THE CROONIAN LECTURES ON THE CHEMISTRY AND THERAPEUTICS OF URIC ACID GRAVEL AND GOUT.

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LECTURE I.—CHEMISTRY OF URIC ACID AND THE URATES: COMPARATIVE PHYSIOLOGY OF URIC ACID.

MR. PRESIDENT AND GENTLEMEN,—The morbid phenomena associated with uric acid divide themselves naturally into those which have reference to gravel and calculus and those which have reference to gout. In the former uric acid is thrown down in the free state from the urine as concretions in the urinary channels; in the latter uric acid is thrown down in a state of combination, as sodium biurate, in the interior tissues of the body. In both conditions the precipitated substance necessarily acts as a foreign body, and tends to cause inflammatory incidents and obstructions in the parts implicated. In regard to gravel and calculus, the whole of the morbid sequences are thus accounted for; no suspicion is entertained that uric acid concretions lodged in the kidneys or bladder produce any disturbances above and beyond those which are due to mechanical injury. But in regard to gout, uric acid is supposed to play a double part. It is commonly believed that, besides the irritation consequent on the precipitation of crystals of sodium biurate in the joints and elsewhere, uric acid floating in solution in the bodily fluids acts as a true poison, and it is assumed that a large part of the symptoms associated with the gouty state are directly due to this poisonous action. The soundness of this assumption will be hereafter called in question. It will be shown to be more probable that uric acid does not possess any inherent poisonous quality, and that when mischief arises from it that mischief is consequent on the acid being precipitated in the solid form as sodium biurate in the fluids or tissues of the body. The substantiation of this view would bring gout and uric acid gravel into close parallelism. Gout would then become, like gravel, in so far as its phenomena depend on uric acid, but of course no further, a disease of which the manifestations are proximately due to mechanical injury. On this view it becomes evident that the chemical reactions of uric acid and the urates, and especially those reactions which govern the holding in solution of these substances, have a more direct bearing on clinical and pathological problems than those conditions which have reference to the mode of origin of uric acid. In either case, whether uric acid be poisonous or not, the pathological history of uric acid is intimately bound up with its chemical properties, and a knowledge of these properties is an essential prerequisite for a scientific apprehension of the problems that arise in connection with uric acid gravel and the uratic phenomena of gout.

The amorphous urate deposit of human urine forms a convenient starting point for the study of the pathological chemistry of uric acid. This is the most familiarly known and yet perhaps the least understood of all urinary deposits. The amorphous urate is frequently deposited in the urine of perfectly healthy persons, especially during the colder seasons of the year, and at all seasons after sharp exercise and severe sweating. It is also habitually seen in the urine of persons suffering from slight catarrhal conditions or trifling dyspeptic derangements. Lastly, it is a common accompaniment of pyrexia and of grave organic wasting diseases of all kinds. The amorphous urate deposit coincides with an acid reaction of the urine and is never thrown down in a neutral or alkaline urine. It is recognised clinically by its disappearance when the urine is warmed. It is always more or less stained with the proper pigments of the urine, and its tint varies accordingly. Under the microscope it presents a granular appearance, without any obvious crystalline structure. All this is matter of common knowledge. But when we carry our inquiries further and ask: What is the chemical nature of this substance, what are its physiological analogies and pathologi-

cal relations? no clear answers are forthcoming. Indeed, such questions are nowadays scarcely asked at all. The amorphous urate deposit has for some time past been relegated almost to the position of a clinical curiosity, devoid of any real bearing on pathological and physiological questions. But if it can be shown that this substance is a representative body, that it typifies the exclusive mode in which nitrogen is eliminated in vast tribes of the animal series, that it represents the chemical combination, and the sole combination in which uric acid subsists normally in the healthy organism, and that, moreover, the pathological troubles connected with uric acid are due to deviations, in one direction or other, from this normal combination, then it becomes obvious that the chemical composition and reactions of the amorphous urate possess a very real interest both for the physician and the biologist. Before entering on this inquiry it is necessary to recall to your memories what is already known and established in regard to the chemistry of uric acid and its combination with bases.

Uric acid is regarded by chemists as a bibasic acid, that is to say, as an acid containing two atoms of replaceable hydrogen. It is represented by the formula $H_2(C_4H_3N_3O_6)$, or, more simply, as H_2u . It forms, like other bibasic acids, two regular orders of salts, namely, neutral urates, with the general formula M_2u , and acid urates, or biurates, with the general formula MHu .

These two orders of uric acid salts were elaborately studied in Liebig's laboratory nearly half a century ago by August Bensch in collaboration with an English student, Dr. James Allan.¹ So reliable and so complete have these researches been regarded, that no chemist has, so far as I know, thought it necessary to repeat and verify them, and they still constitute our principal source of information with regard to these two classes of salts.

The neutral urates, M_2u , were prepared by Allan and Bensch by dissolving uric acid in cold dilute solutions of the caustic alkalis, free from carbonates, and then boiling down the solutions in a retort until crystals made their appearance. The neutral urates are very unstable; they are decomposed by carbonates, and even by the carbonic acid of the air. Of late years these neutral urates have been made to figure prominently in certain theories of gout. Such theories, however, are, on chemical grounds, untenable. The neutral urates can only be produced in the presence of caustic alkalis, and in the absence of carbonic acid and the carbonates. But caustic alkalis cannot exist in the living organism, and carbonic acid and the carbonates are everywhere present. It would, therefore, seem impossible that the neutral urates should ever arise or subsist in the living body, or that they should ever play any part in the physiological or pathological history of uric acid; and until it can be demonstrated that these salts do actually exist in the body, or, at least, that they can be formed under conditions which are known to be possible in the living body, it is futile to frame theories in which these compounds are made to intervene. With these remarks, the neutral urates may be absolutely dismissed from our consideration as having neither part nor lot in the vital history of uric acid, whether in health or in disease.

