4) accessory forms of treatment, such as electric light baths, electrical treatment, massage, etc. With regard to the drinking of a water at a spa there is a tendency with some medical men to consider that the efficacy of a natural mineral water is due solely to its watery constituent—in other words, that its one therapeutic use is that of a flushing agent. Even so astute a physician as the late Sir William Roberts appears to have held this view. In his Croonian lectures, referring to the employment of the waters of certain spas in the

treatment of gout, he said :—“ Now there can be no reasonable doubt that the efficacy of these springs has nothing to do with their scanty mineral ingredients but depends on their watery constituent. . . . Their action would be to temporarily dilute the blood and lower its percentage of urates and sodium salts. This effect would tend to retard or prevent uratic precipitation, and thus give the defective kidneys additional time to overtake their arrears in the task of eliminating uric acid.”

Ionic theory and radio-activity.—If the efficacy of a natural mineral water depended solely on its watery constituent I do not for one moment think that the resort of sufferers to the various natural springs would have successfully stood the test of centuries as it undoubtedly has. The fact is that in judging of the effect of natural mineral waters we have been too much under the domination of analytical chemistry, and that our deductions from these results have been consequently biased and cramped. The more I consider the therapeutic effects of the natural mineral waters the more convinced I am that chemical analysis, although it can inform us what are the mineral constituents of the natural waters, is yet unable to determine exactly the state of the salts dissolved in them. The “ ionic or electrical dissociation theory ” and the existence of the mineral constituents of natural waters as “ ions ” are leading our thoughts to a new and, I believe, correct appreciation of the therapeutic values of these waters.

An element or a group of elements divorced from the rest of the original molecule is an “ ion.” According to the ionic theory metallic salts in very dilute solutions are completely split up into their “ ions,” so that all the properties of these solutions must be the sum of the properties of the separate “ ions.” In concentrated solutions much of the salt remains in the undissociated state and only a small proportion in the form of dissociated “ ions,” whereas in most of the natural mineral waters, which are weak solutions of salts, the

mineral constituents are mainly, if not entirely in many waters, in the form of "ions," and in this form the therapeutic effects and potency may be quite different from those of the undissociated salts. Ionic dissociation does not, therefore, alter the percentage composition of a salt, but may very materially alter its therapeutic properties, so that in all probability the "ions" rather than the salts are responsible in great part for the effects of mineral waters.

In intimate relation with this aspect of the matter is the question of radio-activity in hydrotherapy. Our conception of the atom as an indivisible and finite body is disappearing, and, in view of the recent discoveries that have been made in connection with radio-activity, the atom must be conceived as consisting of an aggregate of corpuscles, and each atom has associated with it a definite charge of electricity, such an electrically charged atom being an "ion." The smallest unit of electric charge is known as an "electron," and the atom is charged with a number of these electrons, which are in a state of vigorous motion among themselves within the atom. Radio-activity consists in the flinging away with great violence of actual atoms. The substance left is also radio-active, and ultimately one of the residues seems to discharge electrons instead of atoms of matter, thus effecting a transmutation of matter.

Now, most, if not all, of the natural mineral waters which have been examined have been found to be distinctly radio-active, and the lower the mineralisation of the water the more intense is its radio-activity. In this, I think, lies the explanation of the fact that an artificially prepared mineral water, although it may be made identical in chemical composition with the natural one, does not possess the same therapeutic effects as the natural water, since it is lacking, at all events to any appreciable extent, in the property of radio-activity. A natural water at the moment of its discharge from the earth is radio-active, whereas an ordinary drinking water does not possess this property in an

appreciable degree. Hence also the desirability of drinking the water at its source, since by the bottling and keeping of a natural water the radio-activity is to a great extent lost. When we consider the marked influence of radio-active emanations on new growths and various morbid tissues, is it too remarkable to conceive that a radio-active mineral water will exercise a potent effect on those morbid changes within the body which are connected with abnormal tissue metabolism ?

Uses of mineral waters in the treatment of gout.—

If gout is primarily due to the absorption of toxins from the intestinal canal dependent upon a catarrh of the intestinal mucosa, many of the natural mineral waters must be efficacious in altering the catarrhal condition and in improving the digestive processes ; also the secondary effect of increasing the flow of bile and of thoroughly washing out all the tissues, so as to get rid of toxic accumulation, is important.

