ON THE
HISTORY OF URIC ACID IN THE URINE,
WITH REFERENCE TO THE FORMATION OF URIC
ACID CONCRETIONS AND DEPOSITS.

BY
SIR WILLIAM ROBERTS, M.D., F.R.S.

Received February 5th—Read March 25th, 1890.

THE occurrence of uric acid in human urine seems to be somewhat of an anomaly. As a vehicle for the elimination of nitrogen it is not needed. Its place is taken by urea, which adapts itself perfectly, by its bland character and easy solubility, to the mammalian plan of a liquid urine. In birds, serpents, insects, and the great majority of invertebrate species, which void a solid or semi-solid urine, uric acid forms the sole and appropriate medium for the excretion of nitrogen, and is therefore physiologically indispensable. But uric acid is not indispensable to the mammal. The pig is said to void none; and the large herbivorous quadrupeds, during the greater of their life, discharge a urine which is free from uric acid. The information we possess on this subject indicates that the occurrence of uric acid throughout the mammalian class is fitful and inconstant; and the inference seems to be

justified that it is not an essential element in mammalian metabolism. These considerations lead up to the conjecture that the continued presence of uric acid in mammalian urine may be a vestigial phenomenon, analogous to the persistence of rudimentary structures. On this view uric acid should, perhaps, be regarded as a reminiscence of some far distant link in the chain of mammalian descent, and as a remnant of an ancestral path of metabolism, now fallen into disuse, and superseded by a better path, more perfectly adjusted to the requirements of the mammalian type.

But although uric acid be thus physiologically of trivial account, it is, from a pathological point of view, by far the most important component of the urine. It owes this prominence not to any inherent deleterious quality, but to its clumsy behaviour in liquid media. All the trouble with uric acid arises apparently from its sparing solubility, and the sparing solubility and unstable constitution of its compounds. Thereupon depends its tendency to form deposits and concretions, which act as irritating foreign bodies in the tissues and urinary passages. Were it not for the occurrence of these deposits—of sodium biurate in gout, of free uric acid in gravel, and of the amorphous urates as a sediment in the urine—we should not probably be more cognizant, clinically and pathologically, of uric acid than we are of kreatinine, which is voided in about the same proportion with the urine.

The history of uric acid is here considered under the following headings :

1. Spontaneous precipitation of uric acid in normal urine.
2. Composition and reactions of the amorphous urate deposit, and of its natural and artificial analogues.
3. Chemical explanation of the spontaneous precipitation of uric acid in urine.
4. The ingredients in the urine which inhibit or retard the precipitation of uric acid in the normal state.
5. Summary of the history of uric acid within the

urinary channels (*a*) in the normal state, (*b*) in the subjects of uric acid gravel.

6. The factors which determine the occurrence of uric acid concretions and deposits.

1. SPONTANEOUS PRECIPITATION OF URIC ACID IN NORMAL URINE.

Uric acid exists in urine in a state of combination with bases as urates. In the course of its transit through the urinary channels it encounters a diversity of physical and chemical conditions, which are calculated to affect the stability of the urates. The urine is generally secreted with an acid reaction; but it is often alkaline, especially after meals. It is sometimes pale, watery, and poor in salts; at other times it is concentrated, rich in salts, and high-coloured. These variations may occur in quick succession, so that there accumulates in the bladder a mixture of urines of all these several characters. In perfect health uric acid maintains itself in solution amid all these various changes, not only so long as the urine is detained in the urinary passages, but even for some time after it has been discharged. But in certain abnormal states this continuity of solution is broken. In the subjects of gravel uric acid is often thrown down in the kidneys or bladder, or is precipitated soon after the urine is voided, while it is cooling, or within an hour or two after emission. Or precipitation may occur somewhat later—in the course of four or six hours, in the form of copious urinary deposits. But this is not all. Numerous observations have led me to the conclusion that every urine which has an acid reaction tends to the eventual liberation of its uric acid. I found that acid urines kept with antiseptic precautions¹ invariably deposited uric acid sooner or later—except when the proportion of that substance was so small that, were it all in the free state, the volume of urine was sufficient to hold it in

¹ This was usually effected by adding a few drops of chloroform to the test-tubes or phials in which the urines were kept.

solution. The time of the occurrence of the precipitation varied greatly. It usually began within twenty-four hours after emission, sometimes in a day or two, and sometimes not for five or six days, or even later. It took place with equal certainty whether the urine was kept in the warm chamber at blood-heat, or was kept at the temperature of the air.¹ The duration of the process varied with the earliness or lateness of its onset. Speaking roughly, urine which began to deposit uric acid in a few hours completed the process in a few hours longer; but if the onset was delayed for some days the deposition of crystals went on slowly for several days subsequently. When the process was at length completed—whether that were early or late—all the uric acid had disappeared from solution. The filtered supernatant urine gave not the least precipitate with hydrochloric acid, nor could there be detected in it, on evaporation to a small bulk and with careful search, any trace of uric acid. This was, at least, the result arrived at with urines of medium density in which free precipitation had taken place.

Neutral and alkaline urines, such as are voided after meals, did not precipitate uric acid, nor any form of urate, however long they were kept. In like manner, urines which were kept without antiseptic precautions, and consequently, after a time, underwent the ammoniacal fermentation, did not precipitate uric acid, unless the occurrence took place early, and before ammoniacal fermentation set in.

