A CONTRIBUTION ✓

TO

THE CHEMISTRY OF GOUT.

BY

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THE chemistry of gout centres round the properties of uric acid and the urates. It has long been known that gouty concretions are composed of sodium biurate; and in 1848–54 Sir Alfred Garrod demonstrated the important fact that the blood and morbid effusions of gouty persons are abnormally impregnated with uric acid. No substantial addition to our knowledge of the chemistry of gout has since been made.

In a paper recently read before this Society I gave an account of the combinations which uric acid forms with bases.¹ It was there shown that uric acid forms three distinct orders of salts, namely, neutral urates, biurates, and quadrurates. The neutral urates are not known to exist in the body. They can only be produced (artificially) in the presence of the caustic alkalies, free from carbonates, and as such conditions never occur in the living economy,

¹ "On the History of Uric Acid in the Urine," &c., communicated March 25th, 1890. It is assumed throughout the present paper that the reader is acquainted with the second section of my previous paper dealing with the composition and reactions of the quadrurates.

the neutral urates cannot, with our present knowledge, be assumed to take any part in the uratic phenomena of gout.¹ The biurates, although existing pathologically in gouty concretions, are not known with certainty to exist in the healthy or physiological state. The quadrurates, on the other hand, appear to be in a special sense the physiological salts of uric acid. They constitute exclusively the combination in which uric acid exists in normal urine; and, in animals which eliminate their nitrogen as uric acid, like birds and serpents, the urinary excretion is composed entirely of quadrurates. It is, moreover, susceptible of proof that uric acid in liquids containing alkaline carbonates and phosphates, such as are the serum of the blood and its derivatives, enters into solution in the first instance as a quadrurate. From these considerations it may be inferred that in the normal state uric acid is primarily taken up in the body as quadrurate, that it circulates in the blood as quadrurate, and that it is finally voided with the urine as quadrurate; and that when uric acid makes its appearance in any other guise, whether as crystalline biurate in gouty deposits or as free uric acid in gravel, this event is due to secondary and abnormal changes in the quadrurate.

In the paper referred to I traced the changes undergone by the quadrurate in the urine which lead up to the separation of uric acid in the free state as gravel and urinary sediments. In the present paper I propose to trace the converse changes which the quadrurate undergoes in the blood, and which lead up to the formation and deposition of sodium biurate in the tissues of the body. These latter changes are, I think, intimately connected with the property possessed by the quadrurates of slowly taking up, in the presence of the alkaline carbonates and phosphates, an additional atom of base, and of being thereby converted into biurates. A knowledge of this property permits a coherent view to be presented of the succession of events

¹ For this reason the notion of W. Ebstein that the neutral urates are concerned in the formation of gouty deposits appears to be untenable.

which culminate in the gouty paroxysm, and which may be expressed in the following terms.

In the normal state the uric acid, which circulates in the blood as quadrurate, is removed unchanged by the kidneys, and is removed with sufficient speed and completeness to prevent any undue detention or any accumulation of it in the blood. But in the gouty state—either from insufficient kidney action, or from increased introduction of urates into the circulation, or from some altered quality of the blood itself—the quadrurate lingers unduly in the blood and accumulates therein. The detained quadrurate, circulating in a medium which is rich in sodium carbonate, gradually takes up an additional atom of base, and is thereby transformed into sodium biurate. This transformation alters the physiological problem. The uric acid, or rather a portion of it, circulates no longer as the highly soluble and presumably easily secreted quadrurate, but as biurate, which, as we shall see, is almost insoluble in blood-serum, and is, moreover, probably, and for that reason, difficult of removal by the kidneys. Under these new conditions sodium biurate accumulates more and more in the blood, and when the accumulation has reached a certain point it is precipitated in the crystalline form in the joints and elsewhere, thereby determining the occurrence of a “fit of the gout.”

The evidence on which this view is based was obtained from a study of the behaviour of uric acid and the urates under various conditions in different media.

It is obvious that the reactions of uric acid and the urates which concern us in gout are not their reactions with simple water, but their reactions with the alkaline and saline media in which they exist and circulate in the body, namely, in the blood and lymph; and herein lies a radical distinction, inasmuch as the reactions in question are wholly different according as the medium is water on the one hand, or blood and lymph on the other.