The acid urates or biurates— MHu —are the most stable salts of uric acid, and tend strongly to assume the crystalline form. They are encountered pathologically in gouty concretions, of which the sodium biurate forms the distinctive constituent. The biurates do not occur in the unchanged urine, neither in health nor in disease; and when biurates are artificially introduced into normal urine they fail to maintain their integrity, and at once undergo a change of composition.² Nor is there any actual proof that uric acid ever exists, as a true biurate, in the healthy blood and interstitial juices; and it will be hereafter shown that when uric acid is brought into contact with these fluids, it is not taken up as a biurate. It may therefore be affirmed that the biurates, although known to us as pathological products in gouty deposits, are not, strictly speaking, known as physiological constituents, neither in the blood nor in the urine. But inasmuch as uric acid in some form of combination does exist normally in minute quantities in healthy blood, and exists in much larger quantities

¹ Liebig's *Annalen d. Chemie u. Pharm.*, vol. 65, p. 181.

² Proof of this statement is given in the author's paper "On the History of Uric Acid in the Urine," *Med. Chir. Trans.*, vol. 73, p. 260.

in healthy urine, the question arises: What then is this other form of combination—this normal and physiological combination, which is neither neutral urate nor biurate—in which uric acid exists in the healthy body? This question brings us back to the consideration of the amorphous urate deposit.

Reactions of the Amorphous Urate Deposit: Identity of it with the Urinary Excretion of Birds and Serpents.—The amorphous urate deposit as we find it in the urine is not chemically pure, and not only so but the urine with which it is mingled entirely masks its most important reactions. In order to study the properties of this substance it is necessary first of all to separate it from the urine. This is effected by filtering off the sediment and washing it thoroughly on the filter with rectified spirit and then drying it. The deposit is still contaminated with pigment, but it is sufficiently pure for the display of its most striking reaction, and that is its behaviour with pure water. When the amorphous urate, thus purified, is mixed with a considerable volume of distilled water it is speedily disintegrated. A portion passes into solution in combination with the bases, and the remainder falls down as an insoluble precipitate of crystalline uric acid. This remarkable transformation may be witnessed in progress, under the microscope, in the following manner. A speck of the purified deposit is intimately mixed on a glass slide with a drop of distilled water, and protected with a covering glass. To keep the preparation thoroughly moist, fresh supplies of water are from time to time insinuated under the covering glass. In the course of five or ten minutes beautiful ovoid 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 entire field of vision is thickly studded with crystals; and the process goes on, provided the preparation be kept from drying, until the amorphous matter seems to be entirely changed into crystals of uric acid. The reaction here described may, according to my experience, be always demonstrated with every freshly collected sample of amorphous urate deposit. The rate of transformation varies a good deal. With fawn-coloured deposits the change is usually completed in from fifteen to twenty minutes; with the more deeply tinted deposits the time is longer and extends to half an hour or an hour.

The interest attaching to the amorphous urate deposit is greatly enhanced when we learn that the urinary excretion of birds and serpents displays identically the same reactions as the amorphous urates. The white mortar-like substance which constitutes the urinary excretion of birds and serpents is usually described as consisting of biurate of ammonia. This view is, however, based on a fallacy. The misapprehension has arisen from the excretion having been examined, not in the unaltered state, but after it had undergone secondary changes subsequent to its emission, either through bacterial decomposition or through contact with water. If the excretion be examined in the fresh and uncontaminated state, it is seen under the microscope to consist of minute spheres about the size of the white corpuscles of the blood. Some are twice this size, and a great many are much smaller. These spheres exhibit a radiated crystalline structure, and display a black cross with polarised light. When tested under the microscope with a drop of distilled water in the manner before described in the case of the amorphous urate, the spheres are seen to melt away gradually with abundant emission of colourless tablets of uric acid. When the excretion is treated with a large volume of water in a beaker, a portion goes into solution as biurate and the rest falls down as crystals of uric acid. In short, the urine of birds and serpents reacts with water precisely in the same way as the amorphous urate sediment, except that the transformation takes place more rapidly. It can, moreover, be shown that the difference in physical form between the two substances is a mere accident of molecular aggregation; for, under certain conditions, the amorphous urate deposit can be obtained in regular crystalline spheres scarcely distinguishable from the spheres of the urine of birds and serpents; and, conversely, if the urine of birds or serpents be dissolved in hot normal urine, and the solution be then rapidly cooled, the substance is reprecipitated as an amorphous tinted deposit indistinguishable from the amorphous urate sediment. These observations point to the conclusion that the amorphous urate deposit of human urine and the solid or semisolid urinary excrement of birds

and serpents are essentially one and the same substance; and the question arises, What is the constitution of this substance? Is it merely a mechanical mixture of biurate with varying quantities of free uric acid, or is it a definite chemical combination, representative of a new and third order of uric acid salts, differing essentially from the two regular orders previously recognised? The elucidation of this question involved a difficult and somewhat protracted inquiry, to which I must now ask your patient attention.