The value of a given mineral water in the treatment of gout depends greatly on the main object with which it is taken. For instance, it may be taken to remove gouty deposits, or to stimulate the action of a sluggish liver and to relieve portal congestion, or for the treatment of gouty dyspepsia, or to relieve the bowels in cases of torpor and gastro-intestinal catarrh, or to act on the kidneys, or to relieve gouty affections of the skin. Now it is manifest that any one mineral water is not likely to produce all these effects, and it is also obviously conceivable that a mineral water which might be most useful to effect one of these purposes might prove injurious if employed to effect another. No doubt considerable error has arisen from indiscriminately sending gouty patients to a particular spa, without giving due consideration to the question as to whether the water of that spa is suitable for the treatment of the specific gouty disorder from which the patient is suffering. It is well to bear in mind that a patient should

not be sent to a spa during the acute stage of gout, nor if suffering from marked organic disease of the heart or kidneys.

It is especially in cases of chronic gout, of gastro-intestinal catarrh and torpor, of gouty dyspepsia, sluggish action of the liver, gouty eczema, gouty glycosuria, and of other forms of irregular gout, that mineral waters prove so valuable, whilst the various baths, combined with massage, are very useful in producing softening and absorption of the deposits in the joints and other tissues.

The explanations given as to the *modus operandi* of a particular mineral water must sometimes be received with a certain amount of caution. For instance, the advocates of one mineral water will extol its efficacy in the treatment of gout on account of the lime salts contained in it and its freedom from sodium salts, whilst, on the other hand, the advocates of another mineral water will insist that the large quantities of sodium salts present in it and the absence of lime salts are the potent factors in its usefulness in the treatment of gout.

With regard to the presence of lime salts, a mineral water containing such does not exercise, by virtue of those lime salts, either a deleterious or a beneficial action on the gouty deposits of sodium biurate. The only objection to a water containing a large quantity of lime salts is the tendency to produce digestive disturbances and to cause constipation.

CLASSIFICATION OF MINERAL WATERS.

The various mineral waters used in the treatment of gout may be classified according to their chemical composition into the six following groups :—

1. The simple waters, or waters comparatively free from sodium salts.
2. The simple alkaline waters.
3. The alkaline sulphated waters.

4. The alkaline muriated waters.
5. The common salt or muriated waters.
6. The sulphur waters.

1. **The simple waters, or waters comparatively free from sodium salts.**—These are the waters that are especially likely to prove useful for the removal of uratic deposits in the joints and tissues. They contain small proportions of calcium carbonate and calcium sulphate, but the quantities of sodium salts present are so small that for all practical purposes they may be neglected. The following table (Table LX.) shows the proportions of sodium salts in the respective waters of this class, represented as grains of sodium per gallon :—

TABLE LX.

Showing the proportions of sodium salts, represented as grains of sodium per gallon, in the principal simple waters.

Mineral water.	Grains of sodium per gallon.
Teplitz	0.20
Strathpeffer	0.45
Contrexéville	0.79
Buxton	1.47
Pfaefers	1.61
Gastein	5.89
Wildbad	7.63
Bath	9.42
Vittel	13.39

Teplitz (Bohemia). The waters are hot (83° to 114° F.). Altitude about 730 feet. Thermal baths and peat baths are provided. Open all the year, but the usual season is from May to September.

Strathpeffer (Scotland, Ross-shire). The waters are cold. Altitude about 200 feet. Strathpeffer also possesses sulphur springs and a chalybeate spring. Various kinds of baths are provided. The sulphur waters are useful

in the treatment of the various skin affections connected with gout. Open all the year, but the usual season is from May to October.

Contrexéville (France). The waters are cold. Altitude 1,150 feet. Baths are provided. The water, in addition to being almost free from sodium salts, contains magnesium sulphate, so that it is useful not only for the removal of uratic deposits, but also in the treatment of gastro-intestinal and hepatic disorders associated with gout, and for the treatment of urinary gravel. The season is from the beginning of June to the end of October.

Buxton (England, Derbyshire). The waters are warm (82° F.). Altitude 1,000 feet. Baths, douches, and douche-massage are provided. The water contains a considerable amount of free nitrogen. On account of the very small proportion of sodium salts present it is an extremely beneficial water to employ with the object of removing uratic deposits. The climate is bracing. Open all the year, but the season is from April to September.

Pfäfers (Switzerland). The waters are warm (89° to 93° F.). Altitude about 1,700 feet. Baths are provided. The season is from May to October.

Gastein (Austria). The waters are hot (78° to 121° F.). Altitude 3,310 feet. Baths are provided. The season is from the beginning of May to the end of September.

Wildbad (Germany). The waters are hot (91° to 105° F.). Altitude about 1,320 feet. Baths, douches, and electric baths are provided. The season is from the beginning of May to the end of September.

Bath (England, Somersetshire). The waters are hot (104° to 120° F.). Altitude 100 feet. Excellent baths, douches, and douche-massage are provided. The water is a very useful one to employ with the object of removing uratic deposits, and chronic affections of the joints can be well treated at Bath by external methods. Open all the year, but the spring and autumn are the favourite seasons.

