Gout, its pathology and treatment / by Arthur P. Luff.

5/-

GOUT

ITS PATHOLOGY AND TREATMENT

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 *; with the addition of some recent investigations concerning the Treatment of Gout, and a detailed account of the Treatment of the various forms of Gout*

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PREFACE.

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 objects 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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31, *Weymouth Street, Cavendish Square, W.*
October, 1898.

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Part 1.

THE PATHOLOGY OF GOUT.

CHAPTER I.

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Gout is the manifestation of a number of morbid tendencies, some of which may be inherited and some acquired, and which result in the different diseases associated with the arthritic diathesis. If the joints are affected, articular or regular gout results; if other organs or tissues are affected, then irregular gout is produced.

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 bibasic 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:—

$$2\underbrace{\left(NaHC_5H_2N_4O_3,\ H_2C_5H_2N_4O_3\right)}_{\text{Sodium Quadriurate}} + \underbrace{Na_2CO_3}_{\substack{\text{Sodium}\\ \text{Carbonate}}} =$$

$$4\underbrace{NaHC_5H_2N_4O_3}_{\text{Sodium Biurate}} + CO_2 + H_2O$$

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.

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 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. The various views held as to the primary cause of gout may be classified into the three following groups:—(1) Excess of uric acid regarded as the primary cause; (2) morbid changes in the structure of tissues regarded as the primary

cause; and (3) nervous disturbance regarded as the primary cause.

The following is a brief review of the various opinions held as to the primary causation of gout, adopting the classification just given:—

I.—Excess of uric acid regarded as the primary cause of gout.

This group may be divided into two sections accordingly as the uric acid compound is regarded as exerting its baneful effect in the crystalline state or in the dissolved state.

1. The uric acid compound regarded as acting passively and physically while in the crystalline state.—Sir Alfred Garrod and Sir William Roberts are 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 proximately 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 is 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 considers 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.

POSSIBLE CAUSE OF IRREGULAR GOUT.

Sir William Roberts even considers 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 is 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 (*see* p. 90), 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 by 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.

Amorphous Quadriurates not Irritants.

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.

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 (*see* pp. 137—139), 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 leucocythæmia and severe anæmia the blood is frequently highly charged with uric acid in the form of sodium quadriurate without the production of any toxic symptoms that could be referred to the uric acid compound.

ALLOXUR BASES REGARDED AS THE POISON OF GOUT.

Kolisch† considers that some antecedents or allies of uric acid are responsible for the toxic

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

† *Wiener klinische Wochenschrift*, 1895, p. 787.

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.

II.—MORBID CHANGES IN THE STRUCTURE OF TISSUES REGARDED AS THE PRIMARY CAUSE OF GOUT.

This group may be divided into two sections

* *Charité Annalen*, 1895, xx., p. 215.
† *Zeitschrift für klinische Medicin*, 1896, xxix., p. 510.
‡ *Berliner klinische Wochenschrift*, 1896, xxxiii., p. 70.
§ *Verhandlungen des Cong. f. innere Med.*, 1896, xiv., p. 33.
‖ *Wiener klinische Wochenschrift*, 1896, ix., p. 723.

accordingly as the morbid changes are produced by the presence of a soluble urate or not.

1. 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 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,

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

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 therefore 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.

* Croonian Lectures: "Uric Acid Gravel and Gout," 1892, p. 118.

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. 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 leucocythæmia 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.

EBSTEIN'S VIEWS AS TO NECROTIC CHANGES IN GOUT.

Ebstein considers that, by dissolving out the crystalline urates from tissues in which they are deposited, he is able to demonstrate the existence of necrosis in the sites previously occupied by the uratic deposit, and insists that the crystalline urates are only deposited in tissues that have undergone necrotising and necrotic changes. This, however, is opposed to the experience of such competent observers as Sir Alfred Garrod, Sir William Roberts, Sir Dyce Duckworth, and Cornil and Ranvier. I have also frequently examined sections of cartilages containing uratic deposits which have not shown any necrosis at the sites of the deposits, and in which the cartilage appeared to be practically uninjured. The changes that may be seen in cartilages containing a dense deposit of sodium biurate are quite intelligible on the assumption that they are caused in part by the mechanical pressure of the crystals, and in part by the inflammation and subsequent degeneration set up by the presence of the crystalline deposit. If the sodium biurate is only formed and deposited in necrosed areas, how is it that crystals of sodium biurate are occasionally found free in the synovial fluid of a gouty joint? As Sir William Roberts*

* Croonian Lectures: "Uric Acid Gravel and Gout," 1892, p. 117.

remarks: "it will scarcely be contended that necrotising and necrotic processes can take place in synovia!"

Sir Dyce Duckworth* in a modified sense believes that a soluble urate may act as an irritant. Although he considers that gout is primarily due to a disorder of the nervous system, he entertains the additional view that the urate in solution may set up degeneration and necrotic changes in tissues. This view is expressed as follows: "It can hardly be doubted that lesions result from the action of uric acid in solution in the tissues, and that thus both acute and chronic inflammatory changes may be set up without the direct influence of uratic deposit as an alleged irritant in joints and in certain viscera, notably in the kidneys. Degenerative changes and necrosis also appear to be thus induced."

2. Inflammatory or degenerative changes in the affected tissues regarded as the primary cause of gout, such initial changes not being caused by urates.—Dr. 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. Dr. Ord, whose views, in this particular, have been supported by Dr. Norman Moore and Mr. Bowlby, also considers that uratic deposits only occur in tissues which

* "A Treatise on Gout," 1889, p. 53.

have previously begun to degenerate. Dr. Berkart * considers that the severity of the local symptoms attending an attack of acute gout are 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 panarthritis, 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. Dr. 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.

* *Brit. Med. Journ.*, 1895, vol. i., p. 243.

III.—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.

Sir Dyce Duckworth, therefore, regards gout as

* "A Treatise on Gout," 1889.

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.

Dr. 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.

* "On Megrim and Sick Headache," 1873, pp. 404-5.

Dr. 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 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. Dr. 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.

Dr. Ralfe held the view that the accumulation of uric acid in the blood in gout was due to non-conversion into urea of the uric acid normally formed in the tissues, and he considered that the

* "Croonian Lectures," 1886.

conditions which prevent the normal destruction of uric acid in the tissues depend probably on disturbance of innervation.

THE AUTHOR'S VIEW AS TO THE PRIMARY CAUSE OF GOUT.

From a careful consideration of these various views as to the primary cause of gout, I am of opinion that the greatest mass of evidence is in favour of the view that a salt of uric acid is the *materies morbi.* The details of various experiments that support this view will be given later.

CHAPTER II.

Cause of the presence of uric acid in the blood of gout – Deficient excretion of uric acid in gouty subjects—Estimation of uric acid in urine—Detection and estimation of uric acid in blood.

CAUSE OF THE PRESENCE OF URIC ACID IN THE BLOOD OF 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.

This last theory may be dismissed at once. There is no proof that the process of oxidation destroys uric acid; on the contrary, there is proof that uric acid is produced by a process of oxidation. Moreover, not only is there no proof that uric acid is produced during health in the organs and tissues of the body generally, and that it subsequently undergoes more or less destruction, but

there are good reasons for believing that uric acid is, in health, only formed in the kidneys, and never appears in the general circulation except under pathological conditions.

With regard to the second theory of over-production and normal excretion of uric acid, there is abundant experimental proof to show that an increased production of uric acid does not lead to gout, so long as the kidneys remain in a normal condition. For instance, in connection with diseases such as leucocythæmia and severe anæmia there is an over-production of uric acid, but no development of gout. In these diseases the excessive quantity of uric acid produced is readily excreted by the kidneys, as is shown by the large amount of uric acid that may be found in the urine. In addition, gout is essentially a disease of middle age, and is only very exceptionally met with in childhood and in youth, although the formation of uric acid is greatest in early life, and apparently diminishes with the advance of age.

VIEW THAT DEFICIENT EXCRETION OF URIC ACID IS CONNECTED WITH GOUT.

There are many facts to support the view that gout is due to deficient elimination of the uric acid normally produced, and to subsequent absorption of this uric acid from the kidneys in consequence of that deficient excretion. That there is a deficient excretion of uric acid in gout is, I think, justified by the following facts. Judging as far as is possible

by averages, recent accurate estimations of the excretion of uric acid show that in gouty subjects there is a decrease in its daily excretion as compared with healthy individuals. Pfeiffer * compares 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 are given in the following table :—

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

This table indicates 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.

Dr. John Fawcett † also found as the result of several careful determinations of the uric acid elimination of various gouty patients that, in the majority of cases, the amounts excreted were distinctly below the average uric acid excretion of a healthy man on similar diet.

In the following table (Table I.) are the results

* *Berliner klinische Wochenschrift*, 1892, p. 413.

† "Guy's Hospital Reports," 1895.

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 I.

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 grm.	0·578 grm.	1·105 grm.
0·263 ,,	0·617 ,,	1·027 ,,
0·315 ,,	0·665 ,,	1·020 ,,
0·350 ,,	0·715 ,,	1·376 ,,
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)

These results probably justify the view that deficient excretion of uric acid occurs in connection with gout. Later the probable *rôle* taken by

the kidneys in the production of uric acid and in the development of gout will be dealt with in detail.

ESTIMATION OF URIC ACID IN URINE.

One of the lines of investigation that I have pursued required that a very large number of estimations of the total amount of uric acid excreted in the urine per diem should be made. The process that I have employed throughout is the Gowland-Hopkins method, which is a very accurate and reliable process. I have had a very considerable practical experience of the various methods that 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 Gowland-Hopkins process is free. 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 GOWLAND-HOPKINS METHOD FOR THE ESTIMATION OF URIC ACID IN URINE.

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 one 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 then transferred to a flask, 20 c.c. of strong pure sulphuric acid are added, and the mixture is then 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 gramme of pure potassium permanganate in a litre of distilled water. 1 c.c. = ·00375 gramme of uric acid.

ESTIMATION OF URIC ACID IN BLOOD.

Another line of investigation that I have pursued has involved the examination of the blood of man and of several of the lower animals for the presence of uric acid. Quantitative determinations of uric acid in blood have been made within the last few years by Salkowski and Leube, von Jaksch, and Klemperer. Salkowski and Leube* slowly added the fluid blood to ten times its volume of boiling water, boiled for ten minutes, allowed to subside, filtered, and evaporated down to the volume of the original blood used. The uric acid was then determined in this liquid by the Salkowski method.

* "Die Lehre von Harn," p. 94.

Von Jaksch * diluted the blood (using from 100—300 c.c.) with from three to four times its volume of water on the water-bath, and when coagulation commenced acetic acid was added so as to produce weak acidity; the mixture was then heated on the water-bath for 15—20 minutes till the albumen settled, and was then filtered, and the sediment extracted and washed with hot water. The filtrate was further acidified with acetic acid, boiled, cooled, filtered, and sodium phosphate added. The Salkowski-Ludwig method for the estimation of uric acid was then employed. Klemperer † diluted the blood with from six to eight times its volume of water, removed the albumen by Von Seegen's method, and then estimated the uric acid by the Salkowski-Ludwig process.

In order to test the accuracy of the different methods for the estimation of uric acid in blood, a quantity of fresh bullock's blood—which I proved to be free from uric acid by the murexide test—was taken, and to it a known percentage of uric acid was added. I then experimentally tried on different batches of this blood the various methods that have just been described. I obtained, however, such very erroneous and discordant results that I was forced to the conclusion that no reliable process had as yet been devised for the estimation of uric acid in blood. I therefore endeavoured to devise a process that would yield reliable results.

* "Ueber die klinische Bedeutung: Von Harnsäure und Xanthinbasen im Blut," 1891.

† *Deutsche medicinische Wochenschrift*, 1895, xxi., p. 655.

After performing a very large number of experiments, into the details of which it is unnecessary to go, I arrived at the following process, which constitutes the most reliable one for the estimation of uric acid in blood with which I am acquainted.

PROCESS FOR THE ESTIMATION OF URIC ACID IN BLOOD.