Chemical Constitution of the Amorphous Urate Deposit and of the Urinary Excretion of Birds and Serpents: the Existence of a Third Order of Uric Acid Salts, or Quadriurates.—We are indebted to a former distinguished Fellow of this College, Dr. Bence Jones, who was, moreover, one of my predecessors in this office of Croonian Lecturer, for the first real light on the chemical constitution of the amorphous urate deposit. His researches were published in the *Journal of the Chemical Society* for 1862.

He describes the action of water on the sediment. He shows that the portion of the sediment which is not dissolved by the water is pure uric acid, and that the portion which goes into solution is true biurate. He next gives the results of a quantitative analysis of three samples of the amorphous urate sediment, made especially with the object of ascertaining the proportion of uric acid to the quantities of the bases contained in them. He found in each sample that the uric acid was in excess of the quantity required to form biurates with the bases present. The proportion of this excess varied greatly in the three samples; but when the three analyses were thrown together, and the average struck, the mean amount of uric acid was found to be almost exactly double that required to form biurates with the sum of the bases present. He also calculated the corresponding proportions in four similar analyses previously made by Scherer. Here, likewise, the separate analyses gave the most discordant proportions; but again it so fell out that the average of the whole four analyses yielded a proportion of uric acid which was very nearly double the amount required to form biurates with the sum of the bases. These closely approximating averages, although drawn from numbers so divergent that their agreement could obviously only be due to a fortuitous coincidence, seem to have inspired Bence Jones with the happy conjecture that there existed a third order of uric acid salts, of more complex constitution than the two previously known, and in which an atom of biurate was loosely combined with an additional atom of uric acid. And he drew the inference that the amorphous urate deposit consisted of, or at least often contained, such a combination.

In order to test the soundness of this conjecture, he sought to form an artificial sediment of urates, which when treated with water would, like the amorphous urate deposit, be disintegrated into free uric acid and biurate. In this attempt he succeeded both with potash and soda. By dissolving uric acid in potash or soda ley, and then carefully adding acetic acid until the liquid became slightly acid, he obtained a dense white precipitate. This was caught on a filter, washed with alcohol, and dried. This substance was found to possess the characteristic properties of the amorphous urate deposit. It was granular in character, and was decomposed by water, with abundant emission of uric acid crystals. He made a quantitative analysis of two samples of the potash compound thus obtained. He found that the portion that went into solution when the substance was treated with water corresponded exactly with the theoretical formula of potassium biurate; and that the uric acid which remained undissolved approximated in amount to that which went into solution as biurate. Commenting on these results he says: "It appears from these experiments that an artificial granular deposit may be formed, which is decomposed by washing with cold water or by boiling into uric acid and acid urate of potassium. 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 general formula for the quadriurates—or, as they may be more euphoniously expressed, quadriurates—following the analogy of the quadroxalates, would be:

According to this theory, the action of water on the amorphous urate deposit and kindred compounds is to split them up into free uric acid, and biurates of the bases contained in them. If this theory be correct the quantity of uric acid thrown out by water should of course exactly equal the quantity retained in solution as biurate. With regard to this point, however, Bence Jones's analyses of the potash compound did not come out with the desired exactness. In the first analysis the proportion of uric acid separated by water, as compared with that retained in solution as biurate, was not as 1 to 1, as required by the theory, but as 1.27 to 1; and in the second analysis as 1.12 to 1. This discrepancy is considerably greater than could be accounted for by the necessary limits of error in the methods of analysis adopted; and it was impossible to avoid the impression that the proof adduced by Bence Jones of the existence of a true and definite chemical combination, corresponding with the hypothetical formula of a quadriurate, was altogether inadequate. These substances which were disintegrated by water might, after all, be only intimate mechanical mixtures of biurates with

varying quantities of free uric acid; and the action of water upon them might be explained simply as that of a solvent separating a more soluble ingredient from a less soluble ingredient.

Thirty years have elapsed since the publication of Bence Jones's researches. So far as they have had any influence on current views of the pathology of uric acid, they might as well have never been made. For, although these researches have received formal mention in works on urinary chemistry, the deductions and inferences indicated by them have received no recognition, and have been entirely ignored in the numerous inquiries and discussions which have since taken place on the etiology of uric acid gravel and gout. Until the subject was taken up by myself no attempt had been made to repeat and verify the observations and experiments. Yet the main suggestion of Bence Jones's investigations—namely, that there existed a third order of uric acid salts—is obviously one of high scientific and practical interest. The cause of this surprising neglect lay probably in the halting and even ambiguous terms in which Bence Jones expressed himself in regard to his results. After giving a clear experimental proof of the disintegrating effects of water on the amorphous urate deposit, he qualifies his statement without any attempt at explanation in the following unsatisfactory manner:

"In other experiments the deposit, when frequently washed with cold water, gave no uric acid crystals at all. Hot water also frequently dissolved only the urates, and caused the whole deposit to pass rapidly through the filter without leaving any uric acid crystals behind."

And in the final summary of his results he writes:

"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 quadrates, and thus rendering the deposit still more liable to vary in its composition."