The climate of Bath is mild, and it is therefore a good winter resort.

Vittel (France). The waters are cold. Altitude 1,100 feet. The season is from May to September.

2. Simple alkaline waters.—These waters contain sodium bicarbonate. They are useful for gouty patients suffering from hepatic congestion, dyspepsia, and gastro-intestinal catarrh. The principal waters of this class are those of Vichy, Vals, Neuenahr, Salzbrunn, Fachingen, and Bilin.

Vichy (France). The waters are hot (89° to 110° F.). Altitude 736 feet. Baths are provided. The waters are especially useful in the treatment of gouty dyspepsia and gastro-intestinal catarrh, in cases of deranged hepatic function, and for plethoric gouty patients suffering from glycosuria or diabetes. The cases best suited to Vichy are gouty dyspeptics, fairly vigorous, with a tendency to pass acid urine, with deposits of urates and uric acid. It is also very efficacious in promoting the evacuation of renal (uric acid) calculi. Open all the year, but the season is from the middle of May to the end of September. In the middle of summer Vichy is very hot.

Vals (France). The waters are cold. Altitude 300 feet. The waters may be used for the same class of gouty cases as mentioned in connection with the Vichy waters, but those springs containing iron should be avoided by gouty patients. The season is from the middle of May to the middle of October.

Neuenahr (Germany). The waters are hot (75° to 104° F.). Altitude 760 feet. Baths are provided. The waters may be used for the same class of gouty cases as mentioned in connection with the Vichy waters. The season is from May to October, but in the middle of the summer Neuenahr is very hot.

Salzbrunn (Prussian Silesia). The waters are cold. Altitude 1,320 feet. The waters may be used for the same

class of gouty cases as mentioned in connection with the Vichy waters. The season is from the beginning of May to the end of September.

3. Alkaline sulphated waters.—These waters contain sodium bicarbonate, sodium sulphate, and generally a moderate proportion of sodium chloride. They are useful in the treatment of gout connected with congestion of the liver and portal system, and of gout connected with gastro-intestinal catarrh and with some forms of dyspepsia. They may also be employed in the treatment of gouty glycosuria. The principal waters of this class are those of Carlsbad, Marienbad, Tarasp-Schuls, Bridesles-Bains, Cheltenham, Leamington, and Bertrich.

Carlsbad (Bohemia). The Carlsbad waters are rich in sodium sulphate and sodium bicarbonate, and also contain a moderate proportion of sodium chloride. The waters are hot (95° to 162° F.). Altitude 1,160 feet. Baths are provided. The waters are best suited for gouty patients suffering from torpor of the hepatic and gastro-intestinal functions, and especially for cases of congestive enlargement of the liver with a tendency to hæmorrhoids. The Carlsbad waters have a remarkable action on the liver, and they have been especially utilised in the treatment of gout associated with hepatic congestion, hæmorrhoids, and "abdominal plethora." They are also of use in the treatment of gouty glycosuria. The waters are best suited for those of fairly robust constitutions. They are contra-indicated if heart disease is present, or if arterio-sclerotic changes are advanced, or if the kidneys are seriously implicated. The season is from the middle of April to the end of September. A course at Carlsbad may advantageously be succeeded by a stay in Switzerland at a station situated at a high altitude.

Marienbad (Bohemia). The waters are cold. Altitude about 1,980 feet. Baths are provided. The waters are very similar in composition to those of Carlsbad, and

are useful for the same class of cases. The season is from May to September. A course at Marienbad is also advantageously succeeded by a stay at a high altitude.

Tarasp-Schuls (Switzerland). The waters are cold. Altitude 3,870 feet. Baths are provided. The waters are useful for the same class of cases as mentioned in connection with the Carlsbad waters. The season is from the middle of June to the middle of September.

Brides-les-Bains (France.) The waters are hot (95° F.). Altitude about 1,860 feet. Baths are provided. The waters are useful for the treatment of gouty dyspepsia associated with constipation. The season is from the beginning of June to the end of September.

Cheltenham (Gloucestershire). The waters are cold. They are rich in sodium chloride and sodium sulphate; one of them contains in addition a large amount of magnesium sulphate; the Pittville or alkaline water contains, besides sodium chloride and sodium sulphate, a fair proportion of sodium bicarbonate. Baths are provided. The Cheltenham waters differ to a considerable extent from any other mineral waters found in England. They are fairly closely comparable to the waters of Marienbad, Homburg, and Tarasp-Schuls. The waters are useful for the same class of cases as are dealt with at Carlsbad, Marienbad, and Homburg. Cheltenham possesses a comparatively dry atmosphere, and the winters are mild. It is especially suitable for those who have lived long in hot climates.

