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.

(Continued from page 497.)

Let us pass on to another point in the physiology of uric acid. How can we explain the fact that, in proportion to the weight of their bodies, some animals excrete so large a quantity of such an insoluble principle as uric acid, or even as urate of ammonium, the one requiring 8,000, the other 2,400 times its weight of water at the body-temperature to dissolve it? The human subject excretes, on an average, in the twenty-four hours, about one part of uric acid for each 120,000 parts of his weight: or, estimating the weight of a man at about ten and a half stone, throws out about eight grains of this acid daily. This is an average arrived at from a very large number of observations, which you will find detailed in Dr. Edmund Parkes's valuable work.

In the case of the lower animals, I could find no facts on record relating to this subject, and therefore had to undertake to supply them for myself by means of the following observations and experiments. I had a cage constructed, with a glass floor, so as to be able to collect the whole of the excreta of the twenty-four hours from the bird that occupied it, and from such I carefully ascertained the quantity of uric acid—no difficult process.

1. A canary-bird was kept in the cage, its food consisting of a supply of canary-seed, millet, and hemp, together with water. In twenty-four hours, I found that the excretion of uric acid was 2.1 grains, and the weight of the bird was 277 grains; so that the ratio of the uric acid excreted in twenty-four hours to the weight of the bird itself was 1:132.2.

2. An Australian grass-parakeet was next kept for twenty-four hours in the same cage, and fed on the same food. The weight of the excreted uric acid was 3.1 grains; that of the bird, 415 grains. The ratio of the uric acid to the weight of the bird was 1:133.8.

Had I calculated the weight of the bird from the weight of its excreted uric acid, taking the ratio in the case of the canary for my standard, I should have estimated the weight of the parakeet at 409 grains instead of 415, a calculation not very far from the truth for such an estimate, when we consider that a few seeds more or less in the crop of the bird would have covered the difference. The observation was repeated with a second parakeet of the same weight, and the same result was obtained, viz., 3.1 grains of uric acid in the twenty-four hours. In the sparrow-hawk, eating an enormous quantity of flesh, Cazeneuve found the average daily excretion about 34 grains; and, estimating the hawk (he does not give the weight) at nine and a half ounces—a weight which is probably above the true average—the ratio of the weight of uric acid to that of the bird would be 1:110. Let us, then, take 1:120 as a fair ratio, including in the calculation both carnivorous and graminivorous birds, and we arrive at the somewhat startling conclusion that the bird, in proportion to its weight, excretes 1,000 times more uric acid than man.

In cold-blooded animals, as the reptiles, it is difficult to perform such observations as we have now detailed; but there is one observation, bearing upon this point, which I have come across. Dr. Busch, more than twenty years ago, found that the kidney-cells in a common vineyard snail contained a granular matter, consisting of uric acid or an urate, which required fifty times the weight of the body of the snail to dissolve it.

In pursuit of this subject, I made further observations on the relation between the daily weight of the uric acid excreted, and the weight of the renal organs themselves. In the case of a lark, I found that the ratio of the weight of bird to that of kidneys was 125:1; in that of a linnet, 118:1; in that of a turkey, 172:1; but this latter bird was in a fattened condition, so the ratio may be somewhat misleading. Taking the lark and linnet, therefore, after calcu-

lating their daily excretion of uric acid, we find that it amounts to more than the weight of the kidneys of the same birds. Let us reflect on these facts. Is it possible to conceive, if we assume that the uric acid first exists in the blood, that the amount of this fluid passing through the renal organs could excrete as much of this principle as we have found, as a fact, to be thrown out? True, in the case of man, who excretes only one thousandth part of the uric acid thrown out by birds, we could easily imagine this to be the process; but the more we consider the facts about birds, the more difficult does it become to believe in this explanation; and, if we go further, and hold it impossible, then the first view as to the formation of uric acid appears to me to fall to the ground.

As this question is of the utmost importance to physiology, and as its decision must necessarily be followed by weighty consequences, it is essential that nothing should be left undone which might help us to the truth. With this object before us, there arise many points which must be determined; and, first of all, we must ascertain the condition of the blood of various animals, especially with regard to the presence or absence of uric acid. I have obtained many such data from observations made during a long course of years. I have several times examined the blood of man in health, and many hundred times in various diseases; and the conclusion at which I have arrived is this: that, in absolute health, the uric acid in the blood is inappreciable by our tests, and that that fluid does not contain the one hundred thousandth part of its weight of the acid; while, in gout, the blood is very rich in this principle, as I showed in 1847; that uric acid is also found, in much smaller but still appreciable quantities, in individuals who are developing a gouty condition, or who are under the poisonous influence of lead. This subject, however, I have already discussed elsewhere.