The fresh blood is allowed to flow direct into its own volume of rectified spirit, with which it is thoroughly agitated; the mixture is then evaporated on the water-bath until the mass can be reduced to a coarse powder, which is dried in the water-oven and afterwards finely powdered. The admixture of the blood with the spirit precipitates the albuminous matters in a granular form, so that when dried the blood can be reduced with ease to a fine powder. For the experimental work one part of the dried blood is taken as being equal to five parts of liquid blood. For the extraction and estimation of uric acid in blood from 50—100 grammes of the powdered blood should, if possible, be taken. In all my analyses of the blood of animals and birds I employed 100 grammes of the dried blood, and in my analyses of human blood I used 50 grammes of dried blood. The method employed was to mix 100 grammes of the powdered blood with a litre of boiling distilled water, and to allow the mixture to boil for half an hour, during which time it was frequently agitated. It was then filtered firstly through glass-wool, and afterwards through filter paper, and evaporated

down to 50 c.c.; this liquid was filtered, allowed to cool, and then submitted to the Gowland-Hopkins process for the estimation of uric acid. On adding known quantities of uric acid to different specimens of blood—which I had previously proved to be free from uric acid by the murexide test—and then submitting them to this process, I was able to extract from 80–87 per cent. of the uric acid, but the whole of the uric acid could never be extracted from the blood residue. Various solvents were tried in place of the distilled water, such as dilute solutions of sodium acetate, potassium acetate, sodium phosphate, borax, sodium carbonate, etc., in the hope of being able to extract all the uric acid from the blood, but I was unable to find any solvent that acted better than the distilled water. This process that has just been described is the one that I employed, in conjunction with the murexide test, in all the examinations of the various kinds of blood for uric acid, which will be subsequently referred to.

THE SOURCES OF URIC ACID.

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 the direct exciting cause of a gouty paroxysm, the two questions that naturally arise are: (1) Where is the uric acid formed? (2) How is the uric acid formed? I believe that uric acid is formed in connection with some diseases, notably blood

diseases accompanied by leucocytosis, in a different manner to that in which it is produced in health, and also that in connection with such diseases it is formed in different organs to those in which it is produced in health. I also hold the opinion that the source of the uric acid contained in the blood in gout is the same as that from which the uric acid eliminated in the urine in health is derived. It will be well, therefore, first to consider the various views as to the seat or seats of formation of uric acid in health and in gout.

CHAPTER III.

Seat or seats of formation of uric acid—Uric acid not a normal constituent of the blood—Pathological conditions under which uric acid appears in the blood.

VIEW THAT THE KIDNEYS FORM AS WELL AS EXCRETE URIC ACID.

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 has put forward, Sir Alfred

* "Transactions of the Royal Medical and Chirurgical Society," 1848, p. 93.

Garrod * concludes 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 these organs, the 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 concludes 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. Dr. 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

* "Proceedings of the Royal Society," 1893, pp. 482–484.

† *Wiener klinische Wochenschrift*, 1895, viii., p. 787.

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

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, which subsequently become conjugated in the kidneys. The

* "Lumleian Lectures," 1883.

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. Moreover, if the liver of birds contained uric acid, and if it passed thence to the kidneys, it must be present in the blood. As will be shown by and by, the blood of birds is quite free from uric acid. 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.

Dr. 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,

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

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

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 leucocythæmia and severe anæmia show that an exaggerated production of uric acid does not by itself exert any influence on the origin of gout.

VIEWS THAT URIC ACID IS PRODUCED IN VARIOUS TISSUES.

Ebstein, who attributes in cases ot 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. Chrzonsczewsky 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.

Dr. 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. Dr. 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 leucocythæmia, severe anæmia, etc., although large quantities of uric acid are formed, yet they are readily eliminated without storage in the system occurring.

IS URIC ACID A NORMAL CONSTITUENT OF THE BLOOD?

It will be evident that if the various views as to the formation of uric acid in the liver, spleen, connective tissues, muscles, and bone-marrow be correct, then it must be conveyed in the blood in order to be excreted by the kidneys. 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. Dr. 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 Dr. Haig's writings, he has never identified by the murexide test this uric acid reported to be present in the blood and tissues.

URIC ACID NOT PRESENT IN THE BLOOD OF MAN IN HEALTH.

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 individuals, but found no uric acid present. Klemperer ‡ also was unable to find any uric acid in the blood of healthy persons. I have also carefully examined the blood of healthy subjects by the process previously

* "Lumleian Lectures," 1883.

† *Deutsche medicinische Wochenschrift*, 1890, xxxiii., p. 741.

‡ *Deutsche medicinische Wochenschrift*, 1895, xxi., p. 655.

described, and have been unable to find any uric acid present. On the other hand, urea was found in every sample of blood examined.

URIC ACID NOT PRESENT IN THE BLOOD OF MAMMALS OTHER THAN MAN.

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. I have also examined the blood of the ox and sheep, working on very large quantities of blood by the process I have described, but I have never found any uric acid present. On the other hand, urea was found in every sample of blood examined.

URIC ACID NOT PRESENT IN THE BLOOD OF BIRDS AND REPTILES.

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,

* "Lumleian Lectures," 1883.

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 would be easy of detection in the blood of birds. Now it can be demonstrated that the blood of birds is absolutely free from uric acid.

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 considered that these observations of Sir Alfred Garrod as to the absence of uric acid from the blood of birds were of so great importance—in view of the opinion which I strongly entertain that uric acid in health is only formed in the kidneys—that I thought it desirable to re-examine the blood of birds. I accordingly worked on very large quantities of the blood of the turkey, goose, duck and fowl. After the most careful examination, I have never been able to detect any uric acid in the blood of these birds, and I therefore confirm Garrod's observations. I am also able to confirm his observations as to the presence of urea in the blood of birds. I found urea present in the blood of all the birds that I examined, viz. the turkey, goose, duck and fowl.

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

The objection has been raised to the above-mentioned experiments that the quantity of uric acid present in the blood requisite to produce a daily excretion of eight to ten grains might be so minute as to escape detection. This objection, I think, is disposed of by the fact that I have worked on pints of mammalian blood at a time, and have not been able to extract the least trace of uric acid, although urea was always found. That the process was a reliable one was shown by the fact that when I purposely added small quantities of uric acid to either mammalian blood or birds' blood I could always easily extract it and detect its presence. Moreover, the objection as to the supposed difficulty of detecting small quantities of uric acid, if such were normally present in blood, is not a valid one, considering that in the murexide test for uric acid we have a test of extreme delicacy. It can be demonstrated (*see* p. 3) that the one-hundredth part of a milligramme of uric acid gives a very evident murexide reaction. However, the objection that has been raised could not possibly apply to the examination of the blood of birds. The urinary excrement of birds consists almost entirely of compounds of uric acid and contains no urea, and if such uric acid is conveyed by the blood to the kidneys, then it must be capable of easy detection in that medium. Yet, as previously mentioned, no uric acid can be detected in the blood of birds.

This mass of experimental evidence, which

shows that uric acid is never present in the blood of human beings and of other mammals in health, and also that it is never present in the blood of birds and serpents, although their urinary excretion is almost entirely composed of a compound of uric acid, conclusively supports the view that uric acid is normally produced in the kidneys. How is it possible in all these cases that uric acid could be absent from the blood, if the view be correct that uric acid is formed in the system generally, and is conveyed in the blood to the kidneys, which play, as it were, merely the part of a filter in the removal of the uric acid from the blood? I consider that the evidence brought forward renders such a view impossible.

THE SOURCES AND FORMATION OF URIC ACID IN PATHOLOGICAL CONDITIONS, OTHER THAN GOUT, IN WHICH IT APPEARS IN THE BLOOD.

Although I hold the opinion that in health uric acid is only formed in the kidneys, and that the uric acid found in the blood in gout is absorbed from the kidneys after formation in these organs, yet it must be borne in mind that there are other diseases, besides gout, in which uric acid appears in the blood, and in connection with which it has most probably *not* been absorbed from the kidneys, but has been formed elsewhere in the system. It will, therefore, be well briefly to consider what these pathological conditions are, and what are the probable sources of the uric acid in such conditions. The investi-

gations of Von Jaksch, Klemperer, and others have conclusively established that the presence of uric acid in the blood is not a pathognomonic sign of gout, and also that uric acid may appear in quantities in the blood, and be eliminated without causing gout.

BLOOD DISORDERS ACCOMPANIED BY THE PRESENCE OF URIC ACID IN THE BLOOD.

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 leucocythæmia, 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 excretion of 2 grammes (three times the average normal amount). Bohland and

* *Deutsche medicinische Wochenschrift*, 1890, xxxiii., p. 741.
† *Deutsche medicinische Wochenschrift*, 1895, xxi., p. 655.
‡ "Klinische Urinanalyse," 1892, p. 31.
§ *Deutsche Archiv für klinische Medicin*, Band i., p. 13.
‖ *Virchow's Archiv*, Band cix., p. 390.

Scherz * found a daily excretion of 1·4 gramme (twice the average normal amount). Von Jaksch † concluded that the occurrence of uric acid in the blood was due to diminution of the oxidising activity of the red corpuscles, and to consequent storing up in the blood of the uric acid formed in the body, which, according to his view, is normally oxidised and destroyed. Horbaczewski's view, which will be considered later, that the formation of uric acid is due to the disintegration of leucocytes would equally apply, since in all the diseases in which Von Jaksch found uric acid in the blood, leucocytosis was present. Moreover, there is no experimental proof to support the view that uric acid is oxidised and destroyed by oxygenated blood. On the contrary, there is experimental proof that the process of oxygenation can, in the presence of nuclein, produce uric acid instead of destroying it.

Renal Diseases Accompanied by the Presence of Uric Acid in the Blood.

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

* *Pflüger's Archiv*, Band xlvii., p. 13.

† "Ueber die klinische Bedeutung. Von Harnsäure und Xanthinbasen im Blut," 1890.

‡ Loc. cit.

§ Loc. cit.

found uric acid always present. Obviously this furnishes a further proof as to the renal origin of uric acid, when it can be shown that in such cases of kidney disease (not associated with gout) in which the uric acid excretion is diminished, uric acid makes its appearance in the blood.

LEAD POISONING ACCOMPANIED BY THE PRESENCE OF URIC ACID IN THE BLOOD.

Sir Alfred Garrod* examined the blood of nine patients suffering from plumbism, who had never suffered from gout, and found appreciable quantities of uric acid in the blood of seven out of the nine. Dr. Oliver† refers to the early stage at which anæmia becomes a prominent symptom of lead poisoning. Although no doubt the kidney mischief which occurs in connection with plumbism is responsible for the appearance of most of the uric acid in the blood, by interfering with its excretion by the kidney cells, yet it is possible that a small amount of the uric acid may result from the slight leucocytosis accompanying the anæmia of plumbism.

FEVERS AND ABSENCE OF URIC ACID FROM THE BLOOD.

Von Jaksch found no uric acid in the blood of patients suffering from typhoid fever, intermittent fever, and acute rheumatism, nor in connection with diseases of the liver, stomach, and intestines, when unaccompanied by anæmia. His observations

* "A Treatise on Gout," 1876, p. 241.

† Goulstonian Lectures on "Lead Poisoning," 1891.

seem undoubtedly to prove that the presence of uric acid in the blood is not a factor in the production of the so-called uric acid intoxication of fever. Fever, indeed, appears to influence unfavourably the production of uric acid.

FORMATION OF URIC ACID DIFFERENT IN GOUT AND IN BLOOD DISEASES.

It is evident that in connection with certain diseases, especially those in which leucocytosis occurs, uric acid in the form of sodium quadriurate may be present in quantities in the blood, and yet not give rise to gout. The reason, in my opinion, is that in such diseases the kidneys being in a sound condition can readily eliminate the quadriurate. I believe that the seat or site of formation of uric acid is a different one in gout to what it is in these blood disorders, in which uric acid occurs in the blood without the development of gout. In gout I believe that all the uric acid present in the blood is absorbed from the kidneys, owing to some affection of those organs which interferes with the proper excretion of the uric acid formed in the kidneys. In cases of contracted granular kidney disease, and in cases of plumbism, the uric acid present in the blood is, I believe, derived from the same source, viz. from the damaged kidneys. In blood diseases and disorders the uric acid present in the blood is probably derived from the nuclein of the leucocytes, and as the kidneys are in a sound condition it is readily excreted by them.

CHAPTER IV.

The renal origin of gout—Association of kidney affections with gout—Association of renal disease with the presence of uric acid in the blood—Nature of the kidney affection which causes gout.

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. In the first place 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, previously referred to, of Laache, Bartels, Stadthagen, and Bohland and Scherz, on the excretion of uric acid in cases of leucocythæmia. 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 the uric acid-secreting cells of the kidneys.

VIEWS AS TO THE ASSOCIATION OF GOUT AND KIDNEY DISEASE.

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

* "The Uric Acid Diathesis," 1894.

† *Zeitschrift für klinische Medicin*, xxiv., p. 512.

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.

As previously mentioned, 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. Drs. 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. Dr. Norman Moore,† who bases his observations on the results of a large number of post-mortem examinations, states that

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

† "St. Bartholomew's Hospital Reports, 1887," vol. xxiii.

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 some 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 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

* *Zeitschrift für klinische Medicin*, 1894, xxvi., p. 293.

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 have 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 Dr. Cyril Ogle, Dr. F. J. Smith, Dr. Hebb, and Mr. 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 Dr. 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.	Uratic 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. of the cases. These results, taken in conjunction with those of Dr. 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 together 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 Dr. 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 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.