We must, therefore, recognise in normal acid urine an inherent tendency to the spontaneous liberation and precipitation of its uric acid. This tendency only assumes a morbid significance when the event occurs prematurely, while the urine is still sojourning in the kidneys or bladder. Viewed in this light pathological gravel may be regarded

¹ In the latter case the urine often threw down amorphous urates. By this occurrence the urates were in some degree withdrawn from the operation of the disintegrating forces; but this only caused delay. Ultimately the deposit changed entirely into crystals of uric acid.

as due to an exaggeration of conditions which prevail, in a less pronounced degree, in the normal state ; hence an elucidation of these conditions may be reasonably expected to throw a light on the ætiology of gravel and calculus, and perhaps furnish hints which may be turned to therapeutical uses. Before entering on this inquiry it is, however, necessary to clear up certain points in the chemistry of uric acid and the urates concerning which current views require considerable revision.

2. COMPOSITION AND REACTIONS OF THE AMORPHOUS URATE DEPOSIT AND OF ITS NATURAL AND ARTIFICIAL ANALOGUES.

Uric acid is a bibasic acid ; it is represented by the formula $\text{H}_2(\text{C}_5\text{H}_2\text{N}_4\text{O}_3)$. It forms, like other bibasic acids, two regular orders of salts : namely, neutral urates, with the general formula $\text{M}_2(\text{C}_5\text{H}_2\text{N}_4\text{O}_3)$; and acid urates or biurates, with the general formula $\text{MH}(\text{C}_5\text{H}_2\text{N}_4\text{O}_3)$. But, in addition to these, uric acid forms a series of hyperacid combinations of more complex character, of which the hypothetical formula is $(\text{MH}[\text{C}_5\text{H}_2\text{N}_4\text{O}_3], \text{H}_2[\text{C}_5\text{H}_2\text{N}_4\text{O}_3])$. To these hyperacid combinations Dr. Bence Jones gave the name of quadrurates.

The neutral urates were obtained by Allan and Bensch¹ by saturating cold solutions of the caustic alkalies, free from carbonate, with uric acid, and boiling down the solution in a retort until crystals made their appearance. The neutral urates are very unstable, and are decomposed in the presence of carbonates, and even by the carbonic acid of the air. The neutral urates are quite unknown except as laboratory products, and their reactions and mode of preparation are such that it is scarcely conceivable that they should ever exist in the animal body, or play any part in the physiological or pathological history of uric acid.

The acid urates or biurates are the most stable and

¹ Liebig's 'Annalen,' Band lxx, p. 184.

best known salts of uric acid. They readily assume the crystalline form, and are easily obtained in a state of chemical purity. They can be prepared artificially under conditions which are germane to those existing in the animal body ; and they are encountered pathologically in gouty concretions, of which they form the distinctive constituent.¹

The quadrurates appear to be much more widely diffused than the biurates. They are present physiologically in the urine, and probably also in the blood. They are unapt to assume the crystalline form, and are difficult to obtain in a state of chemical purity. Their special and distinctive characteristic is that they are decomposed by pure water, with emission of free uric acid. They exist in nature in the form of the amorphous urate sediment of human urine, and as the essential constituent of the urinary excretion of birds and serpents. They can, moreover, be produced artificially under conditions which closely correspond to those prevailing in the living body. These three varieties of quadrurate require separate consideration.

A. *The amorphous urate deposit.*—The amorphous urate deposit has usually been regarded as consisting of biurates—as a mixture of the biurates of potassium, sodium, and ammonium, in varying proportions. This view is, however, quite untenable. The amorphous urate deposit differs essentially in its reactions from the biurates. The biurates are not decomposed by water. They simply dissolve in water, and are again deposited unchanged on evaporation. In order to study the effect of water on the amorphous urate deposit it must first be separated from the other ingredients with which it is mingled in the urine. This is done by filtering off the sediment and washing it on the filter with rectified spirit and drying. If a minute speck of such

¹ Directions for the preparation of sodium biurate in a pure state are given in a footnote to the first section of a paper by the author on the “Chemistry of Gout” which is printed in the present volume.

purified deposit be intimately mixed with a large drop of distilled water and observed under the microscope, it is seen to be slowly decomposed. In a few minutes—five to fifteen—crystals of uric acid begin to make their appearance. These grow and multiply until, in the course of half an hour or an hour, the field of vision is thickly studded with them; and the process goes on, provided the preparation be kept from drying, until the amorphous matter appears to be almost entirely transformed into crystals of uric acid.

Another way of separating the deposit from its associated urinary ingredients is the following. The sediment is taken up in a pipette, and five or six drops are allowed to fall in slow succession, and on the same spot, on a pad of blotting-paper. The liquid parts of the urine are imbibed all round by the blotting-paper, and there remains in the centre a little heap of damp deposit. If a portion of this be picked off on the point of a pen-knife, and examined in the manner described with a drop of water under the microscope, the same scene of transformation will be observed.

This mode of examination—observation of the behaviour of a speck of deposit with a large drop of distilled water under the microscope—will be again adverted to in the course of this paper, and it may be conveniently referred to as the “speck experiment.”¹

It was known to Berzelius and Lehmann that when the amorphous urate sediment was repeatedly washed on a filter with cold water, crystals of uric acid made their appearance on the filter; but it was reserved for Bence

¹ The speck experiment should by preference be performed with distilled water; but ordinary drinking water will generally answer equally well. This is, however, not always the case. Drinking waters are sometimes a little alkaline, and then the demonstration is apt to miscarry. I found that the Manchester pipe water answered the purpose as well as distilled water, but the London water does not do so. The London pipe water—or, at least, that which is supplied to the district wherein I reside by the West Middlesex Water Company—is slightly alkaline from dissolved carbonate of lime, and it acts very slowly and imperfectly on the amorphous urate deposit.