The serum of the blood and its cognates, the lymph, synovia, and interstitial juices, are closely allied in chemical

composition. Besides albuminoid matters, blood-serum contains certain saline ingredients, on which its behaviour with uric acid and the urates essentially depends. The sodium salts are present in proportion of about 0·7 per cent., the potassium salts in the proportion of about 0·06 per cent., and the calcium and magnesium salts together in the proportion of about 0·05 per cent. It is thus seen that the sodium salts exceed all the other salts put together in the proportion of about seven to one. And practically, for our present purpose, we may consider the saline basis of the blood-serum as consisting essentially of sodium salts, so greatly do these preponderate over the sum of all the other salts put together. The most abundant of the sodium salts is the chloride, which is present in a very constant proportion of 0·5 per cent. The next most abundant salt is the sodium carbonate, probably, chiefly at least, in the condition of bicarbonate. This latter is present in the proportion of about 0·2 per cent. The third sodium salt is the phosphate, which, however, is only present in the proportion of about 0·03 per cent. The serum has always a sharply alkaline reaction, which is due to the large proportion of sodium carbonate contained in it.

From these particulars it may be gathered that a watery solution containing 0·5 per cent. of sodium chloride and 0·2 per cent. of sodium bicarbonate would be a fairly exact imitation of the blood-serum in so far as its saline ingredients are concerned. And it was found experimentally that such a solution behaved in regard to uric acid and the urates in the same manner as blood-serum itself, and in the same manner as a solution composed of all the salines of the serum in their due proportion, as ascertained by the best analyses. A solution was therefore prepared in distilled water, containing 0·5 per cent. of sodium chloride and 0·2 per cent. of sodium bicarbonate. This was called the "standard" solution or solvent. The behaviour of uric acid and the urates with this solution was studied in detail, under varying conditions of temperature and time, and with varying modifications of its composi-

tion. The results thus obtained were then collated with those obtained with blood-serum in similar circumstances, and with parallel modifications of its composition.

By this method of investigation a considerable amount of information was acquired, bearing on the chemistry of the gouty state, and on the genesis of the uratic phenomena of the complaint. The results of the inquiry are considered in the following order. First, the behaviour of the material of gouty concretions, namely, the biurate of sodium, with the standard solvent and with blood-serum is examined. Second, the strongly contrasted behaviour of uric acid and the quadrurates with the same media is followed out. Lastly, some of the conditions which hasten or retard the precipitation of sodium biurate are investigated.

I. BEHAVIOUR OF SODIUM BIURATE WITH THE STANDARD SOLVENT AND ITS MODIFICATIONS, AND WITH BLOOD-SERUM.

When sodium biurate¹ is digested, at blood heat, with pure water it enters pretty freely into solution. Such a solution acidulated with hydrochloric acid throws down a copious precipitate of uric acid. Careful experiments indicated that the solubility of sodium biurate in distilled water, at 100° F., fully amounts to 1 part in 1100. But when sodium biurate was digested at the same temperature with the standard solvent very little went into solution—so little that 100 c.c. of the filtered product, after treatment with hydrochloric acid, only yielded a few scattered crystals of uric acid—a quantity too small to be weighed.

¹ Sodium biurate was prepared by boiling 4 grams of uric acid in 400 cubic centimetres of a 1 per cent. solution of sodium bicarbonate. This was filtered hot and then allowed to stand for twenty-four hours. A copious precipitate of crystalline stars and needles was thus obtained. This was thrown on a filter and washed with cold distilled water, and then dried at 100° F. In experimenting with the urates the investigator should always prepare his own materials. Specimens of the urates supplied to me by dealers proved to be mere crude mixtures of uric acid with the bases, and were wholly unfit for exact experiments.

I estimated that the solubility of sodium biurate in the standard solvent at 100° F. could certainly not exceed 1 part in 10,000. It was, moreover, found that no addition to the solvent of any salts—whether of potassium, lithium, or magnesium—whether as carbonates, chlorides, phosphates, salicylates, iodides, or bromides—made any appreciable difference.¹ On the other hand, if the standard solution was modified in the opposite direction—in the direction of subtraction—its solvent power progressively increased. In other words, the nearer the solution approached to pure water the higher became its power of dissolving sodium biurate; and, on the contrary, the richer it was in sodium salts the more was its solvent capacity reduced.