REASONS FOR BELIEF IN THE RENAL ORIGIN OF GOUT.

There is abundant evidence to show the connection between kidney mischief and gout for the following reasons:—(1) Uric acid has, in every case in which it has been specially searched for, been found in the blood of cases of renal disease; (2) uratic deposits are fairly frequently found in the joints of persons who have suffered from renal disease, but who have never been known to have had ostensible gout; (3) kidney mischief is frequently met with at the post-mortem examinations of gouty subjects; and (4) certain toxic agents predispose to both kidney disease and gout.

The statement has been made that the absence of ostensible gout in those cases of kidney disease

in which uric acid has been found during life in the blood, and in which uratic deposits have been found in the joints after death, would rather point to the conclusion that something more than the presence of uric acid in the blood and the deposition of biurate in the joints is necessary in order to produce gout, and that therefore uric acid may be merely a by-product in that condition of the system called gout. This statement is based on an imperfect acquaintance with the different modes of deposition of sodium biurate. In my opinion, the reason why deposits of sodium biurate are so frequently found at post-mortem examinations in the joints of persons who have suffered from granular kidney disease, but who have never been known to suffer from ostensible gout during life, or to complain of pain in the joints in which the deposits are subsequently found, is that in such cases the deposition of the biurate into the joints has been very slow and gradual and has never become excessive, whereas a somewhat sudden and copious deposit is required to produce an attack of acute or subacute gout, and a considerable amount must be present in the joints to produce the deformities of chronic gout. Moreover, the fact that uric acid is found in smaller proportions in the blood of cases of granular kidney disease than in cases of gout explains why, in connection with the former affection, the deposition of the biurate into the joints may be so slow and gradual as not to produce the symptoms of ostensible gout.

NATURE AND ANATOMICAL SEAT OF THE KIDNEY AFFECTION CAUSING GOUT.

The next question to consider is—What is the renal lesion which, by interfering with the proper excretion of uric acid by the kidneys, allows absorption of it to take place from those organs into the general circulation, and so starts the gouty state? In my opinion the kidney affection may be either a functional one or an organic one. My belief is that a functional affection of the kidneys always precedes any gouty manifestations, and that this functional affection may subside, if the exciting cause of it be removed, or it may pass on to a structural lesion. It is the liability to this functional affection of the kidneys which, in my opinion, constitutes the hereditary factor of gout. Such functional affection may, however, be started by various agents and causes, among which are excessive indulgence in nitrogenous foods, wines and beers, the toxic effect of lead, and the influence of nervous impulses, such as mental shocks, severe accidents, etc. The anatomical seat of the presumed kidney affection giving rise to the development of gout is probably in the epithelium of the convoluted tubes, as that has been shown by Levison * to be the primary seat of disease in granular kidney, and by Oliver to be the seat of the kidney affection associated with lead poisoning. The increase of interstitial tissue is probably a secondary change.

* *Zeitschrift für klinische Medicin*, 1894, xxvi., p. 293.

If this renal view be correct, it is obvious that the kidney condition must always be considered in the treatment of gout, and that, given diseased organs incapable of eliminating the normal amount of uric acid, either some other channel for its elimination must be secured or its formation must be limited to the diminished output, so that absorption of it into the general circulation may be avoided. The retention of uric acid in certain cells of the kidney, and its subsequent absorption into the blood, is analogous, as Sir Alfred Garrod has pointed out, to an attack of jaundice. When no obstruction exists to the exit of bile from the biliary passages, no appreciable amount of its colouring matter is found in the blood, but when its free elimination is checked, then absorption of it into the blood speedily takes place.

CHAPTER V.

Origin of uric acid—Formation of uric acid from urea in the kidneys—Uric acid formation and liver disease—Formation of uric acid from nuclein—Different modes of formation of uric acid in health and in blood disorders.

VIEW THAT URIC ACID IS THE RESULT OF DIMINISHED OXIDATION.

A COMMONLY received notion as to the origin of uric acid is that it results from a less perfect oxidation of the nitrogenous constituents of the tissues than occurs when urea is formed. According to this view urea is the ultimate product of the metabolism of nitrogenised tissues in mammals, whereas the formation of uric acid is considered as occupying an intermediate stage in the metabolism of nitrogenised tissues. In birds and serpents it has been supposed that the nitrogen is eliminated in the form of ammonium quadriurate without having undergone the further change into urea. This notion is mainly based on the observation of the two following facts: (1) That uric acid by means of oxidising agents can be split up into urea and other substances; (2) that in certain reptiles whose respiration is languid, and whose temperature is low, the kidneys excrete uric acid to the entire exclusion of urea. The inference that the production of the uric acid in such reptiles

is the result of imperfect oxidation is, however, disproved by the well-known fact that birds, whose respiration is rapid, and whose temperature is higher than that of mammals, also, like reptiles, excrete uric acid to the exclusion of urea. So that, although uric acid is a less highly oxidised product than urea, it is very doubtful whether it can be considered as an antecedent in the formation of urea

View 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 is true that the ingestion of very large quantities of proteid matter is followed by an increased production of uric acid, and, *vice versâ*, but apparently it makes little, if any, difference whether the proteid matter is of animal or of vegetable

* *Berliner klinische Wochenschrift*, 1884.

origin. The only reason that a vegetable diet is less productive of uric acid than an animal diet, is in the fact that the former is poorer in proteid material, and therefore to consume in the vegetable diet as much proteid matter as is ordinarily consumed in an animal diet would require the ingestion of very large bulks of vegetable food. Therefore the assumption is not altogether correct that the total daily excretion of uric acid is greater on an animal than on a vegetable diet. With the same intake of nitrogen in the two diets, there is practically no difference in the uric acid output. This is shown by the experiments of Bleibtreu,* who examined his urine after three days' flesh diet and after three days' vegetable diet. Although after the flesh diet there was a considerable rise in the amount of urea excreted, there was very little difference in the uric acid excretion. After the three days' flesh diet the uric acid excreted in twenty-four hours was 0·859 gramme, while after the three days' vegetable diet it was 0·791 gramme. Similar results were obtained by Hirschfeld,† who found that on a diet very poor in nitrogen he excreted daily 0·417 gramme of uric acid; on one rich in albumen 0·386 gramme; and on a highly albuminous diet 0·492 gramme.

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

* *Pflüger's Archiv*, Band xlv., p. 401.

† *Virchow's Archiv*, Band cxvii., p. 301.

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.

Sir William Roberts,* comparing the functions of the kidneys of birds and serpents with those of mammals, considers that an immense functional evolution has taken place in the mammalian kidney; that the evolution of mammalian urine has probably turned mainly on the point that the mammalian plan required that the renal excretion should be voided not in the solid or semi-solid form, but as a watery solution. This modification would require the discarding of the sparingly soluble uric acid as a medium for the elimination of nitrogen, and the substitution of a nitrogenous substance readily soluble in water, such as urea. He considers it possible that the reason why this substitution has not been completely effected is that in that particular the mammalian type has not yet reached its ideal perfection, and that the residuum of uric acid in mammalian urine may be something in the nature of a vestigial feature.

VIEW THAT URIC ACID IS FORMED FROM UREA IN THE KIDNEYS.

In mammalia, including man, and in birds uric acid is absent from the blood in health,

* Croonian Lectures on "Uric Acid Gravel and Gout," 1892, p. 33.

while urea is always present in the blood. 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.

One very strong argument against the formation of uric acid in the liver, spleen, connective tissues, etc., is that it is never present in the blood of mammals (including man) and of birds in health. If it were formed in such organs or tissues, it must be conveyed in the blood to the kidneys. Since, according to Sir Alfred Garrod's and my own investigations, urea, and not uric acid, is found in the blood of birds, and since uric acid, and not urea, is found in the urinary excrement of birds, it

* "Proceedings of the Royal Society," 1893.

seems highly probable that urea is at least one of the sources of formation of uric acid, and that the conversion of urea into uric acid is effected in the kidneys. Dr. 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 then 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 Dr. Latham the synthesis of uric acid from urea and glycocine takes place in the following steps :—

1. The urea and glycocine produce hydantoic acid—

$$\underset{\text{Urea}}{CH_4N_2O} + \underset{\text{Glycocine}}{C_2H_2(NH_2)O.OH} = \underset{\text{Hydantoic acid}}{C_3H_6N_2O_3} + NH_3.$$

2. The hydantoic acid becomes dehydrated and forms hydantoin—

$$\underset{\text{Hydantoic acid}}{C_3H_6N_2O_3} = \underset{\text{Hydantoin}}{C_3H_4N_2O_2} + H_2O.$$

3. From more of the urea biuret is produced—

$$2\ \underset{\text{Urea}}{CH_4N_2O} = \underset{\text{Biuret}}{C_2H_5N_3O_2} + NH_3.$$

* "Croonian Lectures," 1886.

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

$$\underset{\text{Hydantoin}}{C_3H_4N_2O_2} + \underset{\text{Biuret}}{C_2H_5N_3O_2} = \underset{\text{Uric acid}}{C_5H_4N_4O_3} + NH_3 + H_2O.$$

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

$$3\,\underset{\text{Urea}}{CH_4N_2O} + \underset{\text{Glycocine}}{C_2H_2(NH_2)O.OH} = \underset{\text{Uric acid}}{C_5H_4N_4O_3} + 3\,NH_3 + 2\,H_2O.$$

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 Dr. 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 urid acid voided was considerably increased. Dr. 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. We may therefore conclude that the conversion of urea into uric acid by the agency of certain of the kidney cells is at least possible, and that this conversion is effected by the conjugation of urea and 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

* Loc. cit.

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, Dr. Murchison considered that gout is a 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. Dr. George 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 in the kidneys.

VIEW THAT URIC ACID IS FORMED FROM NUCLEIN.

Hörbaczewski † has shown that uric acid, as well as xanthin and hypoxanthin, can be prepared from

* "A Treatise on Gout," 1889.

† "Beiträge zur Kentnisse der Bildung der Harnsäure und der Xanthinbasen." Sitzungsb.richt der K. Acad. d. Wiss in Wien. C., iii., 1891.

spleen pulp. The close relationship of these three bodies to one another is shown by a comparison of their formulæ—

$C_5H_4N_4O_3$	Uric acid.
$C_5H_4N_4O_2$	Xanthin.
$C_5H_4N_4O$	Hypoxanthin.

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 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

* *Zeitschrift für klinische Medicin*, 1896, xxix., pp. 174–189.

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, 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 leucocythæmia 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.

From a consideration of all the work that

* *Archiv für Exper. Pathologie und Pharmakologie*, Band xxii., p. 306.

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

has been done in connection with leucocytosis and the excretion of uric acid, it is clear that there is no constant ratio between the number of leucocytes and the amount of uric acid excreted, for there may be leucocytosis without increase of uric acid, as there may be an increase of uric acid without leucocytosis. I think that in cases of leucocythæmia, severe anæmia, etc., where uric acid is present in the blood, it is probably derived from the nuclein of leucocytes or other cells. It is, however, in my opinion, wrong to draw the further inference that the source of the uric acid excreted in health is the nuclein derived from leucocytes throughout the body. If such were the case, uric acid would be found in the blood in health; but, as previously shown, it is not. Moreover, in birds there is no special leucocytosis to account for the large formation and excretion of uric acid that occurs.

In connection with leucocythæmia, anæmia, etc., the excretion of uric acid in the urine may rise to six times the normal amount, and yet no signs of gout appear. The reason for this non-development of the symptoms of gout in connection with these diseases is that *the kidneys remain in a sound condition, and therefore the uric acid (which in these diseases is probably derived from nuclein) is readily and rapidly excreted by them.* This knowledge of the derivation of uric acid from nuclein in connection with diseases associated with leucocytosis has, in my opinion, proved a stumbling-block to many writers and

observers in their conception of the pathogenesis of gout. For it by no means follows that because in diseases associated with leucocytosis the uric acid which appears in the blood is derived from nuclein, therefore such must be its source in gout. The simple fact is that gout is not a disease associated with leucocytosis, and therefore the uric acid of gout cannot be derived from nuclein.

VIEW THAT PART OF THE URIC ACID IS INTRODUCED READY-FORMED IN FOOD.

Dr. 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. Dr. Haig * gives the quantities of uric acid which a man may introduce into his system with an ordinary dinner as follows:—

					grain.
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
½ drachm meat extract	,,	0·80	,,	,,	= 0·24
					1·72

* *Brit. Med. Journ.*, 1894, ii., p. 1299.

As far as I can ascertain from Dr. 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 Dr. 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. That Dr. Haig's view as to the direct introduction of uric acid in articles of diet is an erroneous one is shown by the absence of uric acid from the blood of man and animals in health.