Jones to furnish a rational explanation of the phenomenon.¹ Bence Jones made a minute quantitative analysis of three specimens of amorphous urate deposits, purified by washing with alcohol, and found that the amount of uric acid contained in them greatly exceeded the quantity required to form biurates with the sum of the bases present. He also found, when the purified amorphous urate was treated with water, that a portion of the uric acid was set free and deposited, and that the remainder went into solution as true biurate. Moreover, he succeeded in preparing artificially an imitation of the amorphous urate sediment by dissolving uric acid in weak potash or soda ley, and then adding acetic acid until a slight acid reaction was produced. A dense white precipitate was thus thrown down. This precipitate, when washed with alcohol and dried, presented the properties and reactions of the amorphous urate sediment. It had a finely granular character, it was decomposed by water, and the part which went into solution had the composition of true biurate.

On the ground of these observations Bence Jones concluded that the amorphous urate deposit consisted of a complex compound, in which biurate was united in loose combination with an additional atom of uric acid, and that when the compound was treated with water the loosely combined uric acid was thrown out, and the associated biurate passed into solution. Writing of the potash compound thus artificially produced, he says, "This granular substance may be considered to resemble the quadroxalate of potassa, which differs from the acid oxalate by containing double the amount of oxalic acid, and following this nomenclature it may be called *quadrurate of potassa*." The formula for this compound according to this view, therefore, would be $\text{KH}(\text{C}_5\text{H}_2\text{N}_4\text{O}_3), \text{H}_2(\text{C}_5\text{H}_2\text{N}_4\text{O}_3)$.

Bence Jones, however, qualified his statements respecting the amorphous urate deposit in a way which greatly detracted from their conclusiveness; and this is probably

¹ "On the Composition of the Amorphous Deposit of Urates in Healthy Urine," 'Journ. of Chem. Soc.,' 1862.

the reason why his investigations thereupon have attracted so little attention. He declared that the amorphous urate deposit was not always composed exclusively of the unstable compound which was decomposed by water, but often contained, in addition, a larger or smaller admixture of true biurates; and that in some instances even the deposit was entirely composed of biurates, and did not throw out any uric acid when treated with water. In the final summary of his results he says, "In conclusion, then, it appears that the amorphous deposit of urates in the urine has no constant composition. It is a mixture of different acid urates modified in crystalline form by other substances in the urine. . . . Moreover, uric acid is occasionally found in combination with these acid urates, forming quadrurates, and thus rendering the deposit still more liable to vary in its composition."

In the last three years I have examined a very large number of specimens of the amorphous urate sediment, and have invariably found that they were decomposable by water and exhibited the characteristic reaction with the speck experiment. Sometimes, however, urate deposits are encountered which resist the decomposing effects of water for a considerable time. The cause of this variable resistance to water appears to depend on some kind of contamination. Sometimes it seems due to the varying quantity, and perhaps the varying quality, of the pigment, which adheres so obstinately to the deposits. In other cases it seems to be due to some saline impurity which imparts a slight alkalescence or a slight acidity to the sediment. I doubt whether it is ever due to an admixture of biurates; because, as will hereafter appear, the biurates cannot exist unchanged in normal urine. The only condition in which, so far as I know, true biurate ever appears as a deposit in urine, is when the urine has undergone the ammoniacal fermentation. Under these circumstances biurate of ammonia is thrown down, and may be sometimes recognised under the microscope (mixed with the amorphous and crystalline phosphates) as slender dumb-

bells or globular masses, which are wholly undecomposable by water.¹

B. *Urinary excretion of serpents and birds.*—Serpents and birds eliminate their nitrogen exclusively as uric acid—in the form of a white semi-solid mortar-like urinary excrement. When this substance is examined in the fresh state under the microscope with a drop of spirit, or of normal urine, it is seen to consist of innumerable minute spheres. These spheres present a radiating crystalline structure, and are, for the most part, about the size of the white blood-corpuscles; some are double this size, and a great many very much smaller. If, instead of a drop of spirit or of urine, the spheres are examined with a drop of distilled water, they are observed to undergo speedy decomposition, with abundant emission of uric acid crystals. If the mode of examination be varied, and the mortar-like substance be treated with a large quantity of distilled water, the same results follow as in the case of the amorphous urate sediment. A portion of the uric acid is set free and remains undissolved, and the rest goes into solution as biurate. The urine of serpents and birds, in fact, is entirely composed of quadrurates, mixed with more or less mucus. The urinary secretion of the large serpents is easily obtained from our Zoological Gardens in large solid masses and in a condition of great purity. There are, however, some necessary precautions to be used in collecting serpents' urine for scientific examination. The excretion should be obtained fresh and uncontaminated with water, and should at once be dried at 100° C. Collected in this way serpents' urine may be preserved in stoppered vessels unchanged for an indefinite period, and

¹ An artificial imitation of the amorphous urate deposit can be produced at will in the following manner. A normal alkaline urine, such as is voided after food, or a urine which is rendered slightly alkaline by the addition of alkaline carbonates or phosphates, is heated with excess of uric acid, and filtered hot. The filtrate is cooled rapidly under a running tap of cold water or on ice. An abundant precipitate falls, which is an exact counterpart of the natural amorphous urate sediment.