Dr. Bence Jones did not return to this subject, though he continued for some years in active scientific work. I can only explain his abandonment of so promising a vein of inquiry on the supposition that he was deterred by the difficulty of obtaining a due supply of material for his experiments. He had to collect the amorphous urate deposit in small parcels at different times and from different sources, as opportunity offered. A supply of material of a changeable substance gathered in this way could not possess the purity and homogeneity necessary for the purposes of quantitative analyses.

In taking up and continuing the investigation thus prematurely dropped by Bence Jones I was able to reach a point of vantage in regard to these difficulties. I soon learnt that the urinary excretion of the large serpents furnished an abundant source of material which was identical in reactions with the amorphous urate. I also succeeded, by a method to be presently described, in preparing at will from human urine plentiful and fresh supplies of the amorphous urate deposit.

The questions I had to decide were these: Is the amorphous urate deposit, together with the urinary excretion of birds and serpents, a true and definite chemical compound? and does there exist a third order of uric acid salts differing essentially from the two urates already known and having a composition corresponding to the hypothetical formula of a quadriurate? As the main argument of these lectures rests on the establishment of an affirmative answer to these questions it is necessary for me to lay before you the experimental evidence on which I rely as sufficing for the purpose.

The materials used in the investigation consisted of:

1. The amorphous urate deposit of human urine.
2. The urinary excretion of birds and serpents—both of these are natural products.
3. Artificially prepared imitations of these natural products made in the laboratory.

Two lines of analysis were pursued in each case. The first was to estimate quantitatively the amounts of the bases, and of uric acid, in the samples. The second was to proceed by way of what may be termed water analysis. That is to say, to decompose the substance with a large volume of water and then to estimate respectively the amount of uric acid which was thrown out in the free state and the amount which went into solution as biurate. If the quadriurate theory be correct these two amounts should be exactly equal.

I now proceed to lay before you the results of these analyses:

A. *Analysis of the Amorphous Urate Deposit.*—It was found

that samples of the amorphous urate deposit obtained from hospital wards or from private patients yielded on analysis results so inconsistent that no conclusion with regard to the points under consideration could be drawn from them. In most samples the quantity of uric acid separated by water was larger than that retained in solution, but this excess presented no uniformity of amount. The explanation of this discrepancy lay in the fact (to be more fully noticed in my next lecture) that the amorphous urate, as it exists in the urine, exists under conditions of change, which tend progressively to liberate its uric acid, and as the sediment had to be collected in separate portions from different urines on different days until a sufficient quantity had been gathered for analysis, it is no wonder that gross variations in its composition were observed. It soon became evident that reliable data could not be obtained from materials collected in this way. This difficulty was, however, surmounted, and I succeeded by the following process in obtaining and having always at command an adequate supply of the amorphous urate in a fresh and unchanged state:

Process.—Healthy urine of medium density is treated with successive additions of bicarbonate of potash or soda until it becomes slightly alkaline. It is next heated in a flask to the boiling point, and then shaken up for about a minute with excess of pure uric acid. The mixture is now thrown on a filter, and the filtrate is cooled under a running tap of cold water. As cooling proceeds, a dense voluminous precipitate forms which is an exact counterpart of the natural amorphous urate sediment. The precipitate is separated by filtration, thoroughly washed on the filter with rectified spirit, and dried at blood heat. To obtain a product of uniform composition by this process requires a somewhat nice adjustment of the reaction. If the quantity of alkaline carbonate added be too small, and the alkalescence thereby induced be too faint, the precipitate is apt to be contaminated with free uric acid. On the other hand, if the alkaline carbonate be added too freely, and the resulting alkalescence be excessive, the precipitate is apt to be contaminated with biurate. These risks are greatly minimised by using the acetate of potash instead of the alkaline carbonates. The commercial acetate of potash has a slightly alkaline reaction, and it possesses a considerable power of conserving the integrity of the amorphous urate. I obtained a very uniform product by employing normal urine charged with acetate of potash to the extent of 3 per cent. The other steps of the process were the same as those above described. It was observed that if the filtrate was cooled rapidly the resulting precipitate had a finely granular character, just like that of the natural amorphous urate; but if the cooling was allowed to proceed slowly at the temperature of the room, the precipitate fell down in regular spheres with a radiating crystalline structure, resembling closely the spheres of the urinary excretion of birds and serpents.

Samples of amorphous urate deposit prepared in these ways yielded to analysis very constant results. The water analysis was carried out in the following manner: The dried deposit (usually about 0.4 gramme) was mixed in a beaker with 1,000 times its weight of distilled water; the mixture was next slowly heated to about the boiling point, with constant stirring until the whole went into solution. The beaker was then set aside for forty-eight hours. On cooling, the liberated uric acid fell out in large crystals. The clear supernatant liquor was then nearly all siphoned off, and the remainder, together with the deposited crystals, was thrown on a weighed filter. The crystals were washed very sparingly with cold water, and then more freely with rectified spirit. Finally the filter was dried and weighed. This gave me the weight of the uric acid separated by water.³ The siphoned-off supernatant liquor, together with the washings from the filter, was then heated to near boiling, and strongly acidulated with hydrochloric acid, and set aside for forty-eight hours.⁴ The precipitated crystals were collected, dried, and weighed, as in the preceding case.