RATIO OF URIC ACID ELIMINATION TO THAT OF UREA.

Dr. Haig has also 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) Dr. Herringham and Mr. 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*, Band xlv., p. 401.

† *Journal of Physiology*, 1891.

TABLE III.

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
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 IV.

	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)	·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. Variations in the daily elimination of uric acid in healthy individuals are not due to the sweeping out of uric acid from the different organs and tissues into the blood, for uric acid is never found in the blood of healthy persons. Differences from day to day in the uric acid excretion probably depend upon the amount of glycocine leaving the liver and passing on to the kidneys; this factor would be affected by variations in the metabolism of the liver, which may be induced by changes in the quality or quantity of the diet, by the amount of exercise, and by various nervous influences. Dr. Latham * has suggested a possible reason why those persons who have a tendency to gout and who take little exercise tend to develop the disease. It is that insufficient muscular exercise tends to the formation of glycocine. This is seen in the case of horses which when put to hard work eliminate benzoic acid in the urine,

* "On the Formation of Uric Acid in Animals," 1884, p. 42.

but if kept in the stable for some time benzoic acid appears in the urine in combination with glycocine as hippuric acid, which is benzoyl-glycocine.

DIFFERENT MODES OF FORMATION OF URIC ACID IN HEALTH AND IN BLOOD DISORDERS.

From a consideration of the various views as to the origin of uric acid, I think it is evident that there are two distinct and different ways in which uric acid may originate. (1) In health I believe that it is only formed in the kidneys, probably from urea and glycocine, and that it is at once eliminated in the urine. If, from any functional or organic affection of the uric acid-eliminating cells of the kidneys, its proper excretion is inhibited, then it is absorbed into the general circulation and constitutes the store from which the uratic deposits of gout are formed. (2) In diseases which are accompanied by leucocytosis I believe that uric acid may be formed from the nuclein of leucocytes in the spleen and possibly throughout the system generally, but that such uric acid is readily eliminated by the kidneys, which remain sound as regards their uric acid-secreting structures; consequently gouty deposits never occur in connection with such diseases. The two different modes of formation of uric acid might be distinguished as the urea formation and the nuclein formation of uric acid.

CHAPTER VI.

Composition of the amorphous urate deposit of urine—Causes of uratic deposition—Formation of the gouty deposit—Time occupied in the conversion of sodium quadriurate into biurate—Seats of uratic deposition in gout.

As I take the view that the uratic deposits of gout are derived from uric acid absorbed into the blood from the kidneys, it will be advisable to consider next the various causes for its crystallisation in the form of sodium biurate from the blood, and the reasons why the biurate selects certain tissues as seats for its deposition. It is necessary briefly to consider (*a*) the form in which uric acid is absorbed into and circulates in the blood; (*b*) the form in which it is deposited from the blood or fluids of the body.

FORM IN WHICH URIC ACID EXISTS IN THE CIRCULATION.

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

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

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 the crystalline urinary substance of birds and serpents can be converted into amorphous deposit. Dr. 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 Dr. Bence Jones thirty years before, and has conclusively 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 true and definite 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. They exist normally in the urine, and constitute the only form in which uric acid exists in normal urine. All the morbid phenomena due to uric acid probably arise from secondary changes in the quadriurates. The amorphous urate or quadriurate deposit of urine is generally referred

* *Journal of the Chemical Society*, 1862, vol. xv., p. 201.

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. 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

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

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 :—

	Parts per 100.
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 $NH_4HC_5H_2N_4O_3$, $H_2C_5H_2N_4O_3$–Ammonium quadriurate.
5 molecules $NaHC_5H_2N_4O_3$, $H_2C_5H_2N_4O_3$—Sodium quadriurate.
1 molecule $KHC_5H_2N_4O_3$, $H_2C_5H_2N_4O_3$—Potassium quadriurate.

The uric acid which is formed in the kidneys is probably at once converted into the mixture of these three quadriurates, which in the normal state are then excreted dissolved in the urine. If, however, any absorption of them takes place into the blood, as probably occurs in the gouty state, the ammonium and potassium quadriurates would be converted by the sodium carbonate of the blood into sodium quadriurate, which would constitute the sole compound of uric acid at first circulating in the blood. It is from this body that the sodium biurate, of which the gouty deposits consist, is derived

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 infers from these results that, in the normal state, uric acid is primarily taken up in the system as quadri-

urate, 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 leucocythæmia 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. In connection with gout, if the view is correct that defective elimination of uric acid by the kidneys always occurs, the conditions are quite different. In gout uric acid is absorbed from the kidneys into the general circulation owing to the partial failure of the uric acid-excreting function of the kidneys. The uric acid is absorbed as the sodium quadriurate, which, dissolved in the blood, gradually passes through the maturation process and forms sodium biurate.

When the amount of the biurate in the blood is more than that fluid can retain in solution, then deposits of it occur in those tissues which, either on account of having received previous slight injuries or because of their poor vascular supply, specially favour its deposition.

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.

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. They are conspicuously absent from the muscular tissue, and from the substance of the liver, spleen, brain, and lungs. Uratic deposits have been very occasionally found in the following places:—In the mitral and aortic cardiac valves, in atheromatous patches in the aorta, in the walls of veins, in the crico-arytenoid ligaments, in the vocal cords, in the walls of bronchial tubes, in the mucous follicles of the pharynx, upon the meninges of the brain and spinal cord, upon the spinal nerve sheaths, in the sclerotic coat of the eye, and the fibrous envelope of the retina. It is always in the fibrous tissue which participates in the formation of the nervous envelopes, that the deposit is found. Uratic crystals have also on two occasions been detected in the sputa of gouty patients. Sir William Roberts considers that the visceral neuroses and the thrombosis and embolism met with in gout are not the result of the dissolved uric acid in the blood, but are due to precipitation of minute crystals of sodium biurate either in the substance of the organs or in the blood itself.

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* 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.

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

CHAPTER VII.

Causes affecting the deposition of sodium biurate—Reasons for the special selection of the great toe and ear as seats of gouty deposits—Cause of the inflammation accompanying the gouty paroxysm.

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 on 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 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

* R. Wagner's "Handwörterbuch der Physiologie," 1884, Band iii., Part i., pp. 463–466.

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. In addition it is possible that, as Sir Alfred Garrod suggests, there is some special attraction in the joints for uric acid.

DEPOSITION OF SODIUM BIURATE ENCOURAGED BY NERVOUS INFLUENCES.

It is possible, given the condition in which there is a fair amount of sodium quadriurate or biurate circulating in the blood, the amount not

* "Maladies des Vieillards et les Maladies chroniques," 1874

being quite up to saturation point, that nervous influences may accelerate deposition of sodium biurate. It is well known that whatever produces depression of the nervous system, such as excessive exercise carried to the point of fatigue, rage, fright, worry, excitement or venereal excess, may cause an attack of gout in a gouty subject. It appears to me that a possible explanation of this result is that nervous influence affects the kidneys and depresses their excretory power for uric acid, which is consequently absorbed into the general circulation and rapidly raises the quantity of urate in the blood to the point of over-saturation. Probably the well-known effect of an exposure to cold inducing a paroxysm of acute gout is due to a similar cause.

DEPOSITION OF SODIUM BIURATE ENCOURAGED BY ABNORMAL CONSTITUENTS OF THE BLOOD.

As previously stated, in cases of chronic lead-poisoning there is a deficient excretion of uric acid in the urine and an accumulation of it in the blood. As to the natural way in which the lead favours or hastens the deposition of sodium biurate and so produces gout, there are different opinions. Sir William Roberts* considers that it is difficult to believe that lead-poisoning produces the same constitutional diathesis as that which exists in true gout, and prefers to think that, while gout and plumbism differ in all other respects, they have one

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

tendency or vice in common, namely, the tendency to uratosis—that is, to the deposition of sodium biurate. He considers it is more accurate, instead of speaking of *ordinary gout* and *saturnine gout*, to speak of *gouty uratosis* and *saturnine uratosis*. It appears to me that gout and plumbism have more in common than this tendency to uratosis —that is, to the deposition of sodium biurate—in that they both have the same tendency to cause the presence of an excess of urates in the blood. The association of lead-poisoning with gout has been repeatedly observed, but Oliver* states that in the north of England this intimate relationship between gout and lead-poisoning is not seen. He is not satisfied that the reason why gout is so little known in the north as a symptom of lead-poisoning, while it is so common in the south, is entirely due to the difference in the drinking habits of the people—whisky being the general alcoholic drink in the north and malt liquor in the south. At the same time he confesses his inability to offer any further explanation.

I am of opinion that the influence of lead in producing gout depends solely on the extent to which the kidney parenchyma is damaged. With much damage done to the kidney cells, whose function it is to excrete uric acid, absorption of quadriurate into the blood occurs; the subsequent development of an attack of gout entirely depends on the amount of absorbed quadriurate, which in its turn depends on the amount of kidney mischief.

* Goulstonian Lectures on "Lead Poisoning," 1891.

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. Dr. Latham * thinks it is probable that the uric acid circulating in the blood might exert a toxic effect on certain 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. As a result of the inflammation or nutritive changes in the joints, sodium biurate deposits in them or in the tissues around the affected joints.

* "Croonian Lectures," 1886.

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 (*see* p. 17). 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 leucocythæmia, where an excess of urate is present in the blood, neither local necrosis nor uratic deposits occur. He believes that some unknown 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 re-dissolve 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.

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

† *Deutsche medicinische Wochenschrift*, 1895, vol. xxi., p. 655.

DEPOSITION OF SODIUM BIURATE NOT AFFECTED BY DIMINISHED ALKALINITY OF THE BLOOD.

Various writers have put forward the opinion that uratic deposition is dependent upon a diminution of the alkalinity of the blood. Mordhorst* considers that the tissues affected by gout are less alkaline than the blood, and that, if the alkalinity of the latter becomes lowered, then deposition may take place. Dr. Haig considers that diminished alkalinity of blood causes deposition of uric acid in the liver, spleen, fibrous tissue, and joints, and that increased alkalinity of the blood causes its re-solution. The view that diminished alkalinity of the blood causes uratic deposition, and that increased alkalinity of the blood causes re-solution of the uratic deposits, is in my opinion erroneous and untenable for the following reasons:—(1) The view is apparently based on the deposit being uric acid, whereas it is sodium biurate, the solution of which, as Sir William Roberts has shown, is not increased by increased alkalinity of the blood; (2) the occurrence of a gouty attack is not necessarily accompanied by any diminution in the alkalinity of the blood (*see* pp. 129, 130); and (3) from a series of experiments that I have conducted, and which will be subsequently described, it appears that a diminution of the alkalinity of a medium does not affect the deposition of sodium biurate from that medium.

* "Vorhandlungen des Congress für Innere Medicin," 1896, p. 405.

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.

Cause of the inflammation which accompanies the gouty paroxysm.

The gouty paroxysm is due to precipitation of sodium biurate, which always takes place in the

crystalline form, the crystals being distributed through the implicated tissue in the form of delicate needles, aggregated into tufts, bundles, and stars. When deposition occurs in cartilage the crystalline deposit acts as an irritant and causes inflammation leading to proliferation and necrosis of cartilage cells, which may be followed by erosion of cartilage and of uratic deposits, and consequent displacement of the latter into the cavity of the joint. Along the borders of the cartilage, where the deposits are comparatively small and the tissues are relatively rich in capillary vessels, the inflammatory processes may produce a more luxuriant growth of the cartilage cells, resulting in the formation of ecchondroses at the margins of the articulation. Although I consider that the inflammatory part of the gouty attack is secondary to the deposition of sodium biurate crystals, yet it must be granted that such deposition should occur fairly copiously and suddenly in order to start the inflammatory process. Undoubtedly the biurate may deposit slowly and quietly in joints without the development of any acute attack, or for some time antecedent to the development of an acute attack. The observations of Moxon and Fagge support the conclusion that the discovery after death of uratic deposits in a joint is not always to be regarded as a certain proof that the joint has passed through an inflammatory gouty attack. Sir Alfred Garrod's views, which are shared by Sir William Roberts and supported by abundant

evidence, are in favour of the deduction that the deposition of the crystalline biurate is not merely an accompaniment, but is the direct cause of the joint troubles of gout. It is therefore of practical importance to know what are the various factors or conditions which may influence the conversion of sodium quadriurate into biurate, which may alter the solubility of sodium biurate in the blood, lymph, and synovia, and which may affect the precipitation of the sodium biurate. These points will be dealt with in Part III.

GENERAL CONCLUSIONS AS TO THE PATHOLOGY OF GOUT.