furnishes an abundant and almost pure supply of natural quadrurate. The common notion that the urine of serpents and birds consists of biurate of ammonia, mixed with varying proportions of free uric acid, has arisen from the excretion having been collected and kept without precautions, and having, consequently, undergone diverse decomposing changes which have entirely altered its chemical and physical constitution. Qualitative testing indicated that serpents' urine contained no chlorides, phosphates, nor other salts—or only such traces as might be accounted for by the admixed mucus. Small masses of uric acid crystals were occasionally found. The presence of these may be assumed to be due to secondary changes in the quadrurate spheres.

c. *Artificially prepared quadrurates.*—The quadrurates may be produced artificially in a variety of ways. When uric acid is digested at blood-heat with weak solutions of the alkaline carbonates, or of the dipotassic or disodic phosphates, or of the alkaline acetates, it enters into solution as quadrurate. Under favorable circumstances the quadrurate can be directly precipitated from these solutions by rapidly cooling them, especially by cooling them on ice. The quadrurates may also be prepared by treating solutions of the crystalline biurates with the alkaline superphosphates. This latter method involves a reaction which comes into play in the spontaneous precipitation of uric acid in urine, and will be again adverted to. In one or other of these ways I succeeded in producing quadrurates of potassium, sodium, ammonium, calcium, and magnesium.

Potassium quadrurate was prepared by dissolving uric acid in a hot 5 per cent. solution of potassium acetate, filtering hot, and cooling rapidly under a running tap of cold water until a copious precipitate was produced. This was collected on a filter, washed with alcohol, and dried. *Sodium quadrurate* was prepared in a similar manner with the sodium acetate—but the proceedings have to be carried out very quickly, otherwise the product is apt to

be contaminated with free uric acid. *Ammonium quadrurate* was prepared by boiling a gram of uric acid with 200 c.c. of a 1 per cent. dilution of the strong liquor ammoniæ. The solution was filtered hot, and then rapidly cooled. Through the cold liquid an abundant stream of carbonic acid was passed until a bulky precipitate was produced. This was at once filtered off and quickly washed with alcohol. The whole process must be carried out rapidly—otherwise the quadrurate passes into biurate. *Calcium quadrurate* was prepared by dissolving half a gram of uric acid, in the cold, in 100 c.c. of lime water. To the filtered solution acetic acid was added drop by drop until neutralisation was approached. An abundant precipitate was then thrown down, which was treated in the usual way. *Magnesium quadrurate* was prepared by digesting uric acid and calcined magnesia—both in excess—with distilled water at blood-heat, with frequent agitation for about ten minutes. The mixture was filtered warm, and the filtrate immediately cooled under a running tap. A dense flocculent precipitate formed, which was quickly washed with alcohol and dried.

Summary of the properties and reactions of the quadrurates.—The quadrurates present themselves usually as granular amorphous substances. They readily assume the colloidal modification, and when examined under the microscope in this state appear as large translucent globules. The spheres of birds' and serpents' urine are, however, distinctly crystalline, and, as was pointed out by Sir Alfred Garrod, polarize light. Owing to their instability the quadrurates are very difficult to obtain in a state of chemical purity; they are apt, when produced artificially, to be mixed either with free uric acid or with biurates, and in all cases to be contaminated with traces of foreign saline matters. They cannot be dissolved unchanged in any simple menstruum. It is therefore impossible to purify them, as most other substances are purified, by repeated solution and reprecipitation. They are extremely unstable; and they

tend to change in two opposite directions. In weak solutions of the alkaline carbonates or of the dimetallic phosphates they slowly take up an additional atom of base, and are converted into biurates. On the other hand, in water, and in watery solutions of the neutral salts, they are quickly split up into free uric acid and biurate.

The only appropriate solvent of the quadrurates is healthy urine. In acid urines they dissolve pretty freely with the aid of heat, and are again precipitated unchanged on cooling. Such solutions, however, are not quite stable; after a time their uric acid is slowly and at length completely liberated. The quadrurates are much more freely soluble in warm alkaline (not ammoniacal) urines, and in these media they continue permanently unaltered if guarded against septic changes. When such solutions are made at boiling heat, and are saturated, they throw down on cooling bulky deposits which are identical in appearance and reactions with the natural amorphous urate sediment.

With regard to the chemical constitution of these compounds I have adhered to the views and nomenclature of Bence Jones. Quantitative analyses of the artificially prepared potassium and sodium compounds, and of a purified specimen of the natural amorphous urate sediment, yielded to me results which were strictly conformable to the formulæ of the quadrurates above given.

The general conclusions arrived at with regard to the composition and the physiological and pathological relations of uric acid and the urates are concisely exhibited in the following table:

TABLE I.—*Showing the composition and physiological and pathological relations of uric acid and the urates.*

Uric acid . . .	$\text{H}_2(\text{C}_5\text{H}_2\text{N}_4\text{O}_3)$	{ Not known in the free state in the body nor in the urine, except pathologically as gravel and calculus.
Neutral urates . .	$\text{M}_2(\text{C}_5\text{H}_2\text{N}_4\text{O}_3)$	
		{ Not known physiologically nor patho- logically. Only known as laboratory products.

Biurates	. . .	$MH(C_5H_2N_4O_3)$	{	Known pathologically in gouty concretions. Known in urine only after the secretion has undergone ammoniacal fermentation. Doubtful whether they ever exist physiologically in the body.
Quadrurates		$\begin{cases} MH(C_5H_2N_4O_3) \\ H_2(C_5H_2N_4O_3) \end{cases}$		
			{	These are specially the physiological salts of uric acid. They exist normally in the urine, and probably also in the blood. They constitute the urinary excretion of birds and serpents.
			{	All the morbid phenomena of uric acid arise from secondary changes in the quadrurates.