Leamington (Warwickshire). The waters are cold. Baths are provided. The waters are useful in the treatment of torpid conditions of the liver and of the gastrointestinal tract associated with gout, and also in the treatment of gouty glycosuria.

4. Alkaline muriated waters.—These waters contain sodium bicarbonate and sodium chloride. They are useful in the treatment of gouty dyspepsia and of gouty

catarrhal affections of the respiratory organs. The principal waters of this class are those of Ems, Royat, Assmannshausen, and La Bourboule.

Ems (Germany). The waters are hot (80° to 120° F.). Altitude 300 feet. Baths are provided. The waters are especially useful for patients suffering from gouty bronchitis and asthma, for the treatment of which affections they can be inhaled in a finely divided condition. They may also be employed in the treatment of gouty dyspepsia. The climate is a relaxing one, and is best suited to elderly gouty patients.

Royat (France). The waters are warm (68° to 95° F.). Altitude 1,480 feet. Baths are provided. The waters are useful for the same class of cases as mentioned in connection with the Ems waters. The season is from the middle of May to the middle of September.

Assmannshausen (Prussia). The water is tepid (82° F.), and contains a small proportion of lithium bicarbonate.

La Bourboule (France). The water is hot (130° F.). Altitude 2,780 feet. Baths are provided. The waters are arsenical as well as alkaline muriated, and may be useful in certain cases of chronic gouty skin disorders. The season is from the beginning of June to the end of September.

5. Common salt or muriated waters.—These waters contain sodium chloride as their principal constituent, and some of them also contain a large amount of free carbonic acid gas.

Sodium chloride has a stimulating effect upon the mucous membrane of the gastro-intestinal tract. In the stomach it dissolves the mucus, increases the secretion of gastric juice, and so helps to promote the digestion of albuminous substances. In the intestines it stimulates the flow of pancreatic juice and bile, and owing to its influence on the process of osmosis, promotes the absorption of food. Intestinal peristalsis is also increased. The

waters are of use in the treatment of gastro-intestinal and hepatic gout, especially when accompanied by constipation, and in cases of gouty dyspepsia associated with general atony. They are not indicated in cases of articular gout, when the removal of the uratic deposits is the main object of treatment. The principal waters of this class are those of Homburg, Wiesbaden, Kissingen, Baden-Baden, Nauheim, Llandrindod Wells, Woodhall Spa, Llangammarch Wells, Oeynhausen.

Homburg (Germany). The waters are cold. Altitude about 600 feet. Baths, massage, and electrical treatment are provided. The waters produce slight purgation and diuresis, and are useful for the treatment of gouty dyspepsia with a tendency to constipation, and of gouty gastro-intestinal catarrh and hepatic congestion associated with general atony.

Wiesbaden (Germany). The waters are hot (100° to 156° F.). Altitude 380 feet. Baths are provided. The waters are useful for the same class of cases as mentioned in connection with the Homburg waters, but should be avoided in cases of articular gout. Open throughout the year, but in midsummer Wiesbaden is very hot.

Kissingen (Bavaria). The waters are cold. Altitude about 600 feet. Baths are provided. The waters are useful for the same class of cases as mentioned in connection with the Homburg waters. The season is from May to the end of September.

Baden-Baden (Grand Duchy of Baden). The waters are hot (120° to 150° F.). Altitude about 650 feet. Baths, douches, and electric baths are provided. The waters are useful in the treatment of gastro-intestinal catarrh and sluggish conditions of the liver. Open all the year, but the season is from the beginning of May to the end of October. During July and the first half of August Baden-Baden is very hot.

Nauheim (Germany). The waters are warm (82° to

95° F.). Altitude about 400 feet. This spa is specially known for its baths in connection with the treatment of various affections of the heart. Two of the waters are somewhat similar in composition to the Homburg water, and may be employed in the treatment of gouty dyspepsia. The season is from May to the end of September.

Woodhall Spa (Lincolnshire). This water, in addition to being a highly muriated water, contains bromides and iodides.

Llangammarch Wells (Wales, Brecknockshire). Altitude about 600 feet. This water, in addition to being a muriated water, contains a small quantity of barium chloride.

Brine baths.—The brine baths of Droitwich (England, Worcestershire), Kreuznach (Germany), Ischl (Austria), Rheinfelden (Switzerland), Aussee (Styria), Reichenhall (Bavaria), and Bourbonne-les-Bains (France) are useful in the treatment of stiffness and thickening of the joints in cases of chronic articular gout, but should be avoided if gouty skin affections are present.

