THE LUMLEIAN LECTURES ON URIC ACID: ITS PHYSIOLOGY AND ITS RELATION TO RENAL CALCULI AND GRAVEL.

Delivered before the Royal College of Physicians,

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LECTURE I.

ON being requested to deliver the Lumleian Lectures for the present year, at our College, I naturally felt much gratified by the honour but, none the less, I should have hesitated to accept the responsibility of addressing you in my present capacity, had it not so happened that I was at the time engaged in completing some investigations which I had begun many years before. As these had relation to the production of uric acid in the animal economy, and to its morbid manifestations—subjects of deep interest to the physician—I thought that the results of these researches might not be altogether without attractiveness to my professional brethren, if they were made the subject-matter of the present course of lectures.

Having, therefore, a subject to bring before you which contains some little novelty, and, as it were, breaks new ground, I put this fact forward as my excuse for appearing to-day in the capacity of your Lumleian Lecturer.

I shall not hesitate to dwell somewhat on the physiology of uric acid in my lectures, as I feel sure that any advance in its pathology which the future may show, must largely depend on our having the firm foundation of a correct physiology to build upon—a thing much needed at the present time, if we may draw such a conclusion from the diversity of opinions, as to the production of uric acid, which are in vogue, while we have many holding that the spleen, others that the liver or the lymphatic glands, are the organs devoted to its elaboration. Nor shall I hesitate to dwell upon the condition and composition of the urinary excretion in different classes of animals; for I have long felt that, if in the study of the physiology of uric acid we confine our attention to the human subject, we place ourselves in a position of great disadvantage towards the inquiry, seeing that uric acid and its derivatives pervade the whole animal kingdom. Furthermore, when I considered that, in some animals, the nitrogenised excretion consists almost entirely of uric acid, while in others its amount is extremely small, it occurred to me that, in the study of this principle in various classes of animals we should be most likely to discover the true solution of its formation and the rôle which it plays in the animal economy. For these reasons, I shall lay great stress on the comparative physiology of uric acid in my lectures.

Let us imagine a partition separating the blood from the urinary excretion, such as, in nature, is found in the walls of the renal vessels; then uric acid, free or in combination, may exist either on the one or on the other side of this membranous partition; if on the one side,—that is, in the blood—it originates symptoms which are referable to various organs; it may be deposited in the articular tissues, and produce the typical form of joint-gout, with chalk-stones; or it may affect the skin in the shape of eczema, or cause cramps, neuralgic pains, dyspepsia, etc., according to the part particularly selected. On these, I shall not touch in this course of lectures, having had full opportunities of setting out my views and researches elsewhere. But uric acid is also to be found on the other side of our imaginary partition, that is, in the urinary excretion, and, under certain circumstances, it forms morbid deposits, such as go by the names of gravel and calculi; and it is to these that I shall confine my attention, with special reference to their pathology and treatment.

The metabolism of the various tissues of which the animal body is composed, which occurs during life, is accompanied by the formation of certain products which require to be eliminated. Leaving out of consideration the inorganic salts, such as the phosphates and chlorides, we have certain elements, chief among which are carbon, hydrogen, oxygen, and nitrogen (some of which four elements enter into all organic compounds), to be got rid of. Of these, a large por-

tion of the carbon, united with oxygen, escapes by the lungs as carbonic anhydride (carbonic acid), while the hydrogen, united with oxygen in the form of water, is thrown out by the skin, lungs, and kidneys. There remains the nitrogen—the element *par excellence* characteristic of life—which is eliminated almost exclusively by the kidneys; in what shape or shapes I will now describe.

In some animals, as the mammalia, including man, urea [$\text{CO}(\text{NH}_2)_2$ or $\text{CH}_4\text{N}_2\text{O}$] is the chief nitrogenised principle, and it is the one which is richest in nitrogen, containing as much as 44.66 per cent. This organic body, which was the first to be synthesised or made artificially, being very soluble both in water and in the animal fluids, gives little or no trouble in its elimination, as it forms no concretions, and I am not aware that its presence in the blood produces any marked symptoms; at any rate, it can be injected into that fluid with impunity; for we must take care not to confound a condition of blood showing the mere presence of urea, with the so-called uræmic poisoning.

From many observations it appears that the average quantity of urea excreted in the twenty-four hours is 512.4 grains, and that, for each avoirdupois pound, 3.33 grains are eliminated daily. It is in the form of urea, therefore, that the chief part of the nitrogen in a very large and important class of the animal kingdom is eliminated.