In the blood of various other mammals, as the ox, sheep, and pig, I have never found a trace of uric acid by the uric acid thread test.

I have also examined the blood of several species of birds, as the turkey, common fowl, pigeon, and duck, repeatedly in some instances, and have found it as free from uric acid as that of the mammal.

The turtle is the only reptile whose blood I have analysed; here I found oxalates present, but no uric acid. As seen in this country, however, the turtle can hardly be regarded as being in a normal condition, having in many cases taken no food for weeks, or even months. The only other observation on the blood of reptiles that I know of is one by Dr. John Davy, who examined the blood of two snakes (*Viper communis*), but failed to detect any uric acid in it. The result of these observations must be looked upon as somewhat striking, and even startling, to those who regard the uric acid in the urine as simply a filtration from the blood, when we remember that the blood of birds, whose urinary excretion is almost entirely composed of uric acid, is as free from that principle as the blood of the herbivorous mammal, in whose urine it is usually difficult to detect a trace; or, again, that the blood of the bird is as free as, and often freer than, that of man from uric acid, though it excretes daily about $\frac{1}{125}$ th of its own weight of that principle, man eliminating not more than $\frac{1}{100,000}$ th.

Let us go a step further in the inquiry, and let us assume, for the sake of argument, that the blood of a bird contains, which it certainly does not, $\frac{1}{100,000}$ th of its weight of uric acid—a quantity which, if present, could easily be detected by my so-called "uric acid thread test"—and let us make a rough calculation of the quantity of blood which passes through the kidneys in the twenty-four hours. The figures contained in the table may be regarded as sufficiently correct for the purpose of illustration.

I assume the weight of the bird to be represented by a certain figure, for convenience sake, and all the appended numbers have relation to that number.

TABLE—*Illustrative only.*

Weight of bird	...	...	...	277.0
" heart	...	...	...	4.0
" kidneys	...	...	...	2.5
" blood in body (calculated at 8.5 per cent. from starting)	...	...	...	23.5
Weight of uric acid excreted in 24 hours	...	...	...	2.1
" blood thrown from left ventricle at each beat of heart	...	...	...	1.0
Pulsations of heart in 24 hours (120 per minute)	...	...	...	172,800
Weight of blood passing through kidneys at each beat	...	...	...	0.10 (!)
Weight of blood passing through kidneys in 24 hours	...	...	...	17,280

Assuming that one-tenth of the blood that leaves the left ventricle at each beat passes through the kidneys, in which case nearly seven thousand times the weight of the organs would pass through them in twenty-four hours, then the whole of that quantity would not contain one-sixth part of the uric acid excreted during the same time by the bird. We have, in this illustration, given every possible advantage to the supporters of the first theory; for we have assumed not only that what I should imagine to be a most abnormally large amount of blood passes through the kidneys, but also that the blood contains a much larger quantity of uric acid than is really the case. Add to this that we have assumed, in the calculation, that no trace of uric acid escapes filtration in every passage of blood through the renal vessels—a most improbable assumption—seeing that, if arsenic is given to a person, and after a few days its administration is stopped, the metal can be detected in the urine for two, three, or even four days afterwards, although in constantly decreasing amounts. This I observed for myself many years ago. We shall soon have occasion to see what the filtering powers of the kidneys really amount to; in other words, how much uric acid they can excrete from a blood which is known to be rich in that principle.

Before passing on, I would say a word with respect to the data contained in the above table. The bird was weighed with its feathers on; the weights of the heart and kidneys were the mean of several observations which I had made; the weight of blood in the body was calculated from the experiments of Welcker on the starling, forwarded to me by Dr. Michael Foster; and the number of pulsations of the heart, and the quantity of blood thrown from the left ventricle at each, were the result of calculations from data obtained from different sources. I am desirous, however, that the table should be regarded as being one made only for the purpose of illustration.

The next point is to ascertain what takes place when uric acid, in the form of one of its salts, is administered by the stomach or injected into the blood. In 1849, I gave urates of ammonium, sodium, and potassium, with the following results.