When the analyses were conducted in this way, the amount of uric acid separated by water was found to be almost exactly equal to that retained in solution, as is shown in the two following sample experiments:—

TABLE I.—*Showing the Results of Water Analysis of Two Samples of Amorphous Urate Sediment, prepared by the Acetate of Potash Method.*

	First Sample.	Second Sample.
Uric acid separated by water	0.080 g.	0.164 g.
Uric acid dissolved as biurate	0.077 g.	0.159 g.

These results agree closely with the requirements of the quadriurate theory.

³ To get a true result, it was necessary to take account of that small portion of liberated uric acid which was still retained in solution after complete precipitation. This was experimentally determined to be, at the usual temperature of the room, 0.0055 g. per 100 c.c. This amount was added to the quantity actually found on the weighed filter.

⁴ The advantage of adding the acid when the solution is hot is that the precipitated crystals are much larger, and therefore more easily and perfectly collected, than when the acid is added in the cold. In the latter case the crystals were sometimes so exceedingly minute that it was impossible to avoid serious loss in the processes of filtration and washing.

A complete quantitative analysis of a sample of amorphous urate sediment obtained by the bicarbonate of potash method gave the following results. The substance did not contain any lime nor magnesia:—

TABLE II.—*Quantitative Analysis of a Sample of Amorphous Urate Deposit, prepared by the Pot. Bicarb. Process.*

Weight of substance used=1.328 g.	
This yielded:	
Uric acid ...	1.113 g.
Potassium ...	0.065 g.
Sodium ...	0.027 g.
Ammonium ...	0.008 g.
Moisture, or organic matter and loss ...	0.115 g.
	1.328 g.

Uric acid required to form quadriurates with the bases present ... 1.102 g.
Total uric acid found ... 1.113 g.

These results agree in the closest manner with the supposition that the deposit was composed entirely and exclusively of quadriurates of potassium, sodium, and ammonium.

B. *Analyses of the Urinary Excretion of Birds and Serpents.*

1. *Urine of Birds.*—During a period of dry summer weather my servant collected for me a quantity of the excreta of a number of fowls kept in a large run. The pieces were gathered freshly day by day, and were at once dried in the sun on a sheet of paper. When quite dry the chalk-like stuff encrusting the fecal masses was carefully chipped off with the point of a pen-knife and preserved in a stoppered bottle. In this way, in the course of a week, about 4 g. of urinary excrement were obtained in a state of approximate purity. Qualitative testing showed that the substance contained ammonia. On incineration it yielded 8.68 per cent. of a strongly alkaline ash. This ash consisted almost entirely of potash and soda, with a small quantity of iron. There were also found in it minute traces of lime and silica and sulphuric and phosphoric acids. These traces, it was conjectured, were derived from contamination with the sandy materials strewn on the floor of the fowl-run. For this reason the substance was not judged to be sufficiently pure for the purpose of a complete quantitative analysis, but it was perfectly suitable for water analysis. A number of the cleanest-looking pieces were picked out and divided into two parcels of about half a gramme each. These were finely powdered and subjected to water analysis by the method already described. The results are exhibited in the following table:—

TABLE III.—*Water Analysis of Fowl's Urine.*

	First Sample.	Second Sample.
Uric acid separated by water ...	0.160 g.	0.136 g.
Uric acid dissolved as biurate ...	0.165 g.	0.133 g.

It is seen that the results come out with great exactness in agreement with the requirements of the quadriurate theory.

2. *Urine of Serpents.*—The urinary excretion of the large serpents is easily obtained from our Zoological Gardens in massive pieces, quite unmixed with the fecal discharges and other extraneous impurities. But it is difficult, or even impossible, to obtain the secretion in an absolutely unaltered state, as eliminated by the kidneys. It is liable after being voided to come into contact with the water used for cleansing the cages in which the creatures are confined, and water, as we have seen, speedily disintegrates it. Again, if the substance be not at once completely dried on the hot water bath it undergoes bacterial decomposition, and is thereby transformed into biurate of ammonia. This is the condition in which "serpent's urine" as supplied by the dealers is generally found. But even if both these sources of change are avoided by taking proper precautions, there is yet another which no care can obviate. The large serpents void their urine at long intervals, varying from a week or ten days to six or seven weeks. During this long sojourn in the urinary passages the secretion undergoes slow changes which affect its chemical constitution. I have always found serpent's urine, when examined in the fresh state, to have a sharply acid reaction. Under these conditions a certain amount of decomposition of the urates, with liberation of free uric acid, is inevitable. Accordingly, when samples of serpent's urine were subjected to water analysis, however carefully the samples had been collected and preserved, the amount of uric acid separated by water was always found to be considerably in excess of that which went into solution as biurate. The invariable presence in the secretion of free uric acid was thus demonstrated. The subjoined table exhibits some of the results obtained by water analysis of freshly gathered specimens of the urinary excrement of the boa.

TABLE IV.—*Water Analysis of Four Samples of Serpent's Urine.*

	I.	II.	III.	IV.
Uric acid separated by water ...	0.128 g.	0.110 g.	0.204 g.	0.215 g.
Uric acid dissolved as biurates ...	0.117 g.	0.085 g.	0.141 g.	0.140 g.

* Herein, no doubt, lies the remarkable difference in the results of water analysis of the urine of the fowl and that of the boa. The fowl discharges its urine many times a day. There is no detention of it in the urinary passages, and, therefore, no time for the occurrence of appreciable secondary changes.