3. CHEMICAL EXPLANATION OF THE SPONTANEOUS PRECIPITATION OF URIC ACID IN URINE.

We are now in a favorable position for considering the chemical reactions which occur in the spontaneous precipitation of uric acid in acid urine. The amorphous urate, or quadrurate, is the only combination of uric acid which can be actually shown to exist in normal urine. The amorphous urate is not unfrequently deposited from the urine on mere cooling. When not thus spontaneously deposited it may be often made to appear by cooling the urine still further by the application of ice. When this is insufficient its presence may be revealed by first evaporating the urine to a small bulk on a water-bath, and then cooling it on ice. By this last method the amorphous urate may be demonstrated to exist even in alkaline urine. Moreover, as I shall presently show, the biurate—the only other combination of uric acid which could conceivably be present in urine—cannot maintain its integrity in normal urine, but is forthwith transformed into quadrurate. The analogy of the urinary secretion of birds and serpents also points strongly in the same direction.

We may therefore, I think, conclude with certainty that the quadrurate is the form, and the only form, in

which uric acid exists in normal urine, and may draw the further conclusion that when uric acid makes its appearance therein in any other guise, such an event is due to secondary changes in the quadrurate.

On the other hand, the urine in which this compound is dissolved is an aqueous fluid, containing, besides urea and pigmentary and other extractives, a number of salts. Among the salts the most important in this connection are the phosphates. These regulate, in the main at least, the reaction of the urine. The phosphates easily oscillate between the monometallic forms (superphosphates) which have an acid reaction, and the dimetallic forms which have an alkaline reaction. When the former preponderate, as is usually the case, the urine is acid; when the latter preponderate the urine is alkaline.¹

We have, therefore, in an acid urine the quadrurate existing in the presence of water and of superphosphates. These conditions ensure the ultimate complete liberation of the uric acid. The first step in the process is the splitting up of the quadrurate by the action of the water of the urine into free uric acid and biurate. By this reaction half the uric acid is set free. This decomposition is represented by the subjoined equation:

But the biurate resulting from this reaction is immediately retransformed, in the presence of superphosphate, by a double decomposition, into quadrurate. Two atoms

¹ It is now generally agreed that the normal acidity of urine is due, not to a free acid, but to the preponderance of acid phosphates. The alkalescence of normal alkaline urines is certainly generally due to preponderance of dimetallic phosphates, and not to carbonates. In the alkaline urines voided after meals I have repeatedly tested the point. These do not usually evolve any carbonic acid when treated with acids. In certain cases carbonates are, however, abundantly present in alkaline urines, especially when carbonates, or salts of the vegetable acids, have been medicinally administered.

of biurate with one atom of monometallic phosphate change into one atom of quadrurate, and one atom of dimetallic phosphate, according to the following equation :

These alternating reactions—breaking up of quadrurate by water into biurate and free uric acid, and recombination of quadrurate by double decomposition of biurate with monometallic phosphate—go on progressively until all the uric acid is set free.

That these are the actual steps of the process whereby the totality of the uric acid is eventually liberated in acid urines may be deduced from the following considerations and experiments. The first step—the breaking up of the quadrurate into free uric acid and biurate by the action of the water of the urine—is in accord with what has been already shown to be the reaction of water with quadrurates. The occurrence of the second step—the transformation of biurate in the presence of superphosphate into quadrurate—is directly established by the following experiments.

A saturated solution of potassium or sodium biurate is made in hot water and then allowed to cool. When to this solution a strong solution of one of the alkaline superphosphates is added drop by drop, a dense white precipitate is thrown down, which, on examination, is found to possess all the reactions of the quadrurates. A similar result is obtained when the experiment is repeated with an acid urine instead of a solution of superphosphate. If the biurate solution is mixed with about one third of its bulk of an acid urine of medium density, a copious precipitate forms. This precipitate has the usual characters and the reactions of the amorphous urate deposit, or quadrurates. That the result in this latter case is not due to the precipitation of quadrurate pre-existing in the

urine is proved by repeating the experiment with the same urine after it has been deprived of all its uric acid by repeated filtration through uric acid.¹ It still throws down amorphous urate abundantly with the biurate solution.

The transformation of biurate into quadrurate in the presence of superphosphate explains why true biurates never appear as a deposit in normal and undecomposed urine.² It also explains why in the spontaneous precipitation of uric acid in urine the process goes on, not merely until a moiety, but until the whole of the uric acid is set free and deposited.

4. ON THE INGREDIENTS IN THE URINE WHICH INHIBIT OR RETARD THE BREAKING UP OF THE QUADRURATES IN THE NORMAL STATE.

It has just been shown that uric acid exists in the urine in the form of the amorphous urate or quadrurate, and that when the urine is secreted acid—that is to say, for some sixteen or twenty hours out of the twenty-four—this compound exists amid conditions which, if they stood

¹ It is a curious fact that acid urines are entirely deprived of their uric acid by passing them two, three, or four times through a filter on which a little heap of pure uric acid has been placed. This result is, I believe, brought about in the same way as the spontaneous precipitation of uric acid in acid urines, as already explained; but the process is greatly accelerated by the superadded force of crystalline aggregation. I have given an account of this matter in a paper "On Pfeiffer's Test for Latent Gout," in the 'Lancet' for January 4th, 1890.