The solvent power of the solution seemed to be determined exclusively by the sum of sodium salts contained therein; it mattered little, so long as the quantity of base was constant, what the combination was. The degree of alkalescence had not the slightest influence, and a solution of sodium chloride or sulphate was absolutely on a par with a solution of sodium carbonate containing the same amount of base.

Solutions of the salts of potassium, lithium, and magnesium, containing from 0.1 to 0.5 per cent., dissolved sodium biurate about as freely as distilled water, and consequently very much more freely than equivalent solutions of the sodium salts. These advantages as solvents were, however, completely nullified when the potassium, lithium, and magnesium salts were used not alone, but as additions to the standard menstruum—that is to say, in presence of 0.7 per cent. of sodium salts. Comparison of the chloride with the carbonate of potassium showed that the carbonate had not the least advantage over the chloride.

Salts of calcium and ammonium were found to act, in regard to the point under consideration, in the same way and in about the same degree as salts of sodium—that is

¹ The additions made varied from 0.1 to 0.5 per cent.

to say, they lessened the solvent power of water on sodium biurate in proportion to the strength of their solutions.

The behaviour of sodium biurate with the serum of the blood was next examined. In blood-serum sodium biurate was found to be even less soluble than in the standard solution, as the following observations indicate.

Experiment 1.—Sodium biurate in excess was digested with serum of pig's blood, at 100° F., for twenty-four hours, with frequent agitation. The serum was then twice filtered through a threefold filter.¹ Of this product 50 c.c. were acidulated with strong acetic acid and set aside. After standing forty-eight hours no crystals of uric acid were found to be deposited. A second portion was carefully tested by Sir Alfred Garrod's uric acid thread experiment. Only a few crystals were found sprinkled on the thread. A third portion was simply evaporated, at 100° F., to the consistence of a thick syrup. In this needles of biurate were easily detected under the microscope. These observations showed that sodium biurate, although very sparingly soluble, is not absolutely insoluble in healthy serum.

Experiment 2.—Three metatarsal bones² from the body of a gouty man, which were encrusted on their articulating surfaces with uratic deposits, were treated as follows:—The first (A) was suspended in six ounces of distilled water, the second (B) was suspended in a similar quantity of the standard solution, and the third (C) in the same volume of blood-serum. The phials in which the specimens were contained were tightly corked, and their contents preserved from putrefactive changes by the inclusion of thirty or forty drops of chloroform. They were placed in the warm chamber for a fortnight, and after that were kept at the temperature of the room. In four days the

¹ The crystalline needles of sodium biurate are so minute and delicate that a portion passes through the filter unless extraordinary precautions are taken.

² Kindly presented to me by Dr. Norman Moore. The deposits were tested and found to be composed of urates.

deposit was entirely dissolved out from the first specimen (A). The second specimen (B) showed distinct signs of solution in fourteen days, and at the end of six weeks the deposit had entirely vanished. The third specimen (C), suspended in serum, still remains, at the end of eight months, apparently unaltered; the limits of the encrusted spots are as sharply defined, and the quantity of the deposit appears as great, as when the preparation was first put up.

It was found that the addition to blood-serum of small quantities (0.1 to 0.5 per cent.) of the carbonates, chlorides, or phosphates of potassium, sodium, or lithium did not in the least degree enhance the solvent power of the serum on sodium biurate.

II. BEHAVIOUR OF URIC ACID WITH THE STANDARD SOLVENT, AND WITH BLOOD-SERUM AND SYNOVIA.

Observations on the Standard Solvent and Blood-serum.

The reactions of uric acid with the standard solvent and with blood-serum stand in the strongest contrast with those of sodium biurate in the same media.

When uric acid is digested with the standard solvent or with blood-serum it passes freely into solution in combination with a base. The compound thus formed is, in the first instance, undoubtedly a quadrurate.¹ But the process does not stop here. The quadrurate gradually takes up an additional quantity of base, and is thereby converted into biurate, and the biurate thus formed is, after some delay, eventually precipitated in the crystalline state. In studying this process it is desirable to distinguish two, if not three stages, namely, first, the taking up the uric acid as quadrurate, or *solution*; second, the transformation of quadrurate into biurate, or *maturation*. This

¹ The experimental evidence on which this conclusion is based is given in my previous paper published in the present volume.

latter stage culminates in the precipitation and deposition of the biurate in the crystalline form, and this should perhaps be considered as a third stage, or *precipitation*.