The next principle to be mentioned is uric acid ($\text{C}_5\text{H}_4\text{N}_4\text{O}_6$), which was formerly called lithic acid, and has recently been synthesised. This acid, combined with more or less ammonia, forms the chief part of the nitrogenised excretion of birds and reptiles as also of almost all invertebrate animals, and a small part of that of man and the other mammalia. It contains 33.33 per cent. of nitrogen, but, if estimated as urate of ammonia, as much as 37.83 per cent. Its properties, especially as regards solubility in water or the animal fluids, differ greatly from those of urea, for it is with the greatest difficulty that it is dissolved, requiring, when pure, as much as 8,000 times its weight of distilled water at about the temperature of the blood (100° Fahr.). The salts of this acid are more soluble, but yet, in comparison with others, only slightly so, and they and the acid itself readily crystallise out from the fluids in which they are dissolved. It is owing to this property of insolubility that uric acid, although it forms so small a proportion of the urinary excretion in man, so frequently is a cause of disease. In the first place, it may concrete in the kidneys, forming gravel and renal calculi, which, when they reach the bladder, if they remain there for any time, encourage the precipitation of a further quantity of uric acid or urates upon them, and thus vesical calculi are formed; or, secondly, uric acid may be present in the blood and lead to special symptoms in different organs, or become deposited in the form of urate of sodium in various tissues, producing much discomfort.

As it is important to have a knowledge of the relative solubilities of the principal salts of uric acid, as well as of the acid itself, and as no table is known to me which shows their solubility at the temperature of the body, and as great discrepancies exist in the accounts of their solubility at any temperature, I have had a careful set of experiments made, with the results which are set out in the following table.

Table of Solubilities of Uric Acid and its Principal Salts in Distilled Water. Temperature 100° Fahr.

	Pure	Parts.
Uric acid	...	1 in 8,000.
Urate of ammonium (artificially prepared)	...	1 in 2,400.
Urate of sodium	...	1 in 1,130.
Urate of potassium	...	1 in 500.
Urate of lithium	...	1 in 220.
Urate of magnesium	...	1 in 1,600.
Urate of calcium	...	1 in 2,800.
Urate of lead	...	Insoluble.
Urate of iron	...	Insoluble.

There is a third body, viz., hippuric acid ($\text{C}_9\text{H}_8\text{NO}_3$), which is found in the urinary excretion; largely in that of the herbivorous mammals; in small and varying quantities in the urine of man; but is almost, if not entirely, absent from that of the carnivorous mammals. It will be seen from its formula, that the percentage of nitrogen contained in it amounts to 7.82.

Although hippuric acid has hitherto been regarded as a comparatively insignificant ingredient, at least in the urine of man, we shall, as we advance in our subject, find that it plays an important rôle in the metabolism going on in the system, one which, to us, as students of disease, is of deep interest.

It is in the form of one or other of these three substances, with

comparatively slight exceptions, that the whole of the nitrogenised waste of the body is eliminated from the system by the renal organs, little or none escaping by any other channel.

As uric acid is the principle which will chiefly engage our attention in these lectures, and as a correct knowledge of the mode and place of its formation in the economy is of the utmost importance, if we ever hope to arrive at the solution of the problem of the cause of calculi, and to develop some method of preventing their occurrence, and, more especially, as the views at which I have arrived during the study of the subject differ so much from those held by almost all physiologists, I shall not attempt to apologise for occupying your time with the investigation of the nature of this substance, so interesting in its physiology, and, in its pathological development, leading to much suffering, danger, and even death.

Origin of Uric Acid in the Animal Economy.—There are, at least, two possible theories as to the formation of uric acid. Of these, the first is, that it is formed during the metabolism constantly going on either in the system at large, or in special organs—such as the spleen, lymphatic glands, liver, lungs, etc.; and that, when formed, it reaches the blood, and is afterwards rapidly eliminated by the kidneys. From the point of view of this theory, the renal organs are merely the drawers-off or filterers from the blood of the uric acid which it brings to them. On looking over the principal modern books which deal with this subject, and on ascertaining the opinions held by physiologists, pathologists, and the members of the medical profession in general, I find that this view is so popular with them as to be almost universally accepted; in fact, all the attempted explanations of the influence of respiration, of the cutaneous functions, of different kinds of diet and regimen, are based upon the assumption that uric acid owes its origin to a less perfect oxidation of nitrogenised principles in the system than occurs when urea is formed, and that a meat-diet powerfully favours the formation of this acid. For the sake of brevity, I shall, in these lectures, call this the *first* view.