The main points and conclusions arrived at in the preceding account of the pathology of gout are as follows :—

1. Uric acid is not normally present in the blood of man and other mammals, nor in the blood of birds.

2. Uric acid is normally produced only in the kidneys.

3. Uric acid is normally formed from urea, probably by conjugation of that substance with glycocine in the kidneys.

4. Uric acid is present in the blood in gout as the soluble sodium quadriurate. In its soluble form it is not a toxic agent. It deposits from the blood as sodium biurate, which acts passively and physically as a foreign body in the tissues or organs in which it is deposited.

5. The presence of uric acid in the blood in

gout is due to its deficient excretion by the kidneys, and to the subsequent absorption of the non-excreted portion into the blood from those organs.

6. Gout is probably always preceded by some affection of the kidneys, functional or organic, which interferes with the proper excretion of uric acid. The probable seat of the kidney affection giving rise to gout is in the epithelium of the convoluted tubes.

7. In certain blood diseases and disorders accompanied by leucocytosis uric acid is formed within the system from nuclein. In such circumstances it passes at once into the blood and is rapidly eliminated by the kidneys.

Part II.

ÆTIOLOGY OF GOUT — THE VARIOUS FORMS OF GOUT AND THEIR CLINICAL FEATURES — DIAGNOSIS AND PROGNOSIS.

CHAPTER VIII.

Ætiology of gout—Predisposing causes of gout—Exciting causes of gout—Acute gout—Chronic gout—Saturnine or lead gout—Irregular or abarticular 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.

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.

Hereditary predisposition.—This is the most important factor in the development of gout. 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.

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 and inadequate physical exercise also strongly predispose to gout.

Lead-poisoning.—Chronic lead-poisoning predisposes to gout, most probably by causing a chronic affection of the kidneys, which interferes with the proper elimination of uric acid by those organs.

Uric-acid gravel in the kidneys.—Those who suffer much in early life from uric-acid gravel are also prone in later life to develop gout. The reason for this liability probably is that the deposits of uric acid, which no doubt in such circumstances occur in the kidneys, produce that pathological condition of those organs which, by interfering with the proper elimination of uric acid by the kidneys, constitutes the starting-point of gout.

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. For the production of gout, whether of the regular

(articular) or irregular (abarticular) type, the deposition of sodium biurate in the organ or tissue affected is, in my opinion, essential. The mere presence of uric acid in the blood in the form of the sodium quadriurate is insufficient for the production of any form of gout, in the absence of deposition of the biurate from the fluids of the body. That such is the case is illustrated by those blood disorders, such as leucocythæmia and severe anæmia, in which the blood is laden with uric acid, and yet no symptoms of either regular or irregular gout arise. The absence of such symptoms is due to the fact that the uric acid, which is present in the blood as sodium quadriurate, is completely and rapidly eliminated by the kidneys before there is time for the formation and deposition of the biurate.

THE VARIOUS FORMS OF GOUT AND THEIR CLINICAL FEATURES.

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, the skin is tense, shiny, and extremely tender, and the veins are distended. 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 dis-

* *Brit. Med. Journ.*, 1897, i., p. 509.

tinguishing 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. Temporary albuminuria has been frequently observed during the early stages of an attack of acute gout, and occasionally slight albuminuria lasts throughout the attack, owing to the affection of the kidneys which constitutes the primary cause of the gout.

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

CHRONIC GOUT.

With 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 con-

stitute 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.

Considerable enlargement and deformity of joints may occur in connection with chronic gout 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.

When chronic gout is accompanied by much deposition of biurate it is a sure indication that the kidneys are incapable of excreting the whole of the

uric acid formed in them, and that consequently daily absorption of the non-excreted portion is occurring into the general circulation. In such cases a most careful and systematic examination of the urine should be made. 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.

THE HEART AND GOUTY KIDNEY.

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

backworking of the blood from the left side of the heart follow.

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.

SATURNINE OR LEAD GOUT.

As previously described (*see* p. 59), chronic lead-poisoning gives rise to both chronic kidney disease and gout. The cause of the liability of those suffering from chronic plumbism to be attacked by gout has already been considered (*see* pp. 60, 96, 97). Briefly stated, it most probably is due to the action of lead salts on the kidney epithelium causing a diminution in the excretion of uric acid, so that consequently an absorption of the non-excreted portion takes place from the kidneys into the general circulation. This view is supported by the well-known fact that the medicinal administration of lead salts notably diminishes the excretion of uric acid by the kidneys. A prolonged period of lead intoxication —on the average about twenty-one years—is 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.

IRREGULAR OR ABARTICULAR GOUT.

Gout appearing in any situation other than a joint is regarded as irregular or abarticular. Different forms of irregular 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. 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. I believe that all forms of irregular gout are due to the precipitation in the crystalline form of sodium biurate in the organ or tissue affected. Sir William Roberts also considers it quite possible that attacks of irregular gout are due to the irritation produced by deposits of sodium biurate in the affected viscera. Deposits of sodium biurate have been found after death in the valves of the heart, in the walls of arteries and veins, in the vocal cords, in the mucous follicles of the pharynx, in the walls of the bronchial tubes, in the meninges of the brain and spinal cord, and in several other localities. Although deposits of sodium biurate have not been found in the walls of the alimentary tract, yet it is quite possible that such deposits might occur, and either have been overlooked at a post-mortem examination, since they would be most difficult to detect, or have undergone solution before death.

CHAPTER IX.

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—Gouty glycosuria and diabetes—Gouty hepatic congestion—Gouty affections of the eye and ear—Retrocedent or metastatic gout—Diagnosis and prognosis of gout.

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) complications and sequelæ of gout.

IRREGULAR GOUT AFFECTING THE ALIMENTARY TRACT

Gouty pharyngitis is by no means an uncommon condition. The mucous membrane of the pharynx is congested and swollen. The uvula assumes a dusky-red colour and is œdematous. Gouty tonsillitis may also occur.

Gouty œsophagismus occasionally occurs, and may be severe.

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.

Chronic gastro-intestinal catarrh is an occasional form of irregular gout. It is generally accompanied by vomiting, colic, and constipation; occasionally diarrhœa occurs.

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, later, articular gout may develop, 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.

IRREGULAR GOUT AFFECTING THE HEART AND VESSELS.

Cardiac irritability.—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.

Anginal and pseudo-anginal attacks.—These attacks may occur either in connection with chronic gout, or as an occasional manifestation of irregular gout. For a description of the associated symptoms *see* pp. 113, 215, 216.

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.

IRREGULAR GOUT AFFECTING THE NERVOUS SYSTEM.

Migraine and neuralgia.—Attacks of migraine and of neuralgia not unfrequently occur in persons of gouty habit, and are in certain cases dependent on the gouty condition. The commonest form of gouty neuralgia is sciatica, the next commonest is facial neuralgia.

Neuritis.—Peripheral neuritis of gouty origin occasionally occurs. Gouty neuritis or perineuritis may occur; 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 perineuritis or 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.

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.

IRREGULAR GOUT AFFECTING THE GENITO-URINARY SYSTEM.

Gouty kidney.—As previously stated (see pp. 60—63), I hold the view that a functional affection of the kidneys, interfering with the proper elimination of uric acid, is the primary factor in the production of 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 cystitis, urethritis, orchitis, ovaritis, and metritis have been described, but it is doubtful whether they are true gouty affections.

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. It is doubtful whether these skin affections are ever due to the direct irritant effect of either sodium quadriurate or biurate contained in the sweat. They are more probably nervous in their origin. 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 frequently 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: 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 on the arms, legs, and trunk.

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. *Psoriasis, acne, boils,* and *carbuncles* have been stated to be occasionally associated with gout. The nails of gouty subjects tend to become thin and brittle, and usually present a longitudinal striation, producing the condition known as "the reedy nail."

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.

Gouty affections of the eye.—A gouty inflammation of any of the structures of the eye may occur. Conjunctivitis and iritis are the two commonest eye affections caused by the gouty condition.

Deafness.—Occasionally a gouty neuritis affecting the terminations of the auditory nerve causes deafness.

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.

DIAGNOSIS AND PROGNOSIS.

The diagnosis of an attack of acute gout as a rule presents no difficulty (*see* pp. 107, 108). In its sub-acute and chronic forms gout must be distinguished from rheumatism, rheumatoid arthritis, and from synovitis of traumatic, pyæmic, or gonorrhœal origin. The appearance of the joint (*see* p. 108), the discovery of tophi, and the family history are the main points on which to rely.

Distinction of gout from rheumatism.—The sweating in acute rheumatism is much more copious than in acute gout. Rheumatism especially attacks the larger joints, whereas gout attacks the smaller joints most frequently, with the exception of the knees. The œdema around the gouty joint and the pitting on pressure are characteristic and of great assistance in distinguishing the affection from rheumatism. In gout desquamation of the cuticle of the affected joint occurs later, but not in cases of rheumatism. In connection with attacks of gout in the larger joints, such as the great toe and knee joints, inflammation of the contiguous lymphatic vessels occasionally occurs, and the glands in the neighbourhood of the affected part are usually enlarged and tender on pressure. As previously mentioned, the discovery of tophi and the family history are of immense service in distinguishing gout from rheumatism.

Distinction of gout from rheumatoid arthritis.—The severity of the pain generally serves to distinguish gout, there being no very acute pain in

the affected joints of rheumatoid arthritis. Moreover, in connection with rheumatoid arthritis there is a history of the different joints being affected at different times, but without the invasion of a new joint being accompanied by amelioration of those previously affected, and the history of the disease shows a continuity in the affection of the joints, instead of a periodicity as in gout. Chronic gout of the hands may be distinguished from rheumatoid arthritis by the greater symmetry that is generally displayed in the finger joints of the two hands in connection with the last-mentioned disease.

Prognosis.—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. Moreover, although gout has generally been regarded as a more or less incurable disease, the view as to its renal origin renders the possibility of cure much more reasonable.

Part III.

THE AUTHOR'S INVESTIGATIONS OF CERTAIN POINTS CONNECTED WITH THE TREATMENT OF GOUT.

CHAPTER X.

Experimental investigation of certain conditions and factors affecting the solubility and the precipitation of sodium quadriurate and sodium biurate.

THE ALKALINITY OF THE BLOOD IN HEALTH AND IN GOUT.

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 has previously been referred to, and 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, in the first place, is there any substantial proof that the alkalinity of the blood is much reduced in connection with gout? Careful experiments, conducted by Klemperer,* show that the alkalinity of the blood of gout is but very little, if at all, diminished, and that corresponding variations in the alkalinity may frequently be met with in healthy individuals. In the following table (Table V.) are shown the results of the determinations that I made of the alkalinity of the blood † of a patient suffering from subacute gout; the estimations were made mostly on alternate days, throughout the duration of the attack. The normal alkalinity of healthy blood is shown for comparison at the foot of the table. This normal,

* *Deutsche medicinische Wochenschrift*, 1895, xxi., p. 655.

† The process employed for determining the alkalinity of the blood was the one recently devised and described by Dr. A. E. Wright (*The Lancet*, Sept. 18th, 1897). This process is an extremely ingenious and reliable one, and possesses the great advantage of not requiring more than two or three drops of blood in order to make an accurate determination of the alkalinity.

alkalinity is the average of the determinations that I made of the alkalinity of the blood of twenty-five healthy male adults.

TABLE V.

Showing the results of the determination of the alkalinity of the blood of an adult man during an attack of subacute gout.

Dates of determinations, and relations to treatment.		Alkalinity represented as percentage of anhydrous sodium carbonate present in the blood.
Feb. 4th (commencement of attack, and before treatment was begun) ...		0·167
,, 6th	(Treated with colchicum only)	0·167
,, 8th		0·167
,, 10th		0·156
,, 12th		0·167
,, 15th		0·158
,, 17th		0·158
,, 19th	(Treated with citrate of potassium and iodide of potassium only)	0·167
,, 22nd		0·180
,, 24th		0·173
,, 26th		0·161
,, 28th		0·179
Mar. 2nd		0 167
Average alkalinity throughout the attack ...		0 166
Alkalinity of normal blood ... ... (*Average of the determinations of the alkalinity of the blood of twenty-five healthy male adults.*)		0·167

The alkalinity of healthy blood varied from 0·161 to 0·185, the average being 0·167, and it is seen in the table that the alkalinity of the gouty blood varied from 0·156 to 0·180, the average being 0·166, which is practically the same as the normal alkalinity. These results show that in this case of subacute gout the variations in the

alkalinity of the blood were not greater than those met with in healthy individuals. There is certainly no good ground for the belief that an "acid dyscrasia" underlies the gouty condition. Recent researches show that a diminution of the alkalinity of the blood is a common pathological condition in diseases that are in no way associated with uratic precipitation, such as acute rheumatism, leukæmia diabetes, carcinoma and pyrexia. In the second place, 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 EFFECTED 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 VI. and Table VII.) show the results of these experiments.

TABLE VI.

The 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 VII.

The 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 containing 25 c.c. each 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 VIII.