The following experiments may be taken as illustrations of the method of experimentation pursued and of the results obtained.

Experiment 1.—A gram of uric acid was introduced into a flask with 200 c.c. of the standard solvent. The flask was tightly corked and placed in the warm chamber, where the temperature was continuously maintained at 100° F. A considerable amount of uric acid went into solution, but a portion remained undissolved at the bottom of the flask, leaving a clear supernatant liquor. Things remained apparently unchanged until the evening of the second day, when a few stars of biurate were detected amid the undissolved sediment of uric acid. On the third day, however, a rapid change was observed to be taking place, consisting in an abundant precipitation of stars and tufts and detached needles of biurate. On the fourth day the precipitation appeared to be nearly complete, for the supernatant liquor now showed only small traces of uric acid when it was treated with hydrochloric acid.

Experiment 2.—A parallel experiment was made with blood-serum. Fresh serum of pig's blood was treated with uric acid in excess in a 4-oz. phial, tightly corked and chloroformed to prevent decomposition. The phial was gently turned upside down a few times at first, and was not subsequently disturbed. It was then placed in the warm chamber at 100° F. The serum soon cleared, the surplus uric acid fell to the bottom, and the supernatant serum became transparent. For about twenty-four hours no change occurred, but in the course of the second day stars of biurate were detected amid the deposit, and during the third day an abundant precipitation of stars, tufts, and needles of biurate took place, exactly resembling those found in gouty concretions. On the fourth day the process of precipitation was nearly complete, and

the supernatant serum was found to be comparatively free from uric acid.

In order to isolate the stage of maturation from that of solution the experiments were modified in the following manner :

Experiment 3.—Uric acid in excess was digested with frequent agitation with the standard solvent, at 100° F., for twenty minutes. The excess of uric acid was then filtered off, and the clear solution was placed in a corked phial in the warm chamber. It remained unaltered for two days. On the third day it began to precipitate, and on the fourth day a copious deposition of crystalline biurate took place. On the fifth day the process was completed, and the supernatant liquor was found on acidulation to contain only traces of uric acid.

Experiment 4.—Blood-serum of the horse was digested, at 100° F., with excess of uric acid for fifteen minutes with constant agitation. It was then filtered and placed in a corked phial in the warm chamber. In about twelve hours the serum, previously clear, began to lose transparency, and fine needles of biurate were detected in it with the microscope. On the next day copious precipitation took place. On the fourth day the process seemed to be completed, and the supernatant serum was found to be comparatively free from uric acid.

It was impossible not to be struck with a certain rough resemblance between the results observed in these experiments and the phenomena of the gouty paroxysm. In the gouty subject it is assumed that the blood becomes more and more impregnated with uric acid until, after a certain period of incubation has been accomplished, sudden precipitation of sodium biurate takes place in and about the joints, and the "fit of the gout" is declared. Then follows a process of recovery, with restoration of the blood to a purer state—that is, with a lessened impregnation with uric acid. In the artificial counterfeit we observe a similar succession of events: firstly, impregnation of the medium with sodium quadrurate; secondly, a period of in-

cubation or maturation, during which the quadrurate passes into biurate; thirdly, somewhat sudden precipitation of sodium biurate in the crystalline form; and lastly, restoration of the medium to comparative purity.

In the above-recorded experiments the quantity of uric acid in solution was not accurately gauged, but in the light of subsequent experiments I judge it to have been about 1 part in 1500. The speed of maturation (the length of time intervening between solution and precipitation) was found to be greatly influenced by the percentage of uric acid in solution. The richer the medium was in uric acid, the more quickly was maturation consummated, and the earlier was the occurrence of precipitation. In the case of blood-serum, when the impregnation with uric acid amounted to 1 in 800 or 1 in 1000, the first beginnings of precipitation were observed in four to six hours, and copious critical precipitation took place in twelve to fourteen hours. On the other hand, when the proportion of uric acid in solution was only 1 in 4000 or 1 in 5000, precipitation was delayed for six to twelve days, and was even then so slight in amount as to be only detectable by microscopic examination. It was further noted, in these feebler solutions, that the deposition of crystals was throughout gradual, and that there did not occur any sudden or critical fall of crystals, such as was observed to take place in the middle periods of maturation in the stronger solutions. Some of these points will be again adverted to in treating of the circumstances which hasten or retard maturation.