It is seen that in each experiment the quantity of uric acid separated by water was in excess of that which went into solution as biurate, and that, moreover, the proportion of this excess bore no constant relation in the several samples. The urine of the serpent, when at length voided, would thus appear to consist of quadriurates contaminated with a variable admixture of free uric acid.

The explanation above offered to account for the discrepant results obtained by water analysis of serpent's urine would, however, not apply to a quantitative estimation of the uric acid and the bases found in the excretion; for although the changes indicated as occurring during the lengthened sojourn of the secretion in the urinary passages would produce a partial displacement of the relations between the uric acid and its attached bases, the quantities of these would remain unaltered, and they would still form in their due proportions part and parcel of the semisolid excrement as finally voided. The following quantitative analysis of a massive and very pure specimen of the urine of the boa justifies the correctness of this explanation. The material used for the analysis was taken exclusively from the interior portions of the mass.

TABLE V.—*Complete Quantitative Analysis of the Urine of the Boa.*

10 g. yielded:	
Uric acid ...	8.280 g.
Potassium ...	0.333 g.
Sodium ...	0.106 g.
Ammonium ...	0.192 g.
Moisture, organic matter, iron, traces of lime and loss ...	1.089 g.
	10.000 g.
Uric acid required to form quadriurates with the bases present ...	8.071 g.
Free uric acid ...	0.209 g.
Total uric acid found ...	8.280 g.

The results of this analysis came out closely in accordance with the requirements of the quadriurate hypothesis. The quantity of uric acid over and above that required to form quadriurates with the bases present, and which might be regarded as existing in the free state did not exceed 2.5 per cent. of the total uric acid found.

C. *Analyses of Artificially-prepared Quadriurates.*—As already stated, Bence Jones succeeded in preparing compounds of uric acid with potassium and sodium which were decomposable by water, by adding acetic acid to cold solutions of uric acid in potash or soda ley until a precipitate was produced. This method was, however, found to give very uncertain results. If the acetic acid was added too freely, the precipitate was contaminated with free uric acid, and, on the contrary, if too little acetic acid was added, the precipitate was contaminated with biurate; it was almost impossible to hit the mark with precision. The following process was found to yield much more uniform results: 300 c.c. of a 3 per cent. solution of acetate of potash was heated to boiling in a flask, and then shaken up with 2 g. of uric acid for about a minute. The mixture was filtered hot, and the filtrate rapidly cooled under a running tap of cold water. A dense voluminous precipitate formed. This was thrown on a filter, and washed first with rectified spirit, and then thoroughly with absolute alcohol, and finally dried at blood heat. The substance thus obtained had a coarsely granular appearance under the microscope, and it was rapidly decomposed when treated with water. If the cooling was allowed to take place more slowly in the warm chamber, or even at the temperature of a warm sitting room, the precipitate fell down in regular spheres, possessing a radiated crystalline structure, resembling very closely both in size and appearance the spheres of the bird's and serpent's urine.

TABLE VI.—*Water Analysis and Quantitative Analysis of a Sample of Potassium Quadriurate prepared by the Acetate of Potash Method.*

Water Analysis:	
Uric acid separated by water ...	0.84 g.
Uric acid dissolved as biurate ...	0.85 g.

Quantitative Analysis :	Proportion per cent.	
	Found.	Calculated.
Uric acid 0.198 g. ...	89.75	89.60
Potassium 0.0226 g. ...	10.25	10.40

The numbers in both these analyses of the potassium compound come out with almost perfect exactness in agreement with the quadriurate theory of its composition.

The corresponding sodium compound was prepared by shaking up 1 g. of uric acid with 100 c.c. of a boiling-hot 5 per cent. solution of acetate of soda, filtering hot, cooling the filtrate rapidly on ice, collecting the resultant precipitate at once on a filter, washing with absolute alcohol, and drying at blood heat. The operations have to be carried out as rapidly as possible, otherwise free uric acid is thrown out. Analysis of the sodium compound thus prepared yielded the following results :

TABLE VII.—*Quantitative Analysis of a Sample of Sodium Quadriurate prepared by the Acetate of Soda Process.*

	Proportion per cent.	
	Found.	Calculated.
Uric acid 0.329 g. ...	94.00	93.58
Sodium 0.021 g. ...	6.00	6.42

* Here again the quantities of uric acid and sodium found agree closely with the calculated amounts required to form a quadriurate.

The series of analyses just detailed furnish an adequate proof that the compound of uric acid which is decomposable by water is no mere mechanical mixture, but is a true and definite chemical combination, having a centesimal composition corresponding to that of a hypothetical quadriurate with the general formula H_2u, MHu . In deference to the authority of Bence Jones I propose to adhere to the designation "quadriurate," without, however, prejudging the question whether in reality the analogy with quadroxalate be a chemically sound one.

General Characters and Reactions of the Quadriurates.—The quadriurates present themselves usually as amorphous powders; but the spheres of the bird's and serpent's urines are distinctly crystalline, and display a black cross when examined with polarised light. The quadriurates are difficult to obtain in a state of chemical purity; they are apt, when produced artificially, to be mixed with traces either of free uric acid or of biurate; and when obtained from the urine, to be contaminated with pigment or with traces of extraneous saline matters. They cannot be dissolved unchanged in any simple menstruum. They are insoluble in absolute alcohol, ether, glycerine, chloroform, and the volatile and essential oils. When treated with hot water the quadriurates first pass into solution in their integrity; but this integrity is only maintained for a brief moment, and they forthwith disintegrate into free uric acid and biurate. 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 split up into free uric acid and biurate. These two reactions cover the behaviour of the quadriurates in the blood and the urine respectively, and furnish a key to the chemical processes which culminate in the formation of gouty deposits and calculous concretions, as will hereafter be more fully explained.