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 following table shows the results.

TABLE IX.

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 X.

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 XI.

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.

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

CHAPTER XI.

Experimental investigation of the influence exerted by the mineral constituents of meat, milk, and vegetables respectively on the solubility of sodium biurate—The influence of alcoholic beverages on the gouty process.

INFLUENCE OF CERTAIN ARTICLES OF DIET ON THE PRECIPITATION OF SODIUM BIURATE.

It is well known that the excessive consumption of rich nitrogenous food, combined with excesses in wine and malt liquors, both induce and excite 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. Dr. 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.

The generally accepted view that a highly nitrogenous animal diet necessarily produces an excessive amount of uric acid is disproved by

the experiments of Bleibtreu and of Hirschfeld previously referred to. Those experiments show that there is an increased elimination of urea to compensate for an excessive intake of nitrogenous food, and that the amount of uric acid remains practically undiminished. Judging by the results of the experiments which have been previously described, it is highly improbable that any diminution in the alkalinity of the blood, which might be produced by the consumption of an excessive amount of animal food, could in any way affect its solvent powers for uric acid, or accelerate the precipitation of sodium biurate. My own view is that, as regards the production of uric acid from proteid matter, it is of little importance whether the proteid is of animal or vegetable origin. The same harm may result from an excessive consumption of either form of proteid. But although animal and vegetable proteids may react alike with regard to the production of uric acid, 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. As I have been unable to find any record of experimental work bearing on this matter, 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.

Experiments showing the influence of the mineral constituents of meat, milk, and vegetables respectively on the solubility of sodium biurate at 100° F.

A series of experiments were 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 XII.

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 XIII.

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 ,,

From the foregoing table it is seen 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 XIV.

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 XIV. 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 delay the advent of an attack of gout by their increasing the solvency of sodium biurate, and would also exert a solvent effect on gouty deposits.

INFLUENCE OF ALCOHOLIC DRINKS ON THE GOUTY PROCESS.

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. Garrod considers that the reason for the prevalence of gout in the south of England and its rarity in Scotland is chiefly due to the different beverages drunk in the two countries.

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-inducing 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. The arrangement of wines and beers in the order of acidity, beginning with the most acid, is that given by Dr. Bence Jones, while the arrangement in order of their gout-inducing power is that given by Sir Alfred Garrod :—

TABLE XV.

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	Port
Rhine wines	Sherry
Burgundy	Other stronger wines
Madeira	Champagne
Claret	Stout and porter
Champagne	Strong ales
Port	Claret
Sherry	Hock
Malt liquors	Moselle
	Weaker kinds of ales

Claret, hock, moselle and the weaker kinds of ales have comparatively little gout-inducing power.

GOUT-INDUCING PROPERTIES OF CERTAIN WINES AND BEERS NOT DUE TO ACIDS OR SUGAR.

Sir Alfred Garrod considers that 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, such as clarets, are comparatively harmless in this respect. This opinion is entirely borne out by the experiments I have described, which show that a diminution of the alkalinity of blood serum does not hasten the conversion of sodium quadriurate into biurate, does not diminish the solubility of sodium biurate, and therefore cannot promote deposition of sodium biurate, and so be a determining cause of an attack of gout. 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. They are also most probably not due to the

sugar. The late Dr. George Harley experimentally investigated the subject, and stated that the popular notion as to the pernicious effects of sugar in cases of gout is open to grave criticism, seeing that not only can no reliable facts be adduced in favour of the statement, but no reliable authority for the assertion can be cited even by its believers. I have myself found experimentally that sugar has no appreciable effect either on the decomposition of sodium quadriurate, or on the solubility of sodium biurate.

PROBABLE CAUSE OF THE GOUT-INDUCING PROPERTIES OF CERTAIN WINES AND BEERS.

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 exercise 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 on the metabolism of the liver, and the consequent increased amount of glycocine that passes on to the kidneys. This increased amount of glycocine would then cause an increased production of uric acid in the kidneys, and provided there be deficient elimination of it from those organs, absorption of the surplus uric acid would take place into the general circulation. 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.

CHAPTER XII.

Experimental investigation of the relative effects exerted by the mineral constituents of various vegetables on the solubility of sodium biurate—Experimental investigation of the influence exerted by the mineral constituents of various vegetables in retarding the conversion of sodium quadriurate into biurate—The vegetables most beneficial to gouty subjects.

From the results of the preliminary experiments described on p. 144, 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 delay the advent of an attack of gout by increasing 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, which is present in the fluids of the body in gout, into the sodium biurate. Obviously the

elucidation of these points would have a material bearing on the treatment of gout.*

Experimental Inquiry to Ascertain 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 described on p. 142. I operated separately on the mineral constituents of the following vegetables:—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.

TABLE XVI.

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 ,,

* 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 XVII.

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 XVIII.

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 XIX.

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 XX.

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 XXI.

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 XXII.

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 XXIII.

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 XXIV.

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 XXV.

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 XXVI.

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 XXVII.

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 XXVIII.

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 XXIX.

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 XXX.

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 XXXI.

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 an important bearing on the treatment of gout, I next endeavoured to ascertain whether these effects were due to the alkalinity of the vegetable 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 XXXII.

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 before hand that such would not prove to be the case, since Sir William Roberts has 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 following 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 XXXIII.

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 also 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. The following table 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 XXXIV.

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

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 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 XXXV.

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 also 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 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 XXXVI.

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 also evident from this tabie 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 XXXVII.

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

It is also 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 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 XXXVIII.

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 proportion 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

It is also 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 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 XXXIX.

Showing the influence of the 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 XL.

Showing the different influences exerted by the artificial and 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 described on p. 143, 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 XLI.

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 Dr. Bence Jones and of Sir William Roberts that sodium quadriurate, which is the form in which uric acid first appears in the blood in gout, 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 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 XLII.

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 ,, ...	$2\frac{1}{2}$,,
,, ,, beetroot ,, ...	3 ,,
,, ,, green peas ,, ...	$3\frac{1}{2}$,,
,, ,, celery ,, ...	$3\frac{1}{2}$,,
,, ,, Brussels sprouts ash ...	4 ,,
,, ,, cabbage ,, ...	4 ,,
,, ,, turnip tops ,, ...	4 ,,
,, ,, turnip ,, ...	4 ,,
,, ,, Savoy cabbage ,, ...	4 ,,
,, ,, seakale ,, ...	4 ,,
,, ,, French beans ,, ...	$4\frac{1}{2}$,,
,, ,, 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, and if, at the same time, proper measures were adopted for promoting excretion of the quadriurate by the kidneys, 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, as I have shown elsewhere,* 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 and perhaps a main explanation of the known facts that an excessive

* *The Lancet*, April 17th, 1897, p. 1074.

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.

Owing to the undoubted action which I have shown the mineral constituents of several vegetables possess in delaying the conversion of sodium

quadriurate into biurate, and in increasing the solubility of the latter, it is possible that a table salt composed of vegetable ashes might prove advantageous to the gouty. Sir W. Roberts has shown that small quantities of sodium chloride introduced into blood serum containing quadriurate in solution always appreciably hastened the formation and precipitation of the biurate. In addition, sodium chloride very considerably diminishes the solubility of sodium biurate, while the mineral constituents of vegetables increase it. This is well shown in Table XLIII., representing the comparative effects of 0·1 per cent. solutions, respectively, of sodium chloride and of the mineral constituents of vegetables on the solubility of sodium biurate.

TABLE XLIII.

Showing the comparative effects of 0·1 *per cent. solutions respectively of sodium chloride and of the mineral constituents of various vegetables on the solubility of sodium biurate.*

Solvent.	Sodium biurate dissolved.
Water	1·10 per 1,000
Water containing :—	
0·1 per cent. of sodium chloride	0·45 ,,
,, ,, spinach ash	1·90 ,,
,, ,, Brussels sprouts ash ...	1·62 ,,
,, ,, Savoy cabbage ,, ...	1·57 ,,
,, ,, French beans ,, ...	1·56 ,,
,, ,, lettuce ,, ...	1·53 ,,
,, ,, potato ,, ...	1·47 ,,
,, ,, beetroot ,, ...	1·45 ,,
,, ,, carrot ,, ...	1·45 ,,
,, ,, asparagus ,, ...	1·45 ,,
,, ,, celery ,, ...	1·44 ,,
,, ,, turnip ,, ...	1·42 ,,
,, ,, turnip tops ,, ...	1·42 ,,
,, ,, cauliflower ,, ...	1·34 ,,
,, ,, cabbage ,, ...	1·31 ,,
,, ,, seakale ,, ...	1·23 ,,
,, ,, green peas ,, ...	1·10 ,,

This table shows the great advantage that the mineral constituents of vegetables possess over common salt as regards their solvent effect on sodium biurate. I have been able to calculate that with the moderately free use of vegetables, especially if supplemented by the use of a table salt prepared from vegetables, it is quite possible to introduce more than 0·1 per cent. of the mineral constituents of vegetables into the fluids of the body.

CHAPTER XIII.

Reasons for believing the treatment of gout by alkalies to be erroneous—Experimental investigation of the value of the treatment of gout by the various alkalies, by piperazine, and by lysidine—Reasons for believing the treatment of gout by salicylates to be erroneous—Experimental investigation of the value of the treatment of gout by salicylates—General conclusions.

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. As I have for some time believed that both these methods of treatment are wrong in principle and action I thought it expedient to submit the matter to experimental investigation.

Reasons for believing the treatment of gout by alkalies to be erroneous.

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. 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 (*see* p. 87). 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 either in delaying or partially arresting an attack of gout, or 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 experiments to ascertain the effect of drugs employed in the alkaline treatment of gout were conducted in the following manner.

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 a 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 shown in the following table :—

TABLE XLIV.

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	,,

These results show that none of the drugs mentioned in the table exercise 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.

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

* In order to have 0·1 per cent. of any drug in the blood, it would be necessary to introduce 100 grains of that drug at once into the circulation of an adult man of average weight.

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. He fails to find any direct object in the administration of alkalies for gout, and he has seen gouty attacks recur with full severity when the urine has been for a long time maintained persistently alkaline by the administration of bicarbonate and citrate of potassium. 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 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.

* The Croonian Lectures, 1892.

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 that described on pp. 137, 138. I experimented separately with the following drugs—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 XLV.

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 XLVI.

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 XLVII.

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 XLVIII.

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 XLIX.

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 L.

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 LI.

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 portions 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 LII.

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 (*see* p. 181), 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 *viâ* 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 medicinally 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 akalies, 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. Sir William Roberts † does not find any direct object in the administration of alkalies for gout; he has seen gouty attacks recur with full severity when the urine has been for a long time maintained persistently alkaline by the administration of potassium bicarbonate and citrate. Dr. 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

* "The Uric Acid Diathesis," 1894.

† The Croonian Lectures, 1892.

‡ Guy's Hospital Reports, 1895.

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 (*see* p. 177), that in connection with gout there is a general acidity of the system which 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 (*see* p. 130) show that the alkalinity of the blood of gout is but very little, if at all, diminished, and that corresponding variations in the alkalinity of the blood may frequently be met with in healthy individuals. Moreover, the experiments described on pp. 131–139 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.

* *Therap. Monats.*, x., 1896.

NO RELATIONSHIP BETWEEN THE ACIDITY OF THE URINE AND THE AKALINITY 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 versâ*. That this assumption is quite wrong is shown by reference to the following table (Table LIII.), 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 Lépinois.* The estimations were made mostly on alternate days throughout the duration of the attack.

* *J. Pharm.*, 1896 (6), iii., 8—16.

TABLE LIII.

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

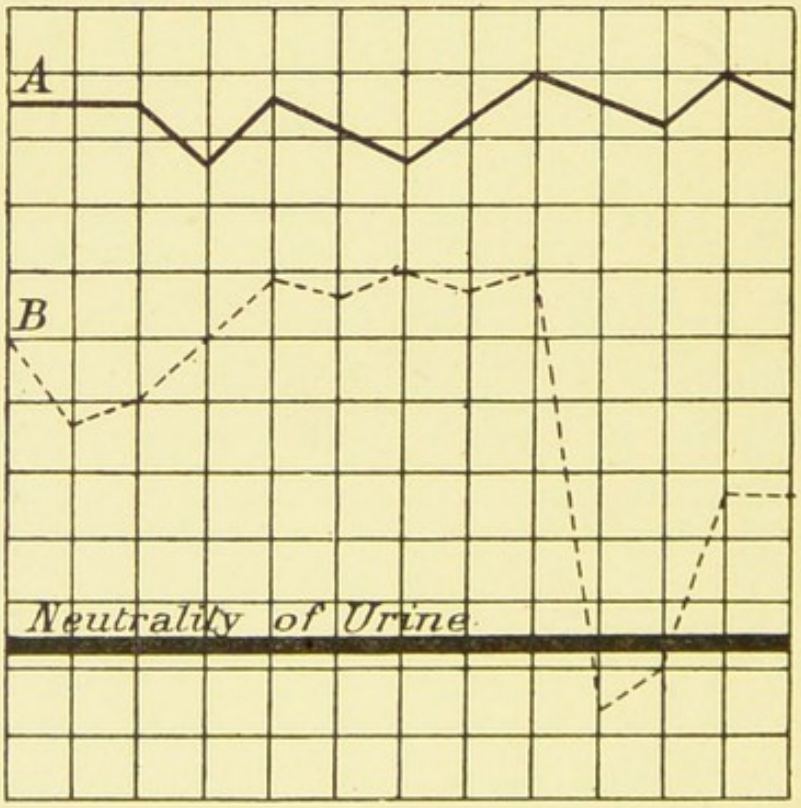

Diagram showing the absence of any constant relationship between the alkalinity of the blood and the acidity of the urine of a patient during an attack of subacute gout.