Observations on Synovia.

It is a marked peculiarity of the uratic phenomena of gout that the deposits occur most commonly in and about the joints; and it was a matter of interest in the present inquiry to ascertain how the synovial fluids which bathe these parts behave when impregnated with uric acid, and especially whether these fluids, as compared with blood-

serum, and when impregnated to an equal degree, had the property of promoting or hastening the precipitation of biurate. This part of the investigation is beset with difficulties, and my information thereupon is very scanty. The synovial pouches are shut sacs, entirely detached from one another, and it is conceivable that slight differences in the composition and the percentage of their saline constituents may exist between them, and that such differences may account for the preferential order in which the joints are attacked in the gouty paroxysm. The quantity of synovia obtainable from the smaller joints is very scanty, even in the case of the large quadrupeds which are dealt with in our slaughter-houses. I have so far only been able to make satisfactory experiments with synovial fluid drawn from the hip of the ox. From this source about a couple of ounces may be obtained from the two joints. Butchers tell me that the synovia from the hip is thinner as well as more abundant, than that obtained from the other joints.

On two occasions I was able to examine and compare the synovial fluid of the hip-joint with the blood-serum of the same ox. The behaviour of the two fluids with uric acid was substantially the same, but in both instances I found that, when impregnated with uric acid in an equal degree, precipitation of biurate began distinctly a little earlier in the synovia than in the serum. And my impression is, but it is only an impression, that with the thicker and more concentrated synovia of the smaller joints this difference would be more pronounced. Whether there is in this distinction between serum and synovia a key to the preference of uratic deposition for the joints is a question well worthy of further inquiry. It is at any rate conceivable, supposing the blood and its derivative fluids to be equably impregnated with uric acid, and supposing the synovial fluids to be more largely charged than their congeners with salts, and especially with sodium and calcium salts, that precipitation of biurate would take place earlier, and by preference, in and about the joints than elsewhere.

Behaviour of the Quadrurates with Blood-serum.

The quadrurates behave with the standard solvent and with blood-serum substantially in the same way as uric acid. This might have been expected from the fact that these media take up uric acid in the first instance as a quadrurate. There is, however, this difference, that the quadrurates pass into solution much more rapidly than uric acid, and, consequently, the period of precipitation of biurate has its advent considerably accelerated.

III. THE CONDITIONS WHICH ACCELERATE OR RETARD THE PROCESSES WHICH CULMINATE IN THE PRECIPITATION OF SODIUM BIURATE.

Assuming a real analogy to exist between the processes which go on in serum artificially impregnated with uric acid, and the processes which go on in the blood of a gouty patient, and which culminate in the deposition of uratic concretions, it is a matter of interest, as bearing on the pathology and treatment of gout, to investigate the conditions which, in the artificial parallel, accelerate or retard these processes. In pursuing this study from our chemical standpoint the three stages or phases in the development of the gouty paroxysm should be kept distinct in the mind, namely, the stages of solution, maturation, and precipitation. The *juvantia* and *obstantia* of these three stages are necessarily different and require separate consideration.

The gouty man may be regarded as living on the brink of a critical outbreak. His uric acid function is in a state of unstable equilibrium, and it is conceivable that a little quickening or favouring circumstance in any of the three stages might determine the occurrence of a paroxysm which would not otherwise have taken place. In the gouty state it is probable, as Dr. Haig suggests, that there may be stores of uric acid (or quadrurates) lodged in certain organs, as the spleen or liver, or diffused more generally through the tissues of the body. An elevation

of the dissolving power of the lymph or blood, acting on these stores, might lead to a sudden irruption of urates into the blood, transcending the capacity (perhaps already impaired) of the kidneys for their elimination, and so lead to an outbreak. In like manner some new conditions in the blood, some variation in its chemical or physical properties, might hasten or retard the other stages of maturation and precipitation, and thereby determine the occurrence or non-occurrence of a gouty paroxysm.

The rising and falling activity of the kidneys, in the matter of separating the urates floating in the blood, does not come within the scope of the present inquiry, though doubtless a potent, if not the most potent, factor in the genesis of gouty explosions and of gouty phenomena generally.