² This transformation of biurate into quadrurate takes place even in alkaline (not ammoniacal) urines. This was proved by adding a solution of potassium biurate to a urine which had first been deprived of its uric acid by being passed repeatedly through the uric acid filter, and then rendered slightly alkaline by the addition of dimetallic phosphate or bicarbonate. A urine so treated, when evaporated to a small bulk, and then cooled, threw down a dense amorphous precipitate, which possessed the properties of quadrurate, and was decomposable by water.

alone and uncontrolled, would lead to speedy precipitation of uric acid in the free state. But in the normal course no such early precipitation occurs ; it only occurs as a remote and postponed event after the urine has been voided. It is obvious, therefore, that the urine contains certain ingredients which inhibit or greatly retard the water of it from breaking up the quadrurates. Were it not for the presence of these inhibitory ingredients uric acid would be thrown out daily in the urinary passages, and everyone would be subject to gravel. Hence an inquiry into the nature of these inhibitory agents has a pathological as well as a physiological interest, and bears directly on the ætiology of calculous disorders. The inquiry is not a simple one. The urine is a very complex fluid. It contains, besides urea, a number of saline constituents, together with pigmentary and other extractives. Where among all these are the inhibitory agents to be found ?

Salts of the urine.—Attention was first directed to the saline constituents. It was found that when urine was dialysed, whereby its crystalline ingredients were for the most part removed, it lost to a considerable extent its power of retarding the decomposition of the quadrurates. This observation indicated that the inhibitory power resided, partly at least, in the crystalloids of the urine. The chief crystalloids of the urine are urea, and the chlorides, phosphates, and sulphates of potash, soda, ammonia, lime, and magnesia. Solutions of these several substances in distilled water were prepared, and their effect on the quadrurate was tested by the speck experiment in the following manner. A speck of a purified specimen of the amorphous urate deposit was placed on a glass slide, and intimately mixed with a drop of the solution to be tested. The covering glass was then applied and the result watched under the microscope. The time at which crystals of uric acid began to make their appearance was taken as a measure of the activity of the tested solution in decomposing the quadrurate. The standard of comparison was distilled

water, which usually caused crystals to appear in five minutes. Solutions of urea of various strengths acted precisely with the same speed as distilled water. The chlorides and sulphates, in the proportion of one per cent. and upwards, imparted to water a considerable power of retarding the appearance of crystals. The potash salts were found to have more effect in this respect than the corresponding salts of soda and ammonia. The common disodic phosphate (rendered perfectly neutral to test-paper by the addition of phosphoric acid) showed about the same inhibitory power as sodium chloride. None of these solutions nor any admixture of them approached the natural urine in power of postponing the decomposition of the amorphous urate. More pronounced effects were obtained with the dipotassic phosphate. A solution of this salt containing only 0·2 per cent., and perfectly neutralised, appeared to act almost as slowly on the deposit as a normal acid urine. Urines which were alkaline from fixed alkali had absolutely no decomposing effect on the amorphous urate.

Pigments of the urine.—Attention was next turned to the colouring matters of the urine. The amorphous urates have an intense affinity for urinary pigment; the pigment cannot be removed from them by any solvent which does not, at the same time, destroy their integrity. I had noticed that deeply tinted urates were more slowly decomposed by water than pale-coloured urates. It had also been noticed that artificially prepared quadrurates and the quadrurates which constitute the urinary secretion of birds and serpents, all of which are devoid of colouring matters, are much more quickly broken up by water than the natural amorphous urate, which is always more or less tinted. Moreover, it was found that a urine which had been filtered through animal charcoal, and thus deprived of its pigment, acted very much more rapidly on the amorphous urate deposit than the same urine before it had been filtered through charcoal.

It can therefore scarcely be doubted that the pigments

of the urine play an important part among the ingredients which impart to normal urine its remarkable power of retarding the decomposition of the amorphous urate. In the febrile state, and in other wasting disorders, the urine is sharply acid and rich in urates, and yet such urines are not prone to deposit uric acid, though very prone to deposit amorphous urates. In these cases the urine is always deeply coloured; and the pigments are probably the chief agents which prevent the precipitation of free uric acid under these circumstances.

These observations do not, I think, exhaust this part of the inquiry. It is not improbable that, besides the salts and pigments, there are other components of the urine which contribute to retard the liberation of its uric acid. Moreover, urinary pigments are of several kinds, and they may not be all alike in regard to their power of protecting the integrity of the quadrurates.¹

5. SUMMARY OF THE HISTORY OF URIC ACID WITHIN THE URINARY CHANNELS; (A) IN THE NORMAL STATE, (B) IN THE SUBJECTS OF URIC ACID GRAVEL.

Uric acid exists primarily in the urine as a quadrurate. The history of this substance from its birth in the kidneys to its final expulsion—taking a complete cycle from micturition to micturition, with the interposition of a meal—proceeds, as may be gathered from the foregoing observations, on something like the following lines.

(a) *In the normal state.*—Starting with a period of fasting, the urine is secreted and accumulates in the bladder with an acid reaction. During this period incipi-

¹ It was observed in the case of artificially prepared quadrurates and of serpents' urine—both of which are either free or comparatively free from organic admixtures of any kind—that weak solutions (containing 0.1 per cent. to 0.2 per cent.) of the alkaline bicarbonates or dimetallic phosphates slowly decomposed them and threw out uric acid, in spite of these solutions having a distinctly alkaline reaction with litmus-paper. Such a result never followed in the case of the natural amorphous urate deposit.

ent decomposition of the quadrurate goes on with slow liberation of uric acid, but the process does not go far enough to induce actual precipitation. Then follows a meal and digestion of food. This is attended with a change in the reaction of the urine, which now becomes alkaline. As the alkaline stream descends into the bladder, the contents of that viscus become first neutral, and at length alkaline. During this period the decomposition of the quadrurate is arrested, and the previously liberated uric acid is recompounded into quadrurate. As the effects of the meal pass off, the acidity of the urine is restored, and the collected product in the bladder, when finally voided, presents a neutral or slightly acid character; and the quadrurate contained in it is discharged in its original state of complete, or almost complete, integrity.