A, Alkalinity of blood ; B, acidity of urine.

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 diagram on p. 192, a glance at 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 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 LIV.

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 LV.

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. Dr. 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

* Guy's Hospital Reports, 1895.

administration has no effect whatever in delaying the conversion of sodium quadriurate into the biurate, as is shown in the following table:—

TABLE LVI.

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 LV. and LVI. 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 is necessarily formed. Since,

therefore, I believe that the effect of a salicylate is to increase the production of uric acid in the kidneys by bringing additional glycocine to those organs, I am of opinion that salicylates are contra-indicated in gout, as increased production of uric acid in kidneys which are already incapable of eliminating the normal amount of uric acid would lead to increased absorption of uric acid into the general circulation, and, consequently, to intensification of the gouty condition.

GENERAL CONCLUSIONS DRAWN FROM THE INVESTIGATIONS.

1. The alkalinity of the blood is apparently not appreciably diminished 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.

5. The gout-inducing properties of certain wines are not due to their acidity. Probably they owe their gout-inducing action to the effect they exercise on the metabolism of the liver.

6. The solubility of sodium biurate is markedly increased by the presence of the mineral constituents of most vegetables.

7. The solubility of sodium biurate is dimin-

ished by the presence of the mineral constituents of meat.

8. The mineral constituents of certain vegetables delay the conversion of sodium quadriurate into the biurate.

9. The vegetables most useful to gouty subjects are spinach, Brussels sprouts, French beans, winter cabbage, Savoy cabbage, turnip tops, turnips, and celery.

10. 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.

11. No general acidity of the system is associated with gout.

12. No relationship exists between the acidity of the urine and the alkalinity of the blood.

13. The administration of salicylates with the object of removing gouty deposits appears to be useless, and their employment in the treatment of gout is contra-indicated.

Part IV.

THE TREATMENT OF GOUT AND OF GOUTY CONDITIONS.

CHAPTER XIV.

The general principles on which the treatment of gout is based—Examination of the urine—Treatment of acute gout—Diet in acute gout—The action of colchicum—Treatment of subacute and chronic gout—Means of checking the excessive formation of uric acid—Means of promoting the elimination of uric acid—Local treatment of gouty joints.

THE 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.

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 chronic condition and the prevention of the recurrence of an attack, which may be effected by the promotion of the elimination of uric acid, by checking any excessive formation of uric acid that occurs in some subjects, and by careful attention to diet and general hygiene; and (3) the treatment of the affected joint or joints, with the object of removing the uratic deposits, and of preventing permanent deformity.

EXAMINATION OF THE URINE.

In all cases of gout a very careful examination of the urine should be made, and it is especially important to endeavour to ascertain whether the kidney affection is in the functional or organic stage. The indications that the gouty affection of the kidney is passing from the functional into the organic condition 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.

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 process that I always employ for such determinations is the Gowland-Hopkins process (*see* p. 30), which is a very accurate method for the estimation of uric acid in urine. 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.

THE TREATMENT OF ACUTE GOUT.

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 arranged so as to take the weight of the bed clothes off 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 :—

Sodæ carb.	ʒiij.
Linim. belladonnæ	℥ij.
Tinct. opii	ʒj.
Aq. ad	ʒviij.

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 eight or twelve 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 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 ten 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 it is left off. Sir Alfred Garrod regards acute gout and the acute exacerbations of chronic gout as the chief indications for employing colchicum.

From three to four grains of blue pill should be given the first night, followed by a dose of Epsom salts in the morning. Mercury should be given only in sufficient doses to produce its cholagogue effect, as owing to the defective action of the kidneys the mercury absorbed into the general system may be eliminated with great difficulty. In my opinion it is advisable in the treatment of gouty patients in the acute or subacute stages to avoid the use of saline purgatives owing their efficacy to salts of sodium, on account of the undoubted power possessed by all sodium salts of diminishing the solubility of sodium biurate. In the employment of purgatives for gouty patients the great object is not to produce powerful purgation, but to relieve portal congestion, since a congested condition of the liver means that an excessive quantity of glycocine is transmitted to

the kidneys, where an excessive quantity of uric acid is consequently produced. A pill containing either two grains of euonymin or a quarter of a grain of podophyllin combined with a grain of extract of hyoscyamus and a grain and a half of the compound extract of colocynth will, in many cases, be found to be very useful.

If the pain of an acute attack of gout is so severe as to prevent sleep, chloral, sulphonal, or trional may be given, or a full dose of extract of hyoscyamus given with blue pill at night 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 on account of the kidney affection, and also on account of its diminishing the amount of urine, and its tendency to derange digestion and to check hepatic metabolism.

DIET IN ACUTE GOUT.

During an attack of acute gout a diet must be given which, in the first place, shall be non-irritating to the affected kidneys, and, in the second place, shall be one that does not produce an excessive quantity of uric acid. For the first day or two of an acute attack the patient should be restricted to a milk diet, which may consist of milk, arrowroot and milk, bread and milk, milk puddings made with rice, sago, or tapioca, 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 mineral water free from sodium salts (for list of such waters, *see* p. 230), 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 so to interfere with the elimination of uric acid. 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. For the dietary suitable for gouty subjects after the acute attack has subsided, see pp. 222—225.

THE ACTION OF COLCHICUM.

Although no satisfactory explanation of the beneficial action of colchicum in gout has hitherto been put forward, I believe that its beneficial effect is mainly due to its diminishing the uric acid production, thereby arresting the absorption of uric acid from the kidneys, and so preventing the further deposition of biurate in the affected parts. Colchicum is a powerful direct cholagogue, and it is probably owing to its action on the liver that its

efficacy in mitigating the severity of the pain and relieving an attack of gout is due. If, as a cholagogue, it inhibits the formation of glycocine, then the amount of uric acid formed in the kidneys must be diminished, and if the uric acid formation is lowered to the quantity that can be eliminated by the affected kidneys, then the absorption of quadriurates from the kidneys into the general circulation is prevented, and so the formation of further gouty deposits is arrested. This view renders intelligible the efficacy of colchicum not only in connection with articular gout, but also in connection with the various forms of irregular gout.

The explanation just given of the mode of action of colchicum is at once supported by the fact recorded by so many observers that the uric acid elimination is always diminished during the period of administration of colchicum, whereas the elimination of urea is practically unaffected by the drug. The following table (Table LVII.) shows the diminished elimination, and, as I believe, the diminished formation of uric acid, that occurred during the administration of colchicum to one of my patients while suffering from an attack of subacute gout of both hands and knees. That deficient production of uric acid accompanied the deficient excretion was shown by the fact that the gouty affection of the joints rapidly improved during the treatment with colchicum, whereas if the formation of uric acid had remained the same, and merely deficient elimination of it had occurred, the articular condition would have become worse.

TABLE LVII.

Showing the decreased elimination of uric acid in a case of sub-acute gout during the administration of colchicum.

	Uric acid in grammes.
Daily elimination at the commencement of the attack	0·438
Average of the daily eliminations for fourteen days while under treatment with colchicum. (Vin. colchici ♏xxx were given as the first dose, and then ♏xv three times a day throughout the fourteen days of treatment.)	0·234

This diminished excretion of uric acid that occurs during the administration of colchicum is a good sign, since it points, in my opinion, to diminished formation of uric acid. It is in marked contrast to the action of sodium salicylate, which considerably increases the excretion of uric acid by increasing its formation in the kidneys. As previously stated (*see* pp. 196, 197), the employment of salicylates in the treatment of gout is, in my opinion, contra-indicated.

Although colchicum does not directly affect the solution of uratic deposits, yet indirectly it may produce that result, since, by diminishing the formation of uric acid, it allows the kidneys to eliminate the sodium quadriurate circulating in the blood of the gouty patient, and if the blood can be kept free from quadriurate, then the solution of the sodium biurate from the joints and tissues, where it is deposited, will slowly but surely proceed. The mitigation of the pain of an acute gouty

paroxysm is probably owing to colchicum acting as a cardio-vascular depressant, lowering the tension and frequency of the pulse, and so relieving the pressure and pain felt in the affected joint.

THE TREATMENT OF SUBACUTE AND CHRONIC GOUT

Means of checking the excessive formation of uric acid.—These consist in careful attention to diet and regimen, the promotion of the metabolism of the liver, so as to check the excessive production of the antecedents of uric acid, and in the relief of congestion of the portal system, which can be effected by keeping the bowels open at least once a day. 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 generally acts as a laxative. If constipation occur, a sulphur and guaiacum tablet, or a dose of compound liquorice powder, should be taken at night. An occasional dose of blue pill and euonymin, followed by a purge of Epsom salts, will be found useful. Sir Alfred Garrod considers that guaiacum relieves gouty inflammation, and that a similar result is produced by the administration of serpentary. If guaiacum is given in too large doses it may produce a papular or urticarial rash accompanied by considerable itching. If the patient is suffering from

atony and debility of the stomach, nux vomica or strychnine may be given with potassium citrate. Iron preparations are not as a rule well tolerated by the gouty, but if anæmia is present the citrate of iron and ammonium or the carbonate of iron will be found the best to administer.

Means of promoting the elimination of uric acid.—The elimination of uric acid may be effected by medicinal treatment, and by diet and regimen. Citrate 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 citrate of potassium may with advantage be pushed until moderate alkalinity of the urine is produced, as by such means the quadriurates are rendered more soluble and more stable than they are in acid urine, and so 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. A patient suffering from gout should avoid, as far as possible, the use of common salt at table, owing to the power it possesses of diminishing the solubility of sodium biurate, and thereby hastening the precipitation of that body. The dietetic treatment of chronic gout is described on pp. 222—225.

Further treatment of chronic 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 last-mentioned 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. This drug should not, however, be regarded as a solvent of gouty deposits, and it is contra-indicated if advanced kidney disease exists. It should be given in doses of five to ten grains three times a day, and may usefully be combined with from five to ten minims of tincture of iodine. Sir Alfred Garrod advises the administration of guaiacum in those cases where the gouty pains are relieved by the application of warmth, but considers that it is contra-indicated when any marked inflammatory symptoms are present, as shown by the increase of pain when the patient is warm in bed. In such cases potassium iodide is likely to be more beneficial than guaiacum. The lithium salts are not, in my opinion, solvents of gouty deposits (*see* pp. 183, 184, 189), but since they are powerful diuretics they may, on that account, be of some use in the treatment of chronic gout. They should never, however, be given in sufficient quantities to keep the urine alkaline, as their depressing effect in such doses is too great.

If the signs of organic renal mischief exist (*see* p. 200), then particular attention must be paid to the prevention of an excessive formation of uric acid. This can be accomplished by placing the patient on a suitable diet, by promoting elimination from the kidneys by the administration of suitable diuretics, such as potassium citrate and ammonium

acetate, and by the thorough flushing of the kidneys by a water as free as possible from sodium salts. If marked albuminuria occurs then, in addition to the above-mentioned treatment, vapour baths or Turkish baths may be employed, provided they do not produce debility.

THE 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. 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, 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. Successful results have been reported from the localised application of very hot dry air, which appears not only to relieve the pain and congestion of the joints, but also to assist in the dispersion of the gouty deposit, probably by increasing the circulation in the various structures of the affected joint. 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.

CHAPTER XV.

Treatment of retrocedent or metastatic gout—Treatment of the various forms of irregular gout—Treatment of gouty glycosuria and diabetes—Preventive treatment of gout—Diet in gout—Alcohol in gout.

THE 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 supervene, 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.

THE TREATMENT OF THE VARIOUS FORMS OF IRREGULAR GOUT.

Affections of the gastro-intestinal tract and of the air-passages and lungs due to irregular gout require treatment on general principles. For lists of the mineral waters best suited for these forms of irregular gout, *see* p. 241.

