THE LUMLEIAN LECTURES

ON

URIC ACID: ITS PHYSIOLOGY AND ITS
RELATION TO RENAL CALCULI
AND GRAVEL.*Delivered before the Royal College of Physicians.*By ALFRED BARING GARROD, M.D., F.R.C.P., F.R.S., ETC.,
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LECTURE II.

HAVING stated to you, in the former lecture, my views as to the production of uric acid in the animal economy, reserving only certain points to be discussed as we proceed; and having shown that the difficulties which beset the theory that the kidneys are nothing more than the strainers-off of this principle are extremely great, if not insuperable, and that, therefore, there is no little probability that uric acid is a true product of the renal organs themselves; I will at once proceed to draw your attention to the subject of human urine and the alterations which it undergoes, under certain conditions, which lead to the production of those morbid formations which are commonly called gravel and calculi.

It will be quite unnecessary for me, in lecturing to such an audience, to detail the characters and composition of healthy human urine; still, there are two or three points in relation to it which I must very briefly allude to. In the first place, healthy urine, omitting the trace of mucoid matter contained in it, which consists of the *débris* or washings from the mucous membrane of the urinary tract, is a perfectly clear fluid. Its weight varies much within the limits of health, according to the ratio between the dissolved solids and the water; a specific gravity of 1.020 may be taken as the average. Its reaction is decidedly acid, but the amount of its acidity depends on the time of its excretion, especially in relation to food; at times the urine may, for a short period, become neutral or even alkaline. Healthy human urine consists of water, holding in solution both organic and inorganic principles; the former are, urea, uric, and hippuric acid; the latter, chlorides of different metals, especially sodium, and phosphates of sodium, magnesium and calcium. In Table I are shown the relative quantities of the principal organic ingredients; also the amount of those ingredients which are thrown out for each pound (*avoirdupois*) of the body weight.

TABLE I.—Mean of Many Observations.

Quantity of water daily excreted by kidneys.....	Fl. ozs.
" " hourly " "	55.5
" " " " "	2.1
Quantity of urea daily excreted by kidneys.....	Grains.
" " hourly " "	512.0
" " " " "	21.0
Quantity of uric acid daily excreted by kidneys	8.67
" " hourly " "	0.361
Hippuric acid	(?)

Amounts thrown out in twenty-four hours for each pound (*avoirdupois*) of body weight:

	Minims.
Of water	129
	Grains.
Urea	3.53
Uric acid	0.06
Hippuric acid	(?)

It is to uric acid that we must chiefly direct our attention; and I must endeavour to show you (1) in what state of chemical combination it exists in the urine; (2) why it is held in solution in an acid fluid; (3) what are the causes which lead to its precipitation from the urine; and (4) what are the different shapes which it assumes when it is thus precipitated from its state of solution.

1. About fifty or sixty years ago, when Berzelius and Prout were investigating the subject, there was much discussion as to the condition of the uric acid when in solution in the urine—whether it is free or combined with a base, whether it is held in solution by the colouring matter of the urine, and so forth. For the details of such discussion, if still interesting, I will refer you to Dr. Prout's well known work.

At the present day, I believe that the subject is fully cleared up; and it may be asserted that uric acid, when in solution, is combined chiefly with sodium, but that there are also varying quantities of other bases present, depending on the amounts of different salts contained in the urine. I have already shown you, in my first lecture, that when urate of ammonium is dissolved in blood-serum in which the soda salts are present, it is converted into urate of sodium; and, bearing this fact in mind, we can explain the discrepancies which are found in the different analyses of urate deposits, both in health and disease. I may, however, say that the deposit, which, until recently, was commonly called lithate of ammonia, is composed almost entirely, in healthy urine, of urate of sodium. If, however, the urine, at any time, becomes ammoniacal from the decomposition of the contained urea, then the uric acid, meeting with a large excess of the new-formed base, gets deposited as urate of ammonium, a salt which is very insoluble.

2. The next point to be considered is the reason of its existence as urate of sodium in a fluid having such a well-marked acid reaction as healthy urine. This fact was for a long time difficult of explanation; but Liebig showed that, if to a warm solution of the common phosphate of sodium, which has an alkaline reaction, uric acid be added till it no longer dissolves, the solution becomes strongly acid, and there is contained in it urate of sodium and the acid phosphate of sodium, which latter salt exhibits a full acid reaction, but does not possess the power of precipitating the uric acid. This phenomenon solely depends on the tribasic character of phosphoric acid, which allows of a solution of phosphates, which reddens litmus powerfully without containing any free acid.