6. Sulphur waters.—These waters contain sulphur, some in the form of sulphuretted hydrogen only, while others, in addition to free sulphuretted hydrogen, contain combined sulphur in the form of the sulphides of calcium, magnesium, and sodium. They are frequently very useful in the treatment of gouty skin affections, especially eczema and psoriasis. Sulphur baths are also of benefit for the same purpose.

In my opinion, patients actually suffering from acute or subacute articular gout, or who are apparently on the verge of such an attack, are better without sulphur waters, as in such cases the waters tend to accentuate or precipitate an attack in the joints. At the present time, however, it is far commoner to meet with gout in some of its irregular forms than in the articular form, and in most of the cases of irregular gout the beneficial effects of sulphur waters are beyond question, and especially does this apply to

the forms of gastro-intestinal catarrh, hepatic inadequacy, and eczema due to the gouty condition. The sulphur springs may be classified into the cold and hot springs.

Cold sulphur springs.—The principal waters of this class are those of Harrogate (England, Yorkshire), Strathpeffer (Scotland), Llandrindod Wells (Wales, Radnorshire), Gurnigel (Switzerland), Heustrich (Switzerland), Nenndorf (Prussia), and Weilbach (Germany).

Hot sulphur springs.—The principal waters of this class are those of Aix-les-Bains (France), Aix-la-Chapelle (Germany), Baden (Switzerland), Baden (near Vienna), Uriage (France), Bagnères-de-Luchon (France), Allevard (France), Saint-Honoré (France), and Schinznach (Switzerland).

Harrogate (Yorkshire). The waters are cold. Altitude 400 to 600 feet. The principal waters contain sulphuretted hydrogen and sodium sulphide. The "Kissingen well" water is a muriated chalybeate water. Harrogate is well provided with recent and elaborate appliances for baths, douches, etc. The waters are especially useful in the treatment of the various forms of gastro-intestinal catarrh, hepatic inadequacy, and eczema due to the gouty condition. The various baths are extremely beneficial in the removal of the stiffness and swelling of the joints left after an attack of gout. The spa is open all the year, but the season lasts from May to September.

Llandrindod Wells (Wales). The waters are cold. Altitude 700 feet. The waters are somewhat similar to those of Harrogate, and are used for the same class of cases. The season is from May to October.

Strathpeffer (Scotland). The waters are cold. Altitude 200 feet. The principal waters contain sulphuretted hydrogen and sodium sulphide, and are used for the same class of cases as the Harrogate waters. Various kinds of baths, including peat baths, are provided. The spa is open all the year, but the season lasts from May to October.

Aix-les-Bains (France). The waters are hot (112° F.). Altitude 870 feet. The waters contain free sulphuretted hydrogen. This spa is especially known for its baths, douches, and douche-massage, all of which methods of treatment are most beneficial in the removal of the stiffness and swelling of the joints left after an attack of gout. The waters are also employed in the treatment of cutaneous affections connected with gout. The spa is open all the year, but the season lasts from April to November.

Hot and cold mineral waters.—The following table shows a classification of the various mineral waters used in the treatment of gout into hot and cold waters:—

TABLE LXI.

Classification of the various mineral waters used in the treatment of gout into hot and cold waters.

Hot.	Cold.
Aix-les-Bains	Cheltenham
Aix-la-Chapelle	Contrexéville
Baden	Harrogate
Baden-Baden	Homburg
Bath	Kissingen
Brides-les-Bains	Leamington
Buxton	Llandrindod Wells
Carlsbad	Marienbad
Ems	Salzbrunn
Gastein	Strathpeffer
La Bourboule	Tarasp-Schuls
Nauheim	Vals
Neuenahr	Vichy (some springs)
Ragatz-Pfaefers	Vittel
Royat	
Teplitz	
Vichy (some springs)	
Wiesbaden	
Wildbad	

Choice of a spa.—In the selection of a spa, so many factors have to be considered that it is impossible, in a work of this nature, to deal fully with the subject. I wish,

however, to state clearly that the high state of efficiency to which our home spas have been raised renders it no longer essential to banish our patients to foreign health resorts, and that, unless a complete change of environment is desired by the patient or is essential to recovery, treatment can, in the great majority of cases, be carried out as effectually in our own country.

The following table may be of some value as an attempt to classify the therapeutic indications of mineral waters in the treatment of gouty conditions.

TABLE LXII.

Classification of the various mineral waters according to their therapeutic value in the treatment of the various forms of gout.