Gouty vertigo is generally due to gastric disturbance, which then requires suitable treatment. If the vertigo is of central origin, then the ordinary

medicinal treatment for acute gout should be employed.

The *gouty heart* is associated with fatty degeneration of the cardiac walls, and is mainly met with among sufferers from irregular gout. The condition is generally evidenced by præcordial pain or oppression, vertigo, faintness, palpitation, or irregular cardiac action, insomnia, and slight anginal attacks; towards the end of an attack a cold sweat generally breaks out on the surface of the body, and is followed by flatulent eructations, after which the attack subsides. 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 (*see* pp. 222—225), 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 abstention from tobacco smoking, or extreme moderation in its use, should be advised.

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 three times 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 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. In cases of gouty sciatica the ordinary treatment of the gouty state must be resorted to.

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 and iodine (for the doses *see* p. 210) combined with small doses of perchloride of mercury should be given.

Diseases of the skin associated with gout.—In dealing with any gouty skin affection the ordinary treatment of the skin disease should be combined with the general treatment of the underlying gouty condition, and careful attention should especially be paid to the diet. Many of the gouty skin affections are considerably benefited by a course of waters and baths at certain spas (a list of these spas is given on pp. 239, 240). The severe itching attending pruritus and urticaria is generally relieved by the application of the following lotion:—

Liq. plumbi subacet.	...	...	℥ij
Tinct. opii	...	...	℥iv
Aq. rosæ ad	...	...	℥viij

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 a delicate coating on the skin, which then probably acts by protecting the cutaneous surface from the air.

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 (*see* p. 230) should be advised.

Irritable temper.—For the treatment of the irritable temper of gout, Dr. Lauder Brunton recommends the administration of twenty grains of bicarbonate of potassium and ten to twenty grains of bromide of potassium.

THE 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. For a list of the mineral waters best suited for the treatment of gouty glycosuria and gouty diabetes, *see* p. 241.

THE PREVENTIVE TREATMENT OF GOUT.

If uric acid is manufactured in the kidneys and, in gout, is absorbed therefrom into the general circulation only when the kidneys are incapable of getting rid of the whole of the uric acid, then whatever will promote the elimination of the uric acid, and thereby prevent its absorption into the general circulation, will strike at the origin of the development of gout. This can be effected by (1) the promotion of increased diuresis, by which means the solution and removal of the quadriurates from the kidneys is encouraged; (2) by the production, at all events intermittently, of a moderate degree of alkalinity of the urine, by which means the quadriurates are rendered more soluble and more stable than they are in an acid urine, and so the tendency to the deposition of uric acid or of sodium biurate in the kidney tissues is removed; and (3) by stimulation of the metabolism of the liver and of the kidney cells engaged in the excretion of uric acid. The preventive treatment of gout consists in the adoption of measures which

have for their aim the carrying out of these various points.

The first effect can be secured by the patient drinking a sufficient quantity of ordinary water, or of a suitable mineral water. The second effect is attained by the consumption of sufficient quantities of vegetable food, and by the occasional administration of citrate of potassium. The third effect is secured by the administration of guaiacum and other suitable cholagogues, such as an occasional pill containing two grains of blue pill and two grains of euonymin given at night, and followed by a dose of Epsom salts in the morning. Sir Alfred Garrod considers that guaiacum taken in the intervals of attacks of gout is a powerful prophylactic, that it does not appear to lose its prophylactic power by long-continued use, and that only in the cases of a few persons does the drug disagree. I have employed guaiacum for some time as a prophylactic in gout, and can entirely corroborate Sir Alfred Garrod's opinion as to its great utility under such conditions.

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 pp. 222—225. Regular habits of life, with regular 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.

DIET IN GOUT.

A rational mixed diet is the one best suited for gouty patients, care being taken to avoid excess. The assumption that a purely vegetable diet is best for the gouty is erroneous, since the production of uric acid depends on the ingestion of proteid matter, and it makes no difference whether the proteid matter be of animal or vegetable origin. At the same time it must be borne in mind that since animal food is so much richer in proteids than a vegetable diet, the amount of the former taken by the gouty should be strictly limited. Moreover, the results of the series of investigations summarised on pp. 172—175 show that, 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 cannot too strongly urge 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 and agree with him. 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. It is most important that the gouty patient should take a sufficiency of water to drink, so that the various organs are well flushed, the removal of the gouty deposits encouraged, and the specific gravity of the urine kept moderately low. The quantity of fluids taken in the twenty-four hours should not be less than three and a half pints, and may even with advantage reach to four and a half pints.

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 thinly buttered, and tea infused for three minutes and then strained from the leaves.

Lunch and dinner.—No soup should be taken at either meal. The varieties of fish most suitable to the gouty are whiting, sole, turbot, and plaice. Meat should be taken at only one meal, and then in moderate quantity. Beef, mutton, chicken, turkey, pheasant, and calf's sweetbread are admissible. Salted meat, salted and smoked fish, and shell fish, with the exception of oysters, are best avoided. All articles of food pickled in vinegar should also

be avoided. Two vegetables should be taken at both lunch and dinner, and in abundant quantities. The vegetables that, in my opinion, should be avoided by the gouty are asparagus, tomatoes, and green peas. Asparagus is apt to prove irritating to the kidneys of gouty subjects, and also is liable to produce a temporary glycosuria, probably from some irritant effect on the liver. Any of the other ordinary vegetables may be taken, but those that I consider most likely to prove beneficial to gouty subjects are, as, indeed, has already been mentioned, 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 with advantage be taken every day at one meal, and a milk pudding made with rice, sago, and tapioca at the other meal. Rhubarb should be avoided owing to the liability of the calcium oxalate contained in it to irritate the kidneys during its excretion. Rich pastry and all rich sweets should be rigorously avoided by the gouty.

Night.—A pint of hot water, flavoured with a slice of lemon peel, should be slowly sipped before retiring to bed.

Alcohol.—As regards the employment of alcohol, each case must be individually and carefully dealt with. During an attack of acute gout the patient is better without any alcohol. If the gouty person be of robust habit of body, then total abstinence is undoubtedly the best for such a patient. If, however, the cardiac action be weak and failing, then

moderate quantities of alcohol should certainly be given. In cases of chronic gout a moderate amount of alcohol may be necessary for the promotion of digestion. The best form of alcohol for the gouty is a tablespoonful of matured whisky freely diluted with salutaris water or with plain water, and taken towards the end of lunch or dinner. If any wine is taken by the gouty, those which are least open to objection are light but sound clarets and hocks. Old wines with a fine bouquet are very provocative of gouty attacks in most persons predisposed to the disease, probably on account of the large quantities of ethereal compounds contained in them powerfully affecting the metabolism of the liver, and so, by causing an increased quantity of glycocine to pass from the liver to the kidneys, leading to an increased production of uric acid in the last-mentioned organs. Ales and stout should also be avoided by the gouty.

CHAPTER XVI.

The uses of mineral waters in the treatment of gout—The mineral waters best suited for the removal of gouty deposits—Classification of the mineral waters used in the treatment of gout—The simple waters—Simple alkaline waters—Alkaline sulphated waters—Alkaline muriated waters—Common salt or muriated waters—Sulphur waters—Hot and cold mineral waters—Classification of mineral waters according to their therapeutic value in the treatment of the various forms of gout.

THE USES OF MINERAL WATERS IN THE TREATMENT OF GOUT.

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 most 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. Moreover, 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.

The use of a mineral water, so far as its employment with the object of removing gouty deposits is concerned, lies solely in its watery constituent, and does not in any way depend on the mineral constituent dissolved in it. As a matter of fact the salts dissolved in a great many of the natural mineral waters are directly harmful in gout both by encouraging deposition of the sodium biurate and by checking solution of the gouty deposits. The flushing of the system of a gouty patient with abundant quantities of water is undoubtedly beneficial, since it dilutes the blood for the time, and so tends to prevent uratic precipitation, and at the same time promotes diuresis and encourages the elimination of urates. The question, however, naturally arises whether, if the water of a mineral water be its only beneficial constituent for effecting the removal of gouty deposits, the sending of gouty patients to spas for such a purpose presents any advantages over their drinking ordinary water at home. If the conditions of the life of the

patient at home and at a spa were the same, there would be no such advantage, but among the special benefits to be derived from residence at a spa must be reckoned the almost undistracted attention that is given by the patient to treatment, the careful dieting that is frequently observed, the change of surroundings, the absence of business or home worries, and the opportunities for the use of thermal baths for the external treatment of articular gout. It should, however, be carefully borne in mind that, owing to the undoubted fact that sodium salts are directly detrimental to the removal of gouty deposits, those springs should be avoided which owe their activity to those salts, when the removal of the deposits is the main object to be attained. The springs which contain no sodium salts, or traces only, are the ones suitable for such cases—such as the waters of Buxton, Bath, and Strathpeffer in Great Britain; in France the waters of Aix-les-Bains, Contrexéville, and Vittel; in Switzerland the Pfaefers water; in Austria the Gastein water; in Bohemia the Teplitz water; in Germany the Wildbad water. I wish it to be clearly understood that I am by no means condemning the very proper uses to which mineral waters containing sodium salts can be put for the treatment of many gouty affections of the viscera and other structures, but I wish to emphasise the point that when the system is flushed with a mineral water with the object of dissolving and removing gouty deposits, then it is undoubtedly advisable to select a water as free as possible from

sodium salts. On the other hand, in cases of sluggish action of the liver, of gastro-intestinal catarrh and torpor, of gouty dyspepsia, and of other forms of irregular gout where 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.

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. The advantages and disadvantages of sodium salts have already been referred to. 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.

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 LVIII.) shows the proportions of sodium salts in the respective waters of this class, represented as grains of sodium per gallon :—

TABLE LVIII.

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
Aix-les-Bains	1·34
Buxton	1·47
Pfaefers	1·61
Gastein	5·89
Wildbad	7·63
Bath	9·42
Vittel	12·39

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.

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. Sir Alfred Garrod especially recommends the treatment at Aix-les-Bains in cases of chronic gout accompanied by

indolent swelling of the previously inflamed part, and by eczema. The spa is open all the year, but the season lasts from April to November.

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.

Pfaefers (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.

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. 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.

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, Brides-les-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. They are also of use in the treat-

ment 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 (England, Gloucestershire). The waters are cold. The non-chalybeate waters are useful in the treatment of congestive conditions of the liver associated with gout.

Leamington (England, Warwickshire). The waters are cold. Baths are provided. The waters are useful in the treatment of torpid conditions of the liver and of the gastro-intestinal tract associated with gout, and also in the treatment of gouty glycosuria.

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 the waters 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.

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. They 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 exercise a stimulant effect on the gastric glands and on the liver cells. 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, 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.

Llandrindod (Wales, Radnorshire). The waters are cold. Altitude 700 feet. Baths are provided. Muriated waters, sulphur waters, and weak chalybeate waters are found at Llandrindod. The muriated waters are useful in the treatment of

gouty gastro-intestinal catarrh and congestion of the liver, and also in the treatment of gouty glycosuria. The season is from May to October.

Woodhall Spa (England, 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.

SULPHUR WATERS.

These waters contain sulphur, either in the form of sulphuretted hydrogen only, or, in addition to free sulphuretted hydrogen, some of them 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 addition, the Harrogate waters may be employed in the treatment of gouty gastro-intestinal and hepatic affections. 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 (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).

HOT AND COLD MINERAL WATERS.

The following table (Table LIX.) shows a classification of the various mineral waters used in the treatment of gout into hot and cold waters :—

TABLE LIX.

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
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	

THERAPEUTIC USES OF THE VARIOUS MINERAL WATERS FOR THE DIFFERENT FORMS OF GOUT.

In the following table (Table LX.) the various mineral waters are classified according to their therapeutic value in the treatment of the various forms of gout.

TABLE LX.

Classification of the various mineral waters according to their therapeutic value in the treatment of the various forms of gout.

Object of taking the water.	The waters best suited for the purpose.
Absorption of gouty deposits from the joints and tissues.	Aix-les-Bains, Bath, Buxton, Contrexéville, Gastein, Pfaefers, Strathpeffer, Teplitz, Vittel, Wildbad.
Treatment of gouty dyspepsia.	Brides-les-Bains, Carlsbad, Ems, Homburg, Kissingen, Neuenahr, Royat, Vals, Vichy, Wiesbaden.
Treatment of gouty congestion and torpor of the liver, and of gastro-intestinal catarrh and torpor.	Baden-Baden, Bourbonne, Carlsbad, Cheltenham, Contrexéville, Harrogate, Homburg, Kissingen, Leamington, Llandrindod, 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, Kissingen, Leamington, Llandrindod, Marienbad Neuenahr, Vals, Vichy, Vittel.
Treatment of gouty skin affections.	Sulphur waters and baths (*see* pp. 239, 240).

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