A man was passing, on an average, 8.07 grains of uric acid in the twenty-four hours, taking no drug. Urate of potassium was given in five-grain doses three times a day. The dose was afterwards increased to ten grains. During the time he was taking the urates, the average excretion of uric acid was 8.25 grains—i.e., practically the same as before. I find appended to this case a note of no little interest; viz., that, during the administration of the urates, the man, who had some eczema, experienced a great increase of skin-irritation, which subsided on their discontinuance. This goes far to prove, first, that the substance was absorbed into the blood; and, secondly, that some forms of eczema are closely connected with the presence of uric acid in the blood. To another man I gave, at first urate of sodium, and afterwards urate of ammonia, in doses of fifteen to thirty grains, without the slightest detectible increase of uric acid in the urine.

Subsequently, Wöhler and Frerichs found that, when urates of potassium and sodium were taken, there was an increase of the urea and a sediment of oxalate of calcium in the urine, but no augmentation of the uric acid.

Neubauer found that, in rabbits, the administration of large quantities of uric acid was followed by a corresponding increase of the excreted urea, but no uric acid was discovered in the urine. The injection of urates into the veins, was followed by the same negative result as ensued when uric acid was given by the stomach.

If the kidneys act merely as strainers off from the blood of the uric acid brought to them by that fluid, how can we explain these facts? Is it not impossible to do so? If, however, we regard the kidneys as the producers or manufacturers of uric acid from matters brought to them by the blood, then all difficulty with respect to the facts above mentioned vanishes, and we see at once why the amount of uric acid has no necessary relation to the character of the food, but depends on the activity of the formative cells, and the quantity of pabulum brought to them during a given time. Before we proceed to discuss another point in the physiology of uric acid, you must allow me for the moment to assume, what I shall afterwards have an opportunity of proving, that, in the kidney-cells, this acid exists combined with ammonia, or, at any rate, with a base yielding ammonia, and not with any fixed base, as soda, potash, or lime; but that, when it is found in the blood, or deposited in the tissues, either of man or the lower animals, it is in the form of urate of sodium.

As far back as the year 1847, when I first found uric acid in the blood, I proved that it was in the form of the soda salt; this was shown, not only by its crystalline form and by its leaving, when

burnt, an alkaline ash, which imparted to flame the peculiar colour, but also by other chemical tests; and subsequent observations have abundantly confirmed what was then first shown.

Before the beginning of this century, Wollaston had proved that the deposits which occur in gouty subjects, and are commonly called chalk-stones, are composed of this same urate of sodium; and there are, on record, a few instances of such deposits in the lower animals, some natural, others produced artificially by arresting the elimination of uric acid, which latter have been found to have the same composition as the others. A few years ago, an interesting case of this sort came under my notice, which, as it strikingly illustrates the question which we are now considering, I will relate as concisely as possible.

An Australian grass-parakeet, which had been quite recently imported, came into my possession, and within a few weeks of its arrival I found on the digits of its claws little white nodules or protuberances, most of them larger than a pin's head. The bird soon sickened, and slowly died. It was afterwards found that each of these nodules contained a cheesy matter, which, under the microscope, exhibited the appearance of being made up of innumerable very fine needle-like crystals, polarising light with great intensity; and, when chemically examined, yielding an abundance of uric acid, but no ammonia. When incinerated, it yielded the characteristic soda ash. The deposit was, therefore, composed of urate of sodium. It was afterwards discovered that, not only were the digits of the claws studded with this matter, but that it extended along the shaft of each leg, and there was a long rod of the same substance in front of the cervical vertebrae, behind the trachea. On the board will be seen drawings showing not only the microscopic characters of the deposit, but also the appearance of the leg and claw. Unfortunately, the kidneys of this bird were not examined till the contents of the abdomen were dried and shrivelled up.

Zaleski, in his work on the function of the kidneys, has given drawings of the *post mortem* appearances of animals, in the various tissues of whose bodies deposits had been produced as a result of ligaturing the ureters.

Let us now see how these facts can be explained on one or other of the two theories of the formation of uric acid. On the first, it is not difficult to suppose that uric acid may be formed, either in that shape or as urate of sodium (at any rate, it would exist in the blood as the soda salt), and become deposited, under certain circumstances, in different organs and tissues of the body; but then comes the difficulty of explaining how it is that it is thrown out by the kidney combined, not with soda, but with ammonia. I cannot conceive any satisfactory explanation under this theory. I know of no chemical conditions which would render such a change possible, and would cause urate of sodium to be filtered through as urate of ammonium.