Conditions affecting the Stage of Solution.

It may be stated generally that the more alkaline the medium is, the more rapidly and freely does it dissolve uric acid and quadrurates. This is certainly the case with solutions of the alkaline carbonates and phosphates, ranging from 0.5 to 5 per cent. The neutral carbonate is a better solvent of uric acid than the bicarbonate. It is believed that sodium carbonate circulates in the blood partly as neutral and partly as acid carbonate, and that the proportion varies. If this be so a rising proportion of neutral carbonate would promote, and a rising proportion of bicarbonate would retard, the solution of uric acid stored in the tissues.

The solvent power of the blood on uric acid depends exclusively on the alkaline carbonates and phosphates contained in it. The neutral salts—chlorides and sulphates—were not found to have the least influence either way on the act of solution.

The quadrurates are taken up more rapidly by blood-serum than free uric acid. The following experiment illustrates this point. Half a gram of uric acid and the same quantity of serpent's urine (which is composed of

almost pure quadrurates), were separately digested in 200 c.c. of blood-serum, without agitation, at 100° F. In the latter case all went soon into solution, and abundant precipitation of biurate took place in twenty-four hours. In the former case solution was much slower; and precipitation did not begin until the third day, and was not abundant until the fourth day.

Conditions affecting the Stages of Maturation and Precipitation.

The investigation embraced a study of the effects of temperature, percentage of uric acid in solution, and the addition of various saline substances to the maturing medium.

(A) *Temperature*.—It was found invariably that the stage of maturation was more quickly accomplished in the warm chamber at 100° F. than at the temperature of the room, ranging from 60° to 70° F.; but the ultimate result was exactly the same in both cases. For example, serum charged with 1 part of uric acid in 600 began to precipitate in the warm chamber in four hours, and precipitated copiously in six hours. A duplicate specimen kept at the temperature of the room (65° F.) began to precipitate in eight hours, and did not precipitate copiously for sixteen hours. Another sample of serum, impregnated with 1 part of uric acid in 1000, began to precipitate in the warm chamber in six hours, and deposited copiously in fourteen hours; while a duplicate kept at the temperature of the room (60° to 70° F.) only began to precipitate in thirty hours, and copious precipitation did not take place for forty-eight hours.

The absolute constancy of these results led to the idea that maturation would go on more rapidly at a febrile temperature (104° to 105° F.) than at the normal temperature of the body, and that herein might be found an explanation of the circumstance that gouty outbreaks

sometimes follow immediately on the heels of an injury. When, however, this notion was tested experimentally no support was found for it.

It was also conceived that although maturation itself was favoured by warmth, the terminal act of the process, namely, the act of precipitation, might, on the contrary (seeing that sodium biurate is more soluble at higher than at lower temperatures), be favoured by cold, and that this might account for the fact that gouty concretions tend to be deposited in the cooler and more exposed parts of the body, in the joints and subcutaneous tissues, rather than in the warmer interior regions. I failed, however, to obtain any direct experimental evidence in favour of this conception.

(B) *Quantity of uric acid in solution.*—It was found that no condition exercised so great and decisive an influence on the speed of maturation and the advent of precipitation as the proportion of uric acid in solution. The amount or copiousness of the precipitation was likewise, of course, affected in the same way. The following experiment with blood-serum, the results of which are arranged in a tabular form, illustrates these points in a striking manner. The phials containing the serum were placed in the warm chamber for fourteen days, and were afterwards kept at the temperature of the room. Chloroform was added to prevent putrefactive changes.

Table showing the influence of percentage of uric acid in solution on the speed of maturation, and the time of advent of precipitation.

Quantity of uric acid contained in the serum.	Time of precipitation of sodium biurate.	
1 in 1000 . . .	Precipitation began in 6 hours.	Copious
	precipitation in 14 hours.	
1 in 2000 . . .	Precipitation began in 33 hours.	Copious
	precipitation in 3 days.	
1 in 3000 . . .	Slight precipitation began in 3 days, which	
	became a little more copious in 12 days.	