The only appropriate solvent for the quadriurates is healthy urine. In acid urines they dissolve freely with the aid of heat, and are again precipitated unchanged on cooling. Such solutions are, however, not quite stable; after a time their uric acid is slowly and at length completely liberated. The quadriurates are still more freely soluble in hot alkaline urines, and in these media they continue permanently unaltered if guarded against septic changes. When such solu-

tions 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.

Comparative Physiology of Uric Acid: the Evolution of Mammalian Urine.—The study of the amorphous urate and of the urinary excretion of birds and reptiles suggests some interesting reflections. We have seen that the amorphous urate deposit is substantially the same thing as the solid or semisolid urine of birds and serpents; all these consist of the quadriurates of potassium, sodium, and ammonium. But whereas in the urine of man and mammalia the quadriurates are only an insignificant item amid a host of other ingredients, the quadriurates constitute practically the whole of the renal excretion of birds and serpents. The urine of these creatures may be said to be exclusively composed of a substance identical with the amorphous urate sediment of human urine; or, to put it in another way, the amorphous urate is the physiological homologue of the entire renal activity of birds and serpents. The kidneys of birds and serpents are anatomically composed of the same structures as the mammalian kidneys; they are provided with the same kinds of secreting tubes and epithelial elements, the same curious Malpighian tufts and capsules—and yet how widely different is the product of their functional activity! It is not merely that there is a substitution of uric acid for urea as the final term of nitrogenous metabolism, but there is also the strongly contrasted simplicity of the urine of birds and serpents with the complexity of mammalian urine. In birds and serpents the renal function is presented to us in its primitive simplicity. In these creatures the kidneys perform one single and simple physiological act, namely, the elimination of nitrogen as uric acid. For, although the uric acid is excreted in union with bases, the quantity of these bases is the absolute minimum requisite to bring uric acid into a state of chemical combination, and thereby to deprive it of that strong crystalline character which otherwise would make its passage along the delicate exit tubules of the kidney a physical impossibility. The chlorides, phosphates, and sulphates, the lime and magnesia, the pigments, the large volume of water, all of which figure as prominent and even essential components of mammalian urine, are either wholly absent from the urine of birds and serpents, or are only present in such minute traces as might be derived from the lubricating mucus and epithelial debris with which the secretion is incidentally admixed.

It would be interesting to trace the successive steps along which the evolution of the complex mammalian urine took place from this simple beginning. We are familiar with much that has been said and written of mammalian descent from simpler types. The eyes and thoughts of biologists have, however, been chiefly fixed on the anatomical evolution. But there is assuredly also such a thing as a functional evolution. The anatomical evolution of the kidneys seems to have reached its term in the lowest vertebrate forms; the mammalian kidney presents structurally no essential advance on that of birds and serpents, but an immense functional evolution has taken place, and an examination of its progress through the tribes of fishes, amphibia, marsupials, and lower mammals, up to man, would prove an instructive biological study. The results of such a study would probably show that the evolution of mammalian urine turned mainly on the point that the mammalian plan required that the renal excretion should be voided, not in the solid or semisolid form, but in the liquid form, as a watery solution. This modification would at once necessitate the discarding of uric acid as a vehicle for the elimination of nitrogen. Uric acid and its compounds are strongly characterised by sparing solubility; and on no terms compatible with the conditions prevailing in the animal economy could the requisite quantity of uric acid be got into solution in a watery urine. Urea, on the contrary, is an extremely soluble substance. In regard to the prime function of the kidney, therefore, Nature solved the problem easily by substituting urea for uric acid. But why was not the problem solved completely? Why was there left in mammalian urine this small and apparently purposeless, but to man very mischievous, residuum of uric acid? No satisfactory answer can at present be given to this question. It seems not impossible that the explanation lies in the fact

that the mammalian type—the most recently evolved of the vertebrate types—has not yet, in this particular, reached its ideal perfection. A good deal may, I think, be said in favour of this conjecture. The occurrence and proportion of uric acid in the urine of the various tribes of mammalia is remarkably inconstant.

Meissner states that the urine of the carnivora does not always contain uric acid; in the urine of dogs and cats it was repeatedly found to be altogether absent. According to the same authority uric acid is only found regularly in the urine of these animals when fed on flesh and in the fasting state; it disappears when they are fed on food poor in albuminoid matters. Stadthagen found that in the urine of dogs fed on flesh the proportion of uric acid to urea ranged between 1 to 280 and 1 to 800. In the urine of rabbits uric acid is sometimes present and sometimes absent. Salomon found it always present in the urine of the pig, but only in small quantity; and its proportion to urea was only in the ratio of 1 to 150. In the case of man the quantity of uric acid excreted presents great individual variations, both in regard to its absolute quantity and in regard to its proportion to urea. The ratio of uric acid to urea in human urine appears to range between 1 to 30 and 1 to 50, and the ratio, according to Marès, is special for each individual. Dr. Haig estimates this ratio as 1 to 33, and he regards any deviation in the direction of plus or minus from this ratio as due either to temporary retention of uric acid in the body or to elimination of previously stored uric acid.