3. When, however, the least trace of a free acid, even acetic, exists in the urine, the whole of the uric acid is rapidly precipitated; a fact of considerable importance in the study of diseased conditions of the urinary excretion. If our attention is directed to the subject, we see, almost daily, that, when an urine is kept for a time, perhaps only a few hours, the uric acid, which at first was in complete solution, becomes gradually deposited in the crystalline form—a change due to the generation of a free acid in the urine by the occurrence of what is called the acid fermentation.

4. Our last point is to ascertain what shape the uric acid assumes when it becomes insoluble, and is precipitated from the urine. It may be thrown down either in combination with a base, that is, in the form of an urate, or as free uric acid. When, as an urate, it is often, from simple concentration, or from the presence of too small a quantity of water in the urine, and it seldom happens that such deposition takes place in the urinary organs themselves, unless there is a something present, such as a foreign body or the nucleus of a calculus, which greatly facilitates it. When, however, such urine is removed from the body, and cooled down to the temperature of the air, more especially in cold weather, the appearance of turbidity is extremely common, and often becomes, though most unnecessarily, a source of great mental disquiet to patients.

The simple evaporation of healthy urine *in vacuo* will usually cause, at a certain point in its concentration, the deposition of the same urate of sodium, and produce a similar appearance. When the urine, either concentrated or not, becomes abnormally acid, it at first causes the urate existing in it to be less soluble; but soon afterwards the acid itself is separated and deposited in the crystalline condition, forming what is commonly known by the name of *cayenne pepper-gravel*, so called from its resemblance to that condiment. We have been so accustomed, even from our student-days, to see the numerous forms which uric acid assumes, that we may feel little or no surprise that a body of so definite a composition and character as uric acid should be found under so many shapes, and perhaps most of us have paid little or no attention to the subject. Dr. W. Ord, however, has given no little thought to it, and has made a great number of observations and experiments which throw much light on the changes which the crystals of uric acid experience when acted upon by the various colloid substances, some of which are present in healthy urine, and others as the result of disease. Let us take what may be looked upon as pure uric acid, dissolve it in boiling water, and then allow it to cool and crystallise; it will be found in oblong tabular crystals, which are both homogeneous and transparent.

When uric acid crystallises out from urine, it is more or less coloured, from yellow to brown, and in the form of thin rhomboidal prisms, showing that there must exist in the urine something which causes an alteration not merely in the colour, but also in the crystalline form. Dr. Ord makes the following remarks, which I cannot do better than quote, as they express the character of the changes to which I wish to allude. He says: "It follows from this com-

parison of the pure and urinary acids, that there must exist in the urine causes leading to a complete turning away of the substance from its proper crystalline form. The change is also in a definite direction. The faces and angles of a crystal from urine are almost always, some or all of them, curved and rounded. Such a crystal is a resultant of the operation of two distinct influences—of crystalline polarity, under which the flat surfaces and sharp angles are determined; and of 'molecular coalescence,' in which polarity is lost and particles become arranged in spherical masses, by virtue of their unhindered mutual attractions. Furthermore, in urine the crystals are very frequently gathered into large glomeruli, to which such names as 'gravel' and 'cayenne pepper-grains' are given. These, on examination, are found to be regularly constructed of rhombs or prisms."

Dr. Miller, Dr. Beale, and other writers on micrology and chemistry, have suggested that the substances associated with uric acid in urine are the determining causes of the several differences; and the researches of Mr. Rainey have pointed the way to a solution of the problem.

Dr. Ord, in his work on *The Influence of Colloids upon Crystalline Form and Cohesion*, from which I have just quoted, and to which I would refer you for much valuable information, gives the results which he has obtained from the crystallisation of uric acid under the influence of urea, colouring matters, mucus, albumen, cane and grape sugar, gum arabic, starch, gelatine and glycogen.

It appears to me, that the researches of Dr. Ord and Mr. Rainey are not only valuable, but also seem to throw a ray of light—dim, it is true, at present—upon those phenomena which, as it were, connect true chemical changes with those we are accustomed to look upon as due to the agency of life.