Let us now, for a moment, adopt the second view, and assume that urate of ammonium is produced in the kidneys, and that it sometimes becomes resorbed (the word, though uncommon, is the best expression of the process) into the blood after its formation. How is it that it then becomes changed into urate of sodium? There is no difficulty here, for I have shown that, when urate of ammonium is added to a solution containing a large excess of either phosphate or chloride of sodium, it is converted into urate of sodium, and will crystallise out as such. However, in order that I might remove all doubt about this fact in the case of blood, I made the following experiment. I took a considerable quantity of the serum of the blood of a healthy pig, ascertained, by the "thread test," that it was practically free from uric acid, and then proceeded to add to it a concentrated solution of urate of ammonium. The serum was thereupon allowed to remain a short time at the temperature of the body, and subsequently dried on glass and scaled off. On searching for uric acid, it was separated easily in the crystalline form; not, however, as it had been added to the blood-serum as urate of ammonium, but as urate of sodium. All difficulty, therefore, as to the explanation of the change in the salt as it passes from the kidney-cells into the blood is at once removed, and it necessarily follows that the tissue-deposits which occur in disease must be composed of urate of sodium.

It may, however, be asserted that uric acid exists in the urine of man chiefly as urate of sodium, not as the ammonia salt, and that I have only assumed that it exists as urate of ammonium in the kidney-cells. The former of these assertions is doubtless true, with regard to the urine of man and the carnivorous mammal. With reference to the latter, I must still ask that the truth of my assumption may be taken on faith for a short time, until I have an opportunity of proving it.

The explanation of the presence of urate of sodium in the urine is most simple, for urate of ammonium, excreted, as it is, in small quantities by man, meets at once with large amounts both of phosphate and chloride of sodium, and with mere traces of any ammonia salt. Hence the same change ensues as when urate of ammonium is dissolved in blood-serum, and it becomes converted almost entirely into urate of sodium. I have made many observations tending to elucidate this subject. If healthy human urine, dense in character, but not giving any deposit on cooling, has a hot concentrated solution of urate of ammonium added to it, it frequently throws down a copious precipitate, on being kept in the cold; this I have found to consist mainly of urate of sodium, thus showing that a similar change ensues whether the ammonia salt is absorbed into the blood or is sent forwards and united with the other constituents of the urinary excretion. There is no doubt that the urate deposit in urine must vary much, although, as a rule, it is mainly composed of the soda salt; for, if salts of magnesium or calcium, or even potassium, are contained in the urine, some of the soda salt will be replaced by urates of these bases; and, again, if the urine becomes ammoniacal by decomposition, then urate of ammonium, a most insoluble salt, as will be seen from the table of solubilities, will crystallise out.

I may state that urate of sodium in excess of ammonia salts is converted into urate of ammonium in the same way that urate of ammonium in excess of soda salts is changed into urate of sodium; but, when either of these urates meets in solution with equivalent quantities of both ammonia and soda salts, then both urates crystallise out on evaporation, and hence it follows that the crystals, although often mainly composed of one urate, necessarily contain at least traces of the other, and, sometimes, much more than traces, according to the relative amounts of the different salts contained in the urine. I think it will be found that a clear understanding of the action of the different salts upon each other will explain nearly all the discrepant statements to be found in different treatises upon this point.

As I have already said, those who consider that uric acid is formed before it reaches the kidneys, usually look to some other organ as its source, the spleen having been often fixed upon. On this subject, Dr. Michael Foster makes the following remark, in his work on *Physiology*: "The constant presence of uric acid is remarkable, especially since it has been found, even in the spleen of animals, such as the herbivora, whose urine contains none." And again, he says: "No less suggestive is the fact that the increase of uric acid during ague and during ordinary pyrexia seems to run parallel to the turgescence, and therefore, presumably, the activity of the spleen." As I had never examined the spleen for the presence of uric acid, I made the following experiment:

One thousand grains of the spleen of the ox, and the same amount of the spleens of the turkey and common fowl were dried in a water-bath and reduced to powder. This was afterwards treated with distilled water, first made alkaline with carbonate of sodium, and afterwards dialysed for two or three days into distilled water. The dialysed fluid was then evaporated to a syrupy consistence. A drop of that obtained from the ox was strongly acidified with nitric acid, and evaporated to dryness; a very distinct colour from the production of murexide was obtained, which became intensified by the action of the vapour of ammonia. When the same syrupy fluid was acidified by acetic acid, and a few drops allowed to dry spontaneously on glass, distinct evidence was obtained of the presence of uric acid crystals, which became unmistakable when polarised light was employed. On treating the concentrated fluids obtained from the birds in the same way, viz., for the production of murexide and for the crystals, it was with the greatest difficulty that any indication of the presence of uric acid could be detected by either test. These experiments were repeated, and with the same results. Unless the process of dialysis be employed, the uric acid is much masked by a peculiar matter which accompanies it in its solutions. This is at least partially got rid of by dialysis.