Object of taking the waters.	The waters best suited to the purpose.
Absorption of gouty deposits from the joints and tissues.	Bath, Buxton, Contrexéville, Gastein, Harrogate, Pfaefers, Strathpeffer, Teplitz, Vittel, Wildbad, Aix-les-Bains (for baths).
Treatment of gouty dyspepsia.	Brides-les-Bains, Carlsbad, Ems, Harrogate, Homburg, Kissingen, Neuenahr, Royat, Vals, Vichy, Wiesbaden.
Treatment of gouty congestion and torpor of the liver, and of gastrointestinal catarrh and torpor.	Baden-Baden, Bourbonne, Carlsbad, Cheltenham, Contrexéville, Harrogate, Homburg, Kissingen, Leamington, Llandrindod Wells, Marienbad, Neuenahr, Tarasp-Schuls, Vals, Vichy, Vittel, Wiesbaden.
Treatment of gouty affections of the respiratory organs.	Ems, Royat.
Treatment of gouty glycosuria and diabetes.	Carlsbad, Contrexéville, Harrogate, Kissingen, Leamington, Llandrindod Wells, Marienbad, Neuenahr, Strathpeffer, Vals, Vichy, Vittel.
Treatment of gouty skin affections.	Aix-les-Bains, Baden, Bagnères-de-Luchon, Harrogate, Llandrindod Wells, Schinznach, Strathpeffer.

Balneology.—Useful as may be the drinking of a water at a spa, yet equally, and even in some cases more, useful is the encouragement for therapeutic purposes of the functions of the skin by balneological methods. The skin is the largest organ of the body, and, as would be expected of such an organ, it possesses various and complex functions. Amongst its functions are (1) the excretion of toxic bodies, the retention of which proves harmful and ultimately fatal to the organism; (2) the power that it possesses through its nerve-endings of stimulating distant organs and tissues; and (3) its heat-regulating power. The success of balneology, whether in the treatment of chronic joint conditions, of affections of the fibrous tissues, of certain heart and kidney affections, or of certain skin diseases, depends upon the recognition of the powerful aid which can be given by the skin in restoring the normal balance.

Heat, whether applied in the form of water baths or in that of air baths, lowers the arterial pressure and raises the venous pressure, as a consequence of the relaxation of the muscular coats of the arteries and of the arterioles that is induced.

The flushing effect of a course of warm baths on the clogged periphery of the circulation is useful in chronic gout and in chronic renal disease, and this beneficial influence extends to the heart, since the opening up of the peripheral circulation eases the work of the left ventricle, which consequently is able to deliver its load more and more completely, and retain less and less residual blood as the peripheral resistance diminishes.

The cabinet electric light bath in which the whole body is enclosed up to the neck is a powerful means for the reduction of the arterial blood pressure, and is serviceable in the treatment of high arterial pressure, such as that observed in granular kidney. In addition to its

pronounced action on the circulation, it is a powerful stimulant of the cutaneous excretion of waste products.

Warm baths are of great therapeutic value as vaso-motor relaxants, but there is another group of baths possessing quite different properties—namely, those of cardiac and vaso-motor stimulation. These are percussive baths, massage baths, and baths of alternating temperature.

Percussive baths are represented by the various forms of douche and needle baths. The general effect on the blood pressure is to raise the arterial and to lower the venous pressure. George Oliver states that the needle bath, doubly alternating in temperature (*i.e.* falling from warm to cool, then rising to warm, and again falling to cool), with a hot descending spinal douche, has the most powerful effect in raising the arterial pressure. There is no doubt that the effect of the percussion of water on the peripheral vessels is greatly intensified by varying the temperature, and especially by allowing it to dip to the lowest ranges. Apart from percussion, the mere alteration of temperature, when considerable, has a remarkable effect on the blood pressure, and especially is this the case when the cold plunge is taken either after a very hot water bath, or after a hot-air or Turkish bath. It is on this account that the subjects of advanced chronic gout, associated with high arterial tension, should avoid the cold plunge, and the cold needle bath or douche after a hot bath.

Climatic treatment.—A fairly bracing air with a low relative humidity is, in my experience, the most suitable for the gouty. High mountain situations, and valleys where there is an excessive relative humidity of the air, are alike unsuited to the gouty. Especially is it desirable to avoid exposure to the cold east and north-east winds which prevail in this country in the early months of spring, and which are so apt to be provocative of what has been called a “chill on the liver,” a condition which no doubt is brought about by the chilling effects of these winds

on the skin, and a consequent reflex affection of the metabolism of the liver cells.

A typically bracing climate is provided by a place which is exposed and elevated, which has a low relative humidity, and is therefore liable to rapid variations of temperature. A typically relaxing or sedative climate is one in which the opposite conditions prevail. It is sheltered and low-lying, with a high degree of relative humidity, and is therefore remarkably equable, both seasonally and diurnally. The physiological effect of a bracing climate is to increase metabolism, of a relaxing climate to diminish metabolism.