(b) *In the subjects of uric acid gravel.*—Starting as before with a fasting state and an acid urine, the process of uric acid liberation proceeds more rapidly, and results in actual precipitation of crystals in the kidneys or bladder. In the slighter cases of the disorder, and in the milder phases of the more severe ones, the deposited crystals are redissolved on the advent of the alkaline tide after a meal, or they are swept out of the bladder at the next micturition. No permanent concretions remain, and no calculous symptoms are engendered, or only slight and transient renal pains. In severer cases the deposited crystals fail to be entirely dissolved by the alkaline tide; on the contrary, they aggregate into minute but permanent concretions in the kidneys. This event marks an adverse change in the risk of precipitation. The already formed concretions operate—according to a well-known law of chemical physics—as soliciting foci, and give a great additional impulse to the tendency to precipitation. The concretions thus go on increasing until at length the phenomena of renal gravel are fully developed. In severe cases of gravel the alkaline tide after meals is sometimes markedly reduced in strength, or even, as I have occasionally observed, entirely abrogated.

6. THE FACTORS WHICH DETERMINE THE FORMATION OF URIC ACID CONCRETIONS AND DEPOSITS.

The more remote and predisposing causes of urinary precipitations do not come within the scope of the present inquiry.¹ Whatever these causes may be, they must be translated into changes in the composition of the urine before they can determine the occurrence of calculous accidents. No amount of morbid proclivity to uric acid gravel can take effect if the urine be alkaline, nor if the proportion of uric acid in it fall below a certain point. The causes which will be here considered are those which lie exclusively in the chemical constitution of the urine itself.

In the preceding section proof was given that the salines and pigments of the urine exercise a protective influence against premature precipitation of uric acid; and it may hence be inferred that a diminution of these salines and pigments may sometimes act, in a negative manner, as a determining factor in the production of gravel and stone.

Poverty in the salines of the urine is probably an influential factor in the disproportionate frequency of stone among the children of the poor as compared with the children of the easier classes. The prevalence of stone among the natives of India is also probably to be explained in the same way. The children of the poor are fed largely on farinaceous articles, bread, gruels, oatmeal, and potatoes,

¹ It would be of some interest to ascertain whether anatomical deviations in the kidneys, such as exaggerated pouching of the infundibula or calyces, do not sometimes act as predisposing causes of renal gravel. If such abnormalities occur, they would obviously occasion undue detention and stagnation of the urine in the purlieus of the kidney, and thus give opportunity to a tendency, otherwise insufficient, to determine deposition of uric acid. Moreover, slight anatomical differences of this kind between the two kidneys might account for what is so often observed, namely, the unilateral incidence of the symptoms of renal gravel. So far as I know this point has not hitherto been investigated.

with but a scanty allowance of milk, meat, and fish. Wheat-flour contains only 0·51 per cent of mineral matter in proportion to the totality of the dry substance ; oat-meal only 2·50 per cent. ; potatoes only 2·50 per cent. ; whereas milk contains 5·50 per cent., and the various forms of meat and fish 5 to 5·50 per cent. Rice, which forms so large a part of the diet of the natives of India, only contains 0·39 per cent. of mineral matter in proportion to the totality of the dry substance of the grain. These enormous differences in the amount of saline ingredients in the articles of food must, of course, make a corresponding difference in the proportion of the saline constituents of the urine. On the other hand, the well-known immunity enjoyed by sailors from stone and gravel depends, no doubt, as Mr. Plowright has shown, on the prodigious quantity of salt which seafaring men habitually consume with their food. The same observer has pointed out that the dwellers in a district of Norfolk called Marshland, where the drinking water is brackish, are singularly free from stone, as compared with their less fortunate neighbours in the adjacent districts of that county.¹

Deficiency of pigment in the urine.—In chronic Bright's disease with contracting kidneys the urine is conspicuously pale, and is often indeed almost entirely devoid of pigment. There is no excess, but rather a diminution of uric acid in the urine in these cases ; nevertheless deposits of uric acid are by no means uncommon, and sometimes actual renal gravel occurs. The percentage of salines is also low, and this doubtless contributes to the result ; but probably the prepotent factor in the pre-

¹ See a paper by Mr. C. Plowright, of King's Lynn, in the 'Medical Times' for October 10th, 1885. Mr. Plowright, on the evidence of some experiments by Mr. H. C. Brown, attributes the good effect of salt to its alleged property of increasing the solvent power of water on uric acid. This is, however, I am satisfied, on the ground of very exact determinations both by myself and others, not the correct explanation. The real action of the salt is, I believe, as a retarder of the decomposition of the quadrates.

precipitation of uric acid in these cases is the deficiency of pigment in the urine.