The result of our inquiries, as far as they go, may be summed up in a few words. Perfectly healthy urine should show no appreciable deposit; when, however, it becomes concentrated from deficiency of the watery excretion, then the uric acid is thrown down in the form of an urate. This may occasionally occur within the body, but far more frequently after the urine has been voided; sometimes, however, this change ensues so rapidly, that the urine is erroneously supposed to have been passed in that condition. The presence of a solid body in any part of the urinary tract favours deposition very much, and hence urine, which would otherwise remain clear, may yield a deposit to any substance previously present in the same tract, and may thus add considerably to an already existing calculus. The appearance of the numerous layers so frequently seen around a central nucleus, both in renal and vesical calculi, is thus easily explained. When, however, the urine becomes further altered in composition—if, for example, a free acid is either excreted with the urine, or rapidly generated in it through the setting up of the lactic fermentation, the uric acid becomes liberated from its state of combination, and, in a form more or less altered by the presence of colloid matters, is deposited on a previously existing calculus, or is passed as separate rhomboidal crystals or in aggregated masses, constituting gravel or sand. I should feel disposed to confine the name of "sand" or "gravel" exclusively to such deposits, which, I believe, seldom form the nucleus or become the starting-point of any calculus. I may add, that urine possessing these characters is frequently voided for months and years, without the occurrence of any appreciable inconvenience to the patient. It is true, that a calculus may be augmented by contact with such an urine; but, as I have said, it seldom originates in this way.

According to this view, which I feel inclined to adopt, gravel or sand consists of uric acid previously in a state of solution, which has become precipitated by the occurrence of some change in the urinary excretion.

It is a fact, ascertained by repeated analytic observations, that some individuals pass a larger daily quantity of uric acid than others; but, at the same time, those who pass the largest quantity may have a urine little disposed to deposit the principle; and it will be found, as a result of experience, that changes in the urinary excretion, leading to the crystallisation of its contained uric acid, are much more potent factors in the production of sand or gravel than the mere quantity of this acid which is eliminated. If there is a simultaneous occurrence of the two conditions—that is, of increased quantity of the acid and altered state of the urine—this facilitates still more the production of the morbid appearances.

Before we proceed further in the pathology of our subject, it will be necessary that some investigation be made into the physical properties of the uric acid excretion, when it exists in a form which is visible to the eye—that is to say, in a semi-solid state; and this investigation will bring to light facts which are somewhat striking

and full of interest. We have already assumed that the excretion of reptiles and birds consists of uric acid, united with ammonia, and it is usually regarded as being urate of ammonium; under these circumstances, it would be expected to behave like such a salt when acted upon by different reagents. We will now see whether it does so.

Let us take two graduated tubes, divided into one hundred parts, and put into one the ordinary salt, the acid urate of ammonium, so as to stand to the height of five divisions. Into the second tube, let us put the dry and powdered white excretion of some large reptile, such as the python or boa, and fill each tube with a one per cent. solution of carbonate of lithium, up to the one hundredth division. Let us place the tubes upright in a stand, and shake them from time to time. On examining the contents of the first tube, after the lapse of hours, days, or even weeks, no change will be perceptible; the artificial urate will still occupy the same space, five divisions, and no more. In the second tube, very different appearances will be exhibited—a change occurring, to some extent even after a few minutes, with some slight puffing and some little translucency of the substance; while, in the course of an hour or two, the swelling will become very great, and go on increasing for twenty-four hours or more, till at last a solid magma will be formed, occupying 80 to 90 divisions of the tube; so that the natural urate which, in powder, originally occupied a given space, under the influence of a weak alkaline solution, will fill up, as a solid mass, a space seven-teen or eighteen times larger than its original room.

If distilled water be substituted for the solution of carbonate of lithium, a similar puffing takes place, though to a much slighter extent; and the reason of this is not difficult to understand, for the urinary excretion is acid in character, and when water alone is added, a crystallisation out of some free uric acid is apt to ensue. Solutions of carbonate of potassium and sodium, corresponding in strength to those of lithium, cause similar results; still, in some respects, they differ from each other, especially as regards the amount of swelling or turgescence, by reason, apparently, of the varying action of the different carbonates upon the organic matter contained in the natural urate.

When rectified spirit, containing about 16 per cent. of water, is substituted for the alkaline solution, the change which ensues is very slow indeed; in fact, scarcely perceptible for a day or two; still, the substance gradually increases, and at last attains a bulk of several times its original dimensions.

If absolute alcohol—that is, a spirit devoid of water—be employed, no increase takes place, even after the lapse of a week or more; when, however, after the alcohol has been poured off, a solution of carbonate of lithium is subsequently added, the swelling of the urate goes on in the same way as when no spirit has been previously used.