Another, which I shall call the *second* view, may be held. In this, it is assumed that the kidney is the organ whose function it is to produce uric acid; that this principle is formed in the renal cells from nitrogenised matters brought to them by the blood; and that, in so far at least as uric acid is concerned, the kidneys do not act in any degree as filterers or strainers. There are few physiologists or pathologists, at the present time, who hold this opinion; and the discovery of uric acid in the blood, which I made in 1847, seemed, at first sight, to militate against it: for it appears to follow, from the fact of the presence of uric acid in the blood, that it must be formed before the blood reaches the kidneys, and not in those organs.

In the course of our investigation into the value of these two views respectively, we shall have occasion to bring forward almost all the facts at present known with reference to the physiology of uric acid, and these require a satisfactory explanation before we can definitely arrive at any choice between the rival theories. I feel most strongly that a correct knowledge of the physiology of this subject is essential, if we hope to advance further in the pathology of uric acid.

The two theories above mentioned may be shortly summarised as follows. In the first, the kidney is regarded simply in the light of a strainer or filterer of the uric acid which is found in the blood, and passes through to it. In the second, the kidney is held to be the actual producer of uric acid, and the presence of this principle in the blood and tissues is explained by resorption from the renal cells, a process which is scarcely appreciable in health, but becomes more and more marked in proportion to the difficulty which the uric acid has in finding its way to the uriniferous tubes.

In considering the physiology of uric acid, I must, in the first place, draw your attention to the fact that there are great differences between the urine of different classes of animals, both in physical condition and in chemical composition. In some animals, the urinary excretion is very thin and watery; in others, it has the consistency and appearance of thick cream; these differences depending, of course, on the ratio between the water and the solid constituents of the excretion. The constitution of the solid portion of the excretion also varies much; in some urines, the urea is abundant, the uric acid very scanty, or even altogether absent; in others, these two constituents are both present in large quantities; while, in a third class, the urea is either very small in amount, or entirely absent; uric acid, in some form of combination, constituting almost the whole of the solid portion of the urinary excretion.

1. *Mammalia.*—The urine of man we will not discuss at present, as we shall have to speak about it when dealing with the formation of renal calculi and gravel; it may, however, be mentioned in passing that, in constitution, it closely resembles a combination of that

of the carnivorous and herbivorous mammals, as, indeed, might have been anticipated from our knowledge of the anatomical structure and the nature of the food of man.

The urinary excretion of the carnivorous mammals is a watery and heavy fluid, its specific gravity being sometimes as high as 1070. I have found that of the lion and tiger to be 1063 and 1064, of a distinctly acid reaction, and a not disagreeable odour; nor is it liable, as has often been asserted, to rapid decomposition. The urine is rich in urea, so much so often, that a single drop placed on a piece of glass will, after a few minutes, become a mass of crystals; and with nitric acid, it immediately becomes solid, from the formation of nitrate of urea. Uric acid is usually found in it, but in very small quantities; never, at least when the animals are kept in confinement and sparingly fed, reaching the amount contained in human urine. In that of the tiger, I have found it readily, and it even crystallised out from such urine when spirit had been added to preserve it. In the lion, I failed to discover it in the only specimen which I examined, but oxalate of calcium was present, a salt which was probably produced by the decomposition of uric acid.

No hippuric acid is found, at least under ordinary circumstances, in the urine of the carnivorous mammals: a fact on which I wish particularly to insist.

Next, as to the herbivorous mammals; the chief points of relation and difference between the urine of these and the carnivorous mammals may be thus summed up. It is usually a heavy fluid. I have found, in the horse, the weight ranging from 1025 to 1045. In the elephant (female), it was 1033; and in the camel, 1047; but only one examination was made in each case. In the cow and ox, I have found it as low as 1014 and as high as 1035. It is always alkaline in reaction, except in the sucking animal, and of a peculiar but not unpleasant odour; and I may here mention that my experience is opposed to the statements of many writers, for I have found very little tendency in such urine to undergo decomposition; in fact, I have placed it side by side with human urine, and found that it remained free from decomposition when the latter had become completely destroyed.

The urine of the herbivorous mammal is rich in urea, less so than that of the lion or tiger, and will not often crystallise on spontaneous evaporation, but generally becomes more or less solid on the addition of nitric acid, owing to the copious formation of nitrate of urea.

As to uric acid, such urines may be said to be free from this principle, except under peculiar circumstances; but, as these exceptions are most important from a physiological point of view, they will be referred to further on.

One of the most characteristic substances found in the urine of herbivora is hippuric acid, which derives its name from the fact that it was first discovered in the urine of the horse. Under ordinary circumstances, this acid exists in quantity at times equal to that of urea.