There are some types of gout which benefit conspicuously from bracing climates, but these are the less pronounced types, in which stimulating conditions may be tried without danger. On the other hand, those types of gout which are associated with chronic renal disease, and older patients suffering from arterio-sclerosis and high arterial tension, are best treated by sedative climates. In cases of chronic renal disease, care must be taken to avoid any sudden or extreme change of temperature, which would impose an undue strain on the damaged kidneys. It is in such cases that relaxing climates are frequently of immense benefit. In cases of gout associated with fatty degeneration of the heart or with valvular disease, a sedative climate is most desirable.

All gouty individuals should avoid localities in which there are hard chalky waters, or, if they have to reside in such localities, should avoid drinking the water of the district. In such cases they should drink distilled water, plain or aerated, or some of the simple natural mineral waters. As a winter resort for the gouty I know of no better climate than that of Egypt, where, at Helwan (Helouan), thermal, sulphurous, and saline waters exist, and excellent baths are obtainable. The air of Helwan is that of the desert, and almost germ free. The winter

sunshine averages eight hours a day ; the average winter temperature is 60° F. at 9 a.m. and 9 p.m., 70° F. at 3 p.m., and 50° F. at the coldest time of the night, and the relative humidity from November to April only 30 to 60 per cent. There is not much wind, and the amount of dust is less than in most parts of Egypt, while the average rainfall for four consecutive winters was only three-quarters of an inch. For the spring, summer, and autumn months we fortunately have for our selection a large number of health resorts in this country and on the Continent, the climates of which are well suited to the gouty. My experience is that residence by the sea is not suited to most cases of gout, and this especially applies to cases of gouty eczema.