If the spleen be the organ in which uric acid is formed, why should not this acid be present in the urine of herbivorous as well as carnivorous mammals? On the same assumption, should we not expect that uric acid would exist in much larger quantities in the spleen of animals whose urinary excretion consists mainly of that principle, than in others whose urine is often devoid of it? As far as my experiments go, the very reverse is the case; for, while uric acid was easily detected in the spleen of the ox, in that of the bird it was most difficult to discover it.

Again, it would naturally be expected that in animals that throw out uric acid, the spleen would be larger, proportionally, than in

others; but I am not aware that such is the case. It must also be remembered that uric acid has been asserted by different observers to be present in other organs besides the spleen, as the liver, lymphatic glands, and brain; and from this last, W. Müller separated about 1 part of uric acid in 40,000 parts of weight, yet no one would consider that the production of uric acid is one of the functions of the brain.

Assuming that our second view is correct, and that the kidneys are the true formative organs, then an explanation of the presence of uric acid in the spleen, liver, and other parts is not difficult. When, from any cause, there is an appreciable back-flow of uric acid from the renal organs, and resorption, then the blood becomes more or less impregnated with that principle, as we find to be the case in disease; and, under these circumstances, it is attracted by various tissues, and becomes united with them. That such attraction or elective affinity does exist for certain poisons I have full proof in a case of arsenical poisoning which came under my care in the hospital about twenty-five years ago. A young man had swallowed a dessertspoonful of arsenious acid. As he survived this four days, there was plenty of time for the poison to be absorbed. I embraced the opportunity of examining the principal organs of the body for arsenic, and found it in all parts, though in very different amounts. The liver appeared to be most rich in the metal, then the spleen and the skin. May it not be the case that, when uric acid exists in the blood, it is attracted differently by different organs, and thus the spleen and liver more frequently contain appreciable quantities than other tissues? Or again, may it not be that in some organs, as the spleen, the substance of which, if not acid during life, rapidly becomes so after death, while the blood remains strongly alkaline, the uric acid becomes less soluble, and more easily retained? Or yet again, may it not be that, being united to these organs, the uric acid escapes certain destructive influences to which, if it remained in the circulating fluid, it might be exposed?

Although I have been drawn, by the force of the arguments in its favour, into regarding the second view of the origin of uric acid as the more sound, yet I do not wish, even in my own mind, to become a partisan of any theory, desiring only to arrive at truth; and I have, therefore, endeavoured equally to seek out and discuss facts which are antagonistic to one or other view, with those which appear to favour it.

Before concluding this, the purely physiological part of our subject, I will state that there are a few facts which demand full explanation under any theory which claims to be accepted as the true one. For instance, the urine of the sucking calf, and of the young of other herbivora, contains uric acid in notable quantities, while that of the adult animal is usually free from it. How can this be reconciled with the view that uric acid is formed in the kidneys? There are also other facts closely allied to these which appear to be equally difficult of explanation by the second theory.

In the course of these lectures, I hope to be enabled fully to solve these difficulties; and, in so doing, to bring before you many observations, the results of which may prove to be of great service and value, both in pathology and in therapeutics.

THE ALLEGED OUTBREAK OF TYPHOID FEVER IN AN EMIGRANT DEPÔT.—A Plymouth correspondent telegraphs: The allegation contained in Mr. Puleston's question to the President of the Board of Trade last night, as well as in that of which Sir Henry Peek has given notice for Monday, that typhoid fever broke out in the Plymouth Emigrant Depôt, through overcrowding and want of proper accommodation and attention, is found, on inquiry, to be without foundation. Mr. Hassard, the surgeon of the emigration ship, *Oxford*, states that the outbreak is due entirely to the tank water, which the emigrants drank while on board the ship, and that the premonitory symptoms of typhoid made their appearance before the passengers disembarked. The moment he discovered this, he prohibited the further use of the water from the tanks, and in this way prevented the spread of the disease. There were nine cases in all, and one of them has proved fatal. Mr. Hassard speaks in the highest terms of the sanitary arrangements in this hospital, and of the arrangements generally at the depôt, and in this he is borne out by the opinion of Dr. Blaxall, who visited the establishment about two months since, and expressed himself particularly satisfied with everything he saw.

THE Nottingham guardians have passed a resolution to the effect that the medical officers of the union shall announce themselves as such on plates outside their residences, and that the expense shall be defrayed by the guardians.