If we look broadly at the renal function throughout the animal series, we see that in essence it consists in a provision for the elimination of waste nitrogen. This is a function of capital importance and necessity in the nutrition of animals, comparable to the excretion of carbon by the lungs; and according to all physiological analogies it must be at bottom one and the same throughout the animal kingdom. Starting from the highly complex albuminoid molecule, and descending by a train of intermediate steps, the histolytic process ends in some comparatively simple crystalline azotised body. The precise nature of the final term in the histolytic transformation is apparently of small significance, and seems to depend on what may be described as the general convenience of the economy. It may be urea, uric acid, hippuric acid, or guanin, or a mixture of all these. And it is reasonable to assume that all these bodies are physiologically homologous, and that their broad physiological relations are identical. What urea is to the mammal, uric acid is to the bird and serpent; what urea is to man, urea with hippuric acid is to the horse and ox. The office of the kidneys is to separate the final term of proteid metabolism, whatever that final term may be.

These considerations point to the idea that the residuum of uric acid in mammalian urine may be something in the nature of a vestigial feature, analogous with the vermiform appendix, the ductus arteriosus, or the ear point. These rudimentary structures are now regarded by biologists as indications of the line of ontological descent. On this view, the presence of uric acid in the mammal's urine should be regarded as a "memory" of some ancestral form which eliminated its nitrogen as uric acid. The extreme inconstancy of uric acid, both in regard to its presence and its proportion, in the urine of different species and of different individuals of the same species, agrees perfectly with this theory, for vestigial structures are conspicuous for their inconstancy. Such structures, also, like uric acid, although impotent for good, are sometimes powerful for evil.

SHADWELL CHILDREN'S HOSPITAL.—A new out-patient department at the East London Hospital for Children at Shadwell was opened on June 11th by the Duchess of Portland. The hospital is situated in a very poor neighbourhood, and the out-patient practice forms a most important part of its work. The extension (which was much needed, the old out-patient rooms being small, and otherwise not very well adapted to their purpose) has been in contemplation for many years, the Board of Management having prudently decided not to begin to build until the funds in hand were sufficient to justify such a step. The President of the Local Government Board, in proposing a vote of thanks to the Duchess of Portland, made a warm appeal on behalf of the funds.

ABSTRACTS OF LECTURES ON THE TREATMENT OF SURGICAL TUBERCULOUS DISEASES.

Delivered at the Royal College of Surgeons of England.

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LECTURE I.

[BEFORE going on to the discussion of the various methods of treatment, some remarks were made as to the natural tendency of the disease as regards recovery, and in what way spontaneous recovery took place. It was, in the first place, pointed out that in the human body the tubercle bacillus has often a very hard struggle for existence, and that frequently very little is required to turn the scale in favour of recovery.]

The lecturer then proceeded as follows: Recovery may take place by atrophy of the tubercle and formation of a small fibrous scar, often hardly detectable where the tubercles are discrete, or by the formation of fibrous indurations where they are massed together. In other cases the whole of the tuberculous mass is not destroyed, the central part, either caseous or presenting tuberculous structure, being surrounded by a mass of fibrous tissue which forms a capsule. In the former case we have true recovery, tubercle bacilli being entirely absent; the latter is only cessation of the disease, and tubercle bacilli are generally present in an active state, and may again become active if for any cause the fibrous capsule is ruptured. Encapsulation is much more frequent than true cure, and is especially frequent in the case of tuberculous glands. In pure synovial disease we may have true cure not infrequently, but in the case of bones, encapsulation is the rule where apparent recovery has taken place. I have only once found evidence of true cure of a tuberculous osseous deposit. Where bony ankylosis takes place, I have seldom found distinct traces of tuberculous tissue except where tuberculous deposits were present in the bone; but in most cases of fibrous ankylosis where portions of cartilage remain, I have found somewhere or other remains of tuberculous tissue, a point of great practical importance in connection with the question of breaking down these joints with the view of obtaining better position or movement, a procedure shown by experience to be very apt to be followed by recurrence.

In considering the causes which oppose recovery in cases of tuberculous disease, we find that the factors on the part of the body which aid or resist the efforts of the parasite are, perhaps, of greater importance than in the case of any other infective disease, and it is seldom that the bacillus can overcome the body unless the conditions on the part of the host, both local and general, are favourable, or at any rate not unfavourable, to its progress. I must, therefore, refer to these factors:—

1. *General Causes.*—Perhaps the most important of these is the peculiar constitutional condition present in patients who have inherited a tendency to the development of tuberculosis; for although the disease itself is not inherited, or only extremely rarely, it is certain that the children of tuberculous parents are often extremely liable to contract the disease. Two explanations may be given; in the first place, the members of a tuberculous family are very often more exposed to infection than those of healthy families from kissing, inhalation of dried sputum, use of the same food utensils, etc. This great exposure to infection also continues after the death of the patient, because usually no attempt is made to disinfect rooms, bedding, etc. Apart, however, from the greater risk of infection, there can be no doubt that the children of tuberculous patients as a rule yield more readily to an attack of the parasite than others. In explanation of this, we may suppose that some peculiar form of tissue change has been acquired and transmitted which renders the body a better soil for the growth of the bacillus; or that a condition of the tissue cells has been transmitted in which they are not so sensitive in their reac-