Quantity of uric acid contained in the serum.	Time of precipitation of sodium biurate.
1 in 4000 . . .	A few needles of biurate were detected on the 6th day ; more needles and a few tufts in 12 days.
1 in 5000 . . .	A few short needles were detected on the 13th day. In 30 days the needles were somewhat more numerous.
1 in 6000 . . .	No needles were discoverable in 14 days ; a few were detected in 40 days.
1 in 8000 . . .	No needles could be detected after the lapse of 40 days.

Assuming that the inflammatory arthritic attacks in gout are directly due to copious and sudden precipitation of crystalline stars and needles of sodic biurate in the cartilages and fibrous structures of the joints, the evidence before me indicates that such copious sudden precipitation can only take place when the fluids bathing these structures are impregnated with uric acid in, at least, the proportion of 1 part in 2500. Below this point the precipitation occurs slowly and scantily, and only in the form of short scattered needles. When the proportion of uric acid in the serum was only 1 part in 5000 the deposited needles were mostly about as long as the diameter of a red blood-disc, some were twice this length, and a few three times this length, and all were of extreme tenuity. It is quite conceivable that this slighter precipitation in the tissues, of short scattered needles, might account for certain irritations in the various organs, such as characterise irregular or larval gout ; but it could scarcely engender downright inflammatory attacks. It is further conceivable that the presence in the blood of such scattered needles might constitute foci, around which clotting might take place ; and that the thrombosis not unfrequently observed in gouty cases might thus be accounted for.

The impregnation of the blood in gouty persons with uric acid to the extent of these lesser degrees is within the range of observed actualities. Sir Alfred Garrod obtained, by quantitative analysis, from the blood-serum of

one of his patients uric acid to the amount of 1 part in 5714; and he remarks that the quantities thus recoverable from the blood are probably much under the actual amounts, as considerable loss is liable to occur from unavoidable causes.

These considerations lead to the suggestion that a microscopical examination of the blood in gouty persons might sometimes reveal the existence of needles of biurate in that fluid. I tested this point in ten cases of chronic gout, by examining a drop of blood drawn from the finger, but I failed to obtain positive results.

Addition of Various Saline Substances.

Our ideas on the therapeutics of gout are largely coloured by chemical considerations. It is supposed that the efficacy of mineral springs, which are so much resorted to by gouty patients, depends on the saline ingredients which they contain. The results of the present inquiry throw great doubt on the validity of this notion. The springs in repute, and in equal repute, are of the most varied character. Some are charged with bicarbonate of sodium, others with chloride and sulphate of sodium, others again with salts of lime and magnesia, and a few contain traces of lithia. These salts are supposed, when introduced into the circulation, to have the property of rendering the uric acid floating in the blood more soluble, and of thus promoting its elimination by the kidneys. Under the influence of the same ideas the alkaline carbonates are largely prescribed to gouty patients. It has already been shown that these views, so far as they concern the solubility of the material of gouty concretions, are based on an erroneous assumption. The addition to serum of any of these salts did not in the least degree enhance its solvent power over sodium biurate; and with regard to the salts of soda and lime, their effect was, in this respect, distinctly adverse.

A very considerable series of experiments were made with the purpose of ascertaining whether the addition of saline substances to serum impregnated with uric acid exercised any influence on the progress of maturation and the advent of precipitation. The additions made varied from 0·1 to 0·4 per cent., and the experiments were carried out in the warm chamber at 100° F. The salts tried were the carbonate, chloride, sulphate, phosphate, and salicylate of sodium ; the carbonate, chloride, and phosphate of potassium ; the carbonate of lithium ; the chloride and sulphate of magnesium ; and the chloride of calcium. The salts of soda and lime were found to accelerate the process, and to hasten the advent of precipitation. The carbonate and phosphate of potassium, the carbonate of lithium, and the sulphate and chloride of magnesium were indifferent. The addition of 0·1 per cent. of the chloride of potassium appeared to sensibly postpone the advent of precipitation. I obtained no evidence in support of the assumption that increasing the alkalescence of the blood lessened the tendency to the deposition of uratic concretions.

The impression produced by the inquiry in regard to the use of mineral waters in gout was to the effect that their virtues depended a good deal more on the water they contained than on their saline constituents, and that the springs which were most likely to be of service were those which approached nearest to pure water.

(For report of the discussion on this paper, see 'Proceedings of the Royal Medical and Chirurgical Society,' Third Series, vol. ii, p. 132.)