Hippuric acid is always combined with a base, and, on evaporation of the urine of herbivorous animals, hippurate of sodium crystallises out. I may state here, and we shall find the fact to be not unimportant, that the quantity of hippuric acid in the urine of these animals is very liable to vary, especially in relation to the character of the food taken. It has been asserted that benzoic acid is present; this may be so, but it must be remembered that hippuric acid, in the older analyses, was often mistaken for benzoic acid; also that the former, in the process of analysis, may at times be converted into the latter.

2. *Birds.*—The urinary excretion of birds, as far as my observations go, is semi-fluid, cream-like, and very rich in uric acid. After being expelled from the body, it soon sets, and becomes a hard white mass, in appearance not unlike plaster-of-Paris. As much as ninety per cent. of uric acid, or even more, has been discovered in it, together with a varying quantity of ammonia. I have always found it distinctly acid in reaction, whether the bird was living on meat or on grain. Most observers have failed to find urea in the urine of herbivorous, or graminivorous birds. I, myself, have never, as yet, been able to detect it; but, in the carnivorous birds, a small quantity is said to be always present, probably never exceeding a fifth part of the uric acid. Nothing is known as yet about the presence or absence of hippuric acid in the urine of birds. I have examined the urinary excretion of a large number of birds—*e.g.*, the ostrich, different rheas, the vulture, turkey, common fowl, pigeon, skylark, linnet, green parakeet (budgerigar), canary-bird, robin, and many other birds, and the uniformity of the chemical composition, as well as the similarity in their physical condition, been very striking.

3. *Reptiles*.—In so far as the eye can discover, or as chemical analysis has succeeded in making out, the urinary excretion of ophidian and saurian reptiles is identical with, or most closely resembles that of birds. I have carefully examined that of several pythons, boas, cobras, and the common English snake; also of various saurians, as the Australian monitor, etc. Urea is said to be absent, and, with one exception—viz., the common green snake—I have failed to find it. Whether it exists, in traces, in such excreta, as a rule, is at present a moot point. In the chelonian reptiles, the excretion differs from that of ophidians and saurians in that it is almost liquid, usually consisting of a clear watery fluid, containing opaque white flakes of urates. These latter vary much in quantity, depending, as I believe, on the length of time which has elapsed since food was last taken, these animals, as is well known, often fasting for a long period; they differ, also, in amount in different chelonians. In the land-tortoises, for example, I have found much more uric acid in the form of these white masses, than in the terrapins or water-tortoises, although the latter are carnivorous, whilst the former are herbivorous animals.

4 and 5.—*Batrachians and Fish*.—With regard to these classes of animals but little information has as yet been obtained.

6. *Invertebrata*.—Lastly, one word as to the nature of the urinary excretion in the invertebrates. With the exception of animals belonging to the class arachnida, as the scorpion and spider, which excrete guanine ($C_5H_5N_5O_3$), a substance found in guano and probably derived from uric acid, and closely related to it in composition, all the invertebrata throw out uric acid or urate of ammonium. It is from Dr. John Davy, whose name is associated with many physiological researches, that most of our knowledge of the excretion of invertebrate animals is derived. One interesting observation which he makes on the subject of the excretion of caterpillars and moths is this: "The urine of insects in their earlier or their larval state would appear to differ considerably from that of the same insects in their imago or perfect form. Thus, whilst, in the latter, it was found to consist chiefly of urate of ammonium, in the former, urate of ammonium was sparingly detected or not at all; what seemed to be hippuric acid being more abundant." We shall find during the course of these lectures that these facts are not without significance.

Having now given a short sketch of the character and composition of the urinary excretion of the different classes which compose the animal kingdom, we are naturally confronted by the question: Why this difference in the excretion of nitrogen; why in some animals does it chiefly take the form of urea, in others that of uric acid? The supporters of the first view have attempted many explanations; the favourite one being, that it depends on the greater or less activity of the function of respiration. This, I believe, originated with Liebig, and it is a view much insisted on by chemists, for it must be remembered that the uric acid, under the influence of oxidating agents, readily breaks up into urea and other products; thus, a slight oxidating cause splits it up into urea, allantoin and oxalic acid, all of which substances are found at times in the animal economy. Liebig pointed to the fact that mammals, having a high temperature and active respiratory function, throw out but little uric acid and a large quantity of urea; whereas reptiles, with a low temperature and a correspondingly low respiration, throw out their nitrogen chiefly as uric acid. This view was at first sight most plausible, but unfortunately it was founded on limited data; it was, in fact, a most partial view, for we have only to turn to the large class of birds for its refutation. Here we see animals with the highest temperature, and a respiration correspondingly active, eliminating their nitrogen in exactly the same form as the cold-blooded reptiles.