If small masses of the excretion be digested in a strong solution of ammonia for a few hours, and afterwards dried and lightly powdered, it will be found that the property of puffing-up is entirely gone, and the same result ensues when caustic soda or potash is used instead of ammonia.

When the solid urinary excretion is reduced to a very fine powder, as by long-continued and hard friction in an agate mortar, there appears to be some diminution of its puffing-up power; but when the magma which has been produced by the long-continued action of the lithia is washed, dried, and then subsequently powdered, all the power of swelling up appears to be lost.

I may here mention that I have examined the excretion of a large number of different reptiles and birds, and always with the same results whenever the specimens have been in a fairly fresh condition.

Having determined the physical condition of the excretion as it exists in animals whose urine is too deficient in water to hold the urates in solution, it appeared to me to be a matter of great importance to arrive at its chemical composition. The common idea is, as I have already said, that it consists of urate of ammonium; and, in the early analyses, ammonia was always found in it, but in small quantities only. This is shown by the analyses of M. Schriebers, Dr. Prout, Dr. John Davy, and others, in which the amount varied from about 1½ to 4 per cent.

There is no doubt as to the presence of ammonia in the urinary excretion of birds and reptiles, for we have only to add a caustic alkali, and the characteristic odour is at once developed; but it is important to go a step further, and to ascertain whether the uric acid, as it exists in the fresh excretion, is so combined as to form a true urate of ammonium. To effect this, I had many experiments made on the excretion of different birds and reptiles (the results of

which are shown in Table II). From these, the following conclusions may be drawn: first, that the uric acid in the pure substance is not combined with any fixed base, such as soda, potash, or lime, but that it is combined either with ammonia itself, or some organic base which readily yields ammonia.

TABLE II.—*Exhibiting the Results of the Analyses of the Urinary Excretion of Reptiles and Birds, in relation to Uric Acid and Ammonia.*

	Percentage, Bi-urate of Ammonium.	Percentage, Excess of Uric Acid.
Urate of ammonium (dried over lime)	... 99.7	... 0.3
Urinary excretion of Python Regius	... 100.0	...
Urinary excretion of Australian monitor	... 92.0	... 8.0
Urinary excretion of Python Molaris (probably old)	... 49.0	... 50.9
Urinary excretion of Python Reticulatus (rather fresh)	... 32.9	... 67.1
Urinary excretion of Madagascar Boa (fresh)	... 32.0	... 68.0
Urinary excretion of Diamond Snake	... 24.9	... 75.1

No amount of any fixed base was found (such as soda, potash, or lime), though carefully sought for; but, in the ostrich, there was some phosphate of calcium.

It will be seen from the table that the amount of ammonia varied very considerably in the different specimens which were examined; and, contrary to what I had anticipated, the specimens which were most perfect and exhibited least of all the appearance of disintegration were not those which yielded the most ammonia. It was also found that the swelling or puffing-up peculiarity was almost or entirely absent from those specimens in which the quantity of ammonia was greatest. This was well shown in the excretion of the royal python and of the Australian monitor (lizard), both of which specimens were much injured by decomposition.

It would appear, therefore, that beyond a certain percentage, which seems to be equivalent to the formation of about 25 to 32 per cent. of urate of ammonium, the extra amount of ammonia results from some change which has taken place after the excretion has been passed. A close examination by the unassisted eye enables us to see that there has been some disintegration in the substance.

It will also be seen, on reference to the table, that, with the exception of those excreta in which decomposition has occurred, the amount of ammonia is far short of that which is necessary to the formation of the true diurate of ammonium. May it not be possible that the uric acid, when first formed, is in combination with some nitrogenised organic base, such as urea? If so, this would account for the results obtained. Or, again, may not an organic compound be first formed in the renal cells, which readily breaks up, yielding, among its chief products, uric acid and ammonia? This is a subject which I have not had leisure to investigate with sufficient thoroughness to be warranted in giving a decided opinion upon it. We have found, therefore, that the natural urate differs completely from the artificial in its physical properties, at least, in so far as regards its power of becoming distended under the influence of water or carbonated alkaline solutions. It now becomes necessary to examine carefully its microscopic structure.

A paper of mine, published in the *Medico-Chirurgical Transactions*, 1848 (vol. xxxi), under the title of "Observations on Certain Pathological Conditions of the Blood and Urine in Gout, Rheumatism, and Bright's Disease," was illustrated by a plate, which contained, among other drawings, one which exhibited the microscopic appearance of the urinary excretion of the pigeon. This was the first time, I believe, that the minute characters of such excretions had been shown. The results of a re-investigation of this subject, which I have recently made, will now occupy us for a few minutes, as it bears closely on the subject of renal calculi. I have examined the excretion of a large number of reptiles, birds, and invertebrate animals; and the drawings upon the screen, which are selected from a great many others, will give an idea of the appearances presented.