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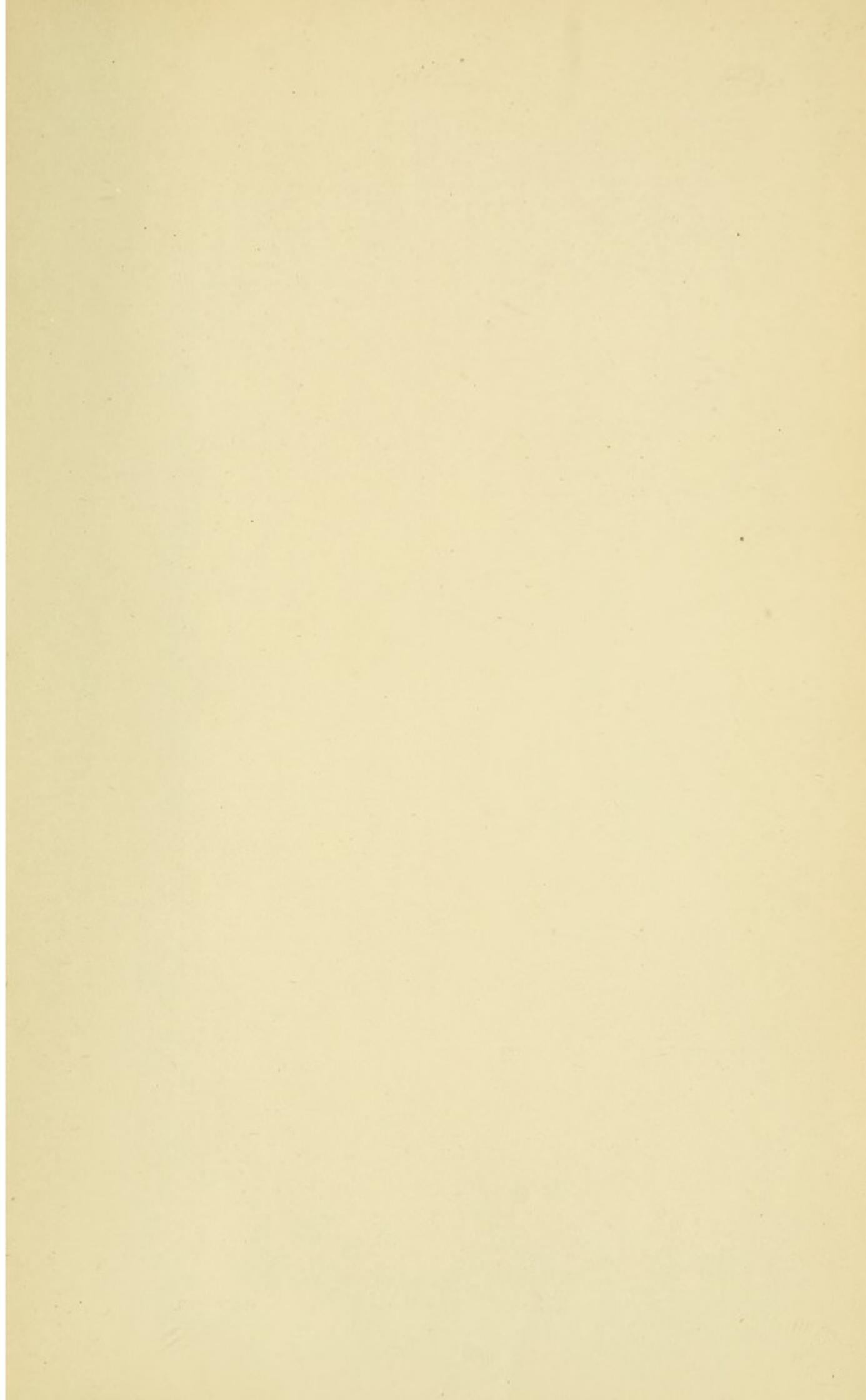
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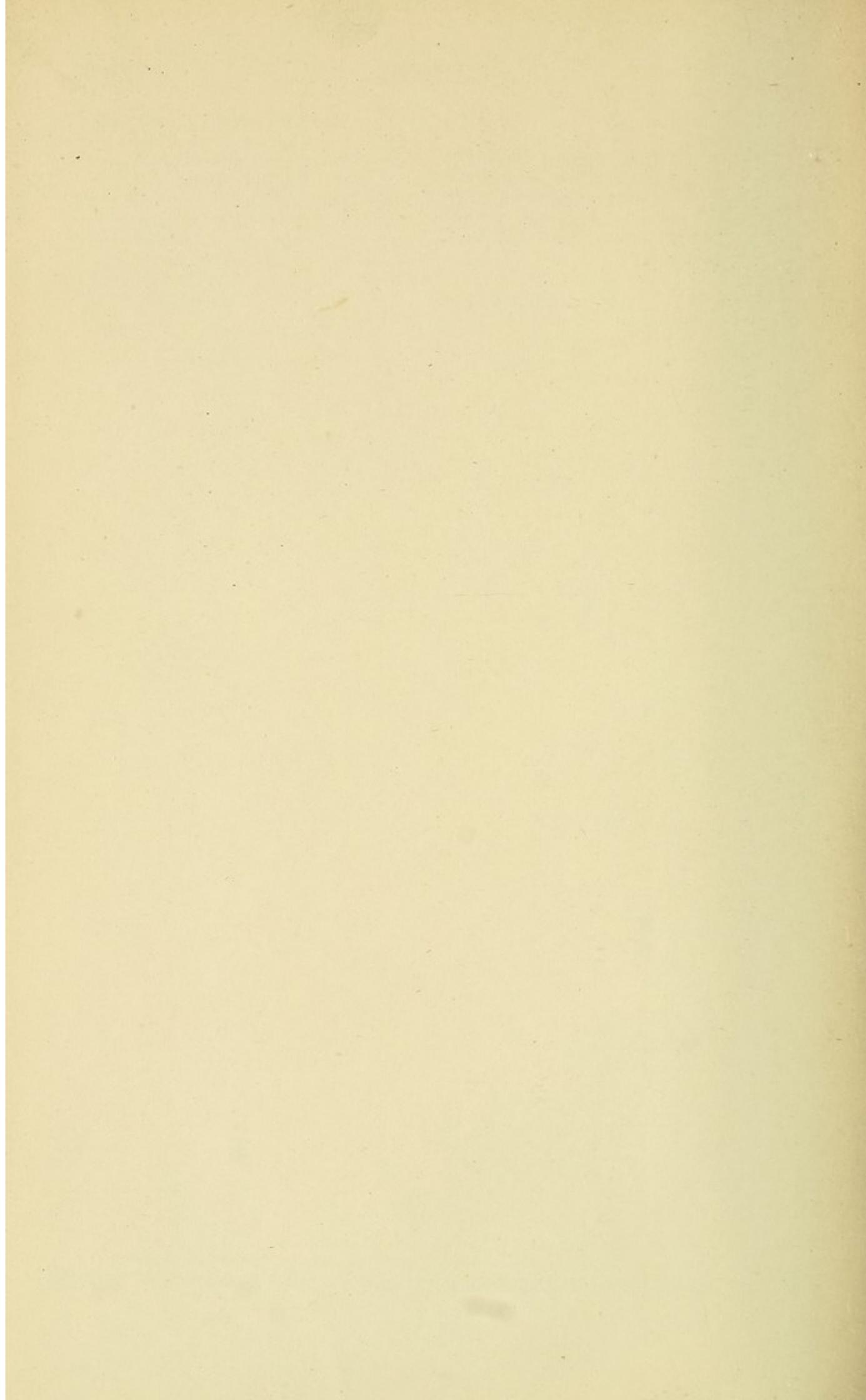
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