If other facts were wanting to show the error of this, at first sight captivating view, the recent experiments, set out in the *Comptes Rendus* of December 1881, would be sufficient. M. Cazeueneuve, in a paper termed "Sur l'Excrétion de l'Acide Urique chez les Oiseaux," describes how he kept a sparrow-hawk in a cage, and fed it on flesh, the bird throwing out a certain quantity of uric acid and urea in the twenty-four hours; he then put it under the influence of a large increase of oxygen, and even kept it for twelve hours in an atmosphere of pure gas. In no instance, however, was the quantity of uric acid diminished or the urea increased, but the ratio between the two remained the same as before. One can hardly help looking upon this fact as conclusive against the idea that urea and uric acid are excreted by animals in proportion to the activity of their respiratory function. Lastly, we may look at the excretion in invertebrate animals, whose temperature is high, while no urea is found in their nitrogenised excreta.

The nature of the food taken has been thought by many to have a powerful influence on the excretion of uric acid, but it needs very little consideration to show the inaccuracy of this idea; for ophidian reptiles, as the python and boa, which live exclusively on animal food; and grain-eating birds, such as the canary and others, whose food consists entirely of seeds; excrete the same nitrogenised products; in fact, it is difficult to separate the urinary excretion of the one class from that of the other, as I have already stated, both consisting of uric acid in combination with some ammoniacal compound. Again, if we compare a toad with a lizard, the little influence of the character of the food is at once strikingly shown; both animals live on flies, yet the urine of the toad is clear and watery, and contains no appreciable uric acid, whereas that of the lizard resembles cream, and consists mainly of urate of ammonium. The excretion of uric acid and of urea, also, is, doubtless, much influenced by the amount of food taken, whether in the same ratio has not yet been determined.

Some physiologists look upon the spleen as the producer of uric acid; others regard, some the liver, some the lymphatic glands, and some the cartilaginous tissues, as the originators of this principle; but there is one fact which must not be lost sight of, viz., that, whether an animal throws out all its nitrogen in the form of uric acid, or in that of urea, it, equally in each case, possesses a spleen, a liver, lymphatic glands, and cartilaginous tissues.

Of course, if we accept the second theory, and regard the kidneys as the producers of uric acid, the difficulty of the question is at once solved; we have only to regard the kidney as containing different cells; some, perhaps, for the formation of urea; some, at least, for the production of uric acid, and to hold that the number of the latter cells, compared with the other excreting cells of the kidney, differs in different classes of animals. The amount of respiration in any animal would then be of little moment with reference to the excretion of uric acid; nor would the nature of the food, provided only that the blood contained sufficient pabulum fitted for its supply. Possibly, however, many of us already see difficulties ahead, which have to be resolved before such a view can win acceptance.

[To be continued.]

THE GULSTONIAN LECTURES, ON THE STERILITY OF WOMEN.

Delivered at the Royal College of Physicians, February 1883.

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LECTURE II, PART II.—ITS THEORY OR CAUSATION.

FINALLY, Shorthouse has pointed out in mares the close alliance between sterility, abortion, and that kind of excessive fertility which is demonstrated by twinning. I quote the examples which he gives in the *Sporting Times* for December 12th, 1874; and, as adding to the force of the evidence, it is to be remembered that, in the mare, twinning is a far rarer event than in woman and the cow: in these it occurs about once in 80 pregnancies; in the mare it is said to be only once in 400:

Miserrima, barren in 1855, 1858, 1867, 1870, and 1871; slipped foal in 1856, 1859, and 1863; had dead twins in 1860 and 1862.

Caricature, barren in 1852, 1854, 1855, 1861, 1867, and 1871; had twins in 1856 and 1863; slipped foal in 1866.

Legerdemain, barren in 1852, 1859, 1864, and 1866; slipped foal in 1849; slipped twins in 1856, 1860, and 1862.

Crystal, barren in 1858, 1860, and 1865; in 1866 slipped twins.

Slander, barren in 1851, 1854, 1864, 1865, and 1866; slipped twins in 1857.

Thimblorig, barren to two horses in 1867; slipped twins in 1869.

Zoe, barren in 1865, 1866, 1867, 1868, 1869, 1870, and 1871; slipped foal in 1860.

No. 1, barren in 1865 and 1868; slipped foal in 1867.

No. 5, barren in 1856, 1858, 1860, 1864, and 1866; slipped foals in 1862 and 1868.

No. 7, barren in 1857 and 1860; had twins in 1858.

No. 8, barren in 1867; had twins in 1861.

No. 9, barren in 1858, 1860, 1864, and 1867; had twins in 1868.

No. 10, barren in 1858, 1860, and 1864; had twins in 1861.