Poverty of the urine in salines and pigments, however, only accounts for certain limited groups of calculous cases. There are other and larger groups in which the urine is neither defective in salts nor in colouring matters. The subjects of calculous disorders among the easy classes—especially those of a gouty type—usually void a urine which is full-coloured and abundantly rich in salts. In these cases the chief determining factors—and the only two which I shall here consider—are the grade of acidity of the urine, and the proportion of uric acid contained in it. The speck experiment was found unsuitable for investigating the influence of these factors. For this purpose another mode of experimentation—one that approximates more nearly to the conditions of the actual clinical problem—was adopted. In the beginning of this paper I drew attention to the fact that all urines with an acid reaction precipitated their uric acid sooner or later, and the inference was drawn that this inherent tendency was the same in kind (though less pronounced in degree) as the tendency existing in actual gravel. On this view it might be reasonably conjectured that whatever helped or hindered in the one case would equally help or hinder in the other case—in other words, that the conditions which hasten or retard the precipitation of uric acid in a sample of urine preserved in a test-tube would, if they could be made applicable, hasten or retard the precipitation of uric acid in the urinary passages. The proceeding followed was to charge a series of test-tubes each with 10 c.c. of a normal acid urine. One of these was a control tube, and had no addition made to it. To the others additions were made of known quantities of various substances, of which it was desired to know the effects on the time of onset of uric acid precipitation. The contents of the tubes were protected from decomposing changes by the inclusion of a few drops of chloroform. They were then corked and kept in the warm chamber at blood-heat. The tubes

were frequently examined, and the time when uric acid began to be deposited was noted. When the experiment was finished the acceleration or postponement of precipitation in the several tubes, as compared with the control tube, was computed.

Grade of acidity of the urine.—The degree of acidity of the urine exercises, as might have been expected, a potent influence on the time of precipitation of uric acid. In some cases of gravel I found the acidity of the urine fully twice as high as the normal average. In two such cases the urine as tested by the speck experiment was found to act on the purified amorphous urate as rapidly as distilled water; but when the acidity was reduced to its normal level by the addition of sodium carbonate, it had then no more power in this respect than healthy urine, showing clearly that in these cases the determining factor in the disorder was solely excess of acidity. It was also found, experimenting in the way described above, that the addition of an exceedingly minute quantity of an alkaline carbonate postponed the time of precipitation very notably. The following table displays some of the results obtained by this method :

TABLE II.—*Showing postponement of precipitation of uric acid by the addition of minute quantities of alkaline carbonates to the urine.*

Additions made to the urine.	Time when uric acid began to be precipitated.	Postponement of precipitation.
No. 1. Urine alone—control tube .	2 hours	—
„ 2. Urine + 0.04% Pot. Bicarb. .	4 „	2 hours
„ 3. Urine + 0.04% Sod. Bicarb. .	5 „	3 „
„ 4. Urine + 0.04% Lith. Carb. .	10 „	8 „

The quantities of the alkaline carbonates added in this

experiment were so small that the reaction of the urine, as tested by litmus-paper, was not sensibly affected ; and yet the postponement of precipitation was very considerable—considerable enough, had the events occurred in the urinary passages, to make the difference between the occurrence and non-occurrence of gravel. It will be observed that the sodium carbonate acted more powerfully as a retarder than the potassium carbonate, and that the lithium salt acted more powerfully than either. This, however, was solely due to the difference in their atomic weights. When these salts were used in quantities proportionate to their saturating power no difference could be detected between them. It need scarcely be said that if the carbonates were added in sufficient quantity to render the urine neutral or alkaline no precipitation of uric acid took place.

When the neutral salts, chlorides, sulphates, and phosphates were tested by this method, the results obtained were conformable to those obtained by the speck experiment. The potash salts were found to be superior as retarders of uric acid precipitation to the soda salts, but all were incomparably inferior in this respect to the carbonates.

Proportion of uric acid in the urine.—It is a common notion that uric acid gravel depends simply on an excess of uric acid in the urine ; and the frequent appearance of copious sediments of this substance in the urine in such cases naturally lends support to this presumption. I am, however, not aware of any reliable analyses which show that the subjects of uric acid gravel have always or even generally a higher percentage of uric acid in their urine than other persons, or that they render a larger amount per day. It is at any rate certain that individuals may habitually discharge a urine rich beyond the average in uric acid, and yet be quite free from the symptoms of gravel.

Cases are sometimes encountered in which the urine is caught, as it were, in the very act of depositing uric acid

gravel—cases in which the urine, as it is voided, sparkles with crystals of uric acid. On four occasions I have been able to estimate the uric acid in such urines. The results are shown in the following table :

TABLE III.—*Showing the percentage of uric acid in four urines which were in the act of depositing uric acid at the time of emission.*

No. 1 contained 0·024 per cent. of uric acid.

„ 2	„	0·076	„	„
„ 3	„	0·032	„	„
„ 4	„	0·022	„	„

In the first and second cases the percentage of uric acid greatly exceeded the average ; in the third case it was slightly below the average ; and in the fourth case it was greatly below the average.

The average proportion of uric acid in normal urine is about 0·04 per cent., and during the prevalence of the alkaline tide after meals it often runs up to 0·10 per cent.—without, of course, involving any risk of precipitation. It would, therefore, appear probable that in clinical gravel the concurrence of other favouring conditions—high acidity and poverty in salines and pigments—is of more importance than mere excess of uric acid.

The general results of this part of the inquiry may be summed up in the following propositions. The conditions of the urine which tend to accelerate the precipitation of uric acid are—(1) high acidity ; (2) poverty in salines ; (3) low pigmentation ; and (4) high percentage of uric acid. And conversely, the conditions which tend to postpone precipitation are—(1) depressed acidity ; (2) richness in salines, especially of potash salts ; (3) richness in pigments ; and (4) a low percentage of uric acid. On the interaction of these factors the occurrence or non-occurrence of gravel appears to depend ; and probably the most important of these factors is the grade of acidity.

(For report of the discussion on this paper, see ‘ Proceedings of the Royal Medical and Chirurgical Society,’ Third Series, vol. ii, p. 87.