There is a great uniformity of appearance in the different specimens; in fact, it would be difficult or impossible to separate by microscopic characters, the urine of a reptile from that of a bird, the only variation in the different drawings is that which appears in the size and prevalence of the larger spherules; for it will be noticed that there are many more of these in the large birds and reptiles than in the smaller birds, while the small spherules are of about the same size in all specimens depicted. No spherule in the

excretion of the canary-bird approaches in size many which are to be seen in that of the rhea. The measurement of the largest spherules is 0.00072 inch, and the smallest about 0.00008 inch.

It seems to me that we should be ignoring all physiological principles if we did not assume that uric acid is originally excreted in the same way by all animals, be they reptiles, birds, or mammals, including man—that, if, as we have shown by fair evidence, it is formed in the cells of the kidney in one animal, it is so formed in another, although the different influences to which it may be subsequently subjected may cause an entire change from its original physical condition.

In reptiles and birds we see that the uric acid, in combination with some base, is contained in the kidneys in the form of larger and smaller spherules, and we also see that these have a tendency to aggregate and form larger and larger balls or spherules, which are ultimately eliminated from the body. We see, in fact, that these animals are perpetually voiding renal calculi, which, although small in size, are yet perfect in form and constitution. Their urinary tract is so constructed that no inconvenience ensues; but, were such urine excreted by the mammal it might at once lead to serious mischief.

May we not, however, get a lesson in pathology from reflecting on these facts which I have now brought before you? May not these spherules, which, as a rule, are soon dissolved in the watery urine of the mammal, occasionally escape solution, and become the nuclei of renal calculi? This idea is one which, up to the present time, I have never seen suggested, but it is at least worthy of some further thought.

I believe that I am correct when I say that hitherto it has been usual to regard both gravel and calculi as arising always from the precipitation of urinary principles which have been in the urine in a state of solution—a view, which, as I have already shown, has some truth in it, though I think that, before I shall have finished the present lecture, I shall be able to lay before you facts which may cause some modification in the opinions which have been commonly held. Dr. Vandyke Carter has made some interesting observations on the structure of calculi, and has come to the conclusion that, in almost all calculi, the nucleus contains uric acid or urates in the spherical or globular form and not in the ordinary crystalline condition; and that, when oxalate of calcium is present, it is in the shape of dumb-bells and not in the characteristic octahedral crystals.

In his work on urinary diseases, Dr. William Roberts makes the following observations, which appear to me to sum up all that is at present known on this subject. He says:—"Considerable light has been thrown on the mode of origin of urinary calculi, by an examination of the microscopic structure of the nuclei. Dr. V. Carter found that the actual nucleus consisted nearly always of urates and oxalate of lime (dumb-bells and spheroids), and not of ordinary crystals of these substances. The researches of Rainey and Ord have shown that these globular forms are only produced when precipitation takes place slowly in a colloid medium; and Carter found that a colloid matrix always exists in the nuclear formations of urinary calculi; It would therefore appear probable that the initial step in the formation of a calculus, is the exudation of some colloid—mucus, or some other albuminoid substance—into the urinary passages. Into this colloid, urates or oxalate of lime, or both, are precipitated, and, combining with it, form molecular aggregations of a globular character, which constitute the foundation of the subsequent growth. Under what conditions the colloid is exuded, cannot be with certainty explained; but the probability is that congestive or sub-inflammatory states of the kidneys, such as occur in the febrile state, give occasion to such an exudation, and supply a starting-point to a process which does not attract attention until after a long lapse of time."

Dr. Roberts, in this passage, thinks that the colloid exudation is the result of subinflammatory disease of the kidney; but, as far as my own experience goes, I have, in most cases of renal calculi, failed to find evidence of any inflammatory renal affection; the patients have, at any rate, been free from all febrile disturbance.

In examining several different calculi which had been passed soon after their descent into the bladder, I have found that some are apparently simple, that is, when cut they exhibit an uniform structure throughout; such calculi, however, are generally very small, the largest not exceeding in size a pin's-head. Others are evidently compound in their structure, containing a central nucleus surrounded by layers which may be more or less numerous in different calculi; in fact they resemble, when seen through a glass, the larger form of the vesical calculus.

[To be continued.]