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 III.

(Continued from page 707.)

Influence of Hippuric and Benzoic Acids.—Before proceeding further with the treatment of gravel and calculus, I must redeem my promise to explain certain difficulties in the physiology of uric acid which had to be passed over in my first lecture; the discussion of these will, I hope, prove useful from a therapeutic point of view. How is it that the urine of the sucking calf contains a notable quantity of uric acid, seeing that the same animal, when it grows up and takes its ordinary food, excretes an urine which is devoid of this principle? Why should the simple alteration of food cause such a result if uric acid is formed in the kidneys themselves? Is not this fact completely opposed to the second view? Before endeavouring to explain these difficulties, I thought it desirable to prove the fact, and examined first the urine of two sucking calves. In both I found distinct evidence of the presence of uric acid. At the same time, I discovered another previously unknown fact—viz., that the cow's urine, also under certain circumstances, contains uric acid, as when taking turnips, mangold, brewers' grains and such like food, with little hay or grass, and that, with such a diet, there is little hippuric acid in it. In the horse's urine, which was rich in hippuric acid, I found no uric acid.

At first sight it would appear to follow from these various facts, that the seat of origin of uric acid is further back than the kidneys, and that these organs merely eliminate it from the circulating fluid; in other words, that what we have called the first view is the correct one; but I have already shown, in my first lecture, that the kidneys will not act as filterers of uric acid, even when that principle is known to exist in the blood. Still, difficulties remain against those who advocate the second view, and, until these be cleared away, I cannot feel that this latter has been placed on a satisfactory basis.

Some little time ago, in thinking over the subject of gravel and calculus, I arrived at the idea that, if the urine of man could be maintained in a condition resembling that of the herbivorous mammal, there would be no such things as uric concretions; uric gravel and calculus would be unknown.

Alkaline remedies, useful though they are, do not effect all that could be desired. They do, indeed, as we have seen, hold the uric acid in solution, but in no degree do they remove it, for analysis has shown that the amount eliminated under the influence of alkalies is not at all decreased. While following up my idea of assimilating the urine of man to that of the herbivorous mammal, I made several experiments, to which I will now allude.

I took a specimen of healthy human urine, of full specific gravity, and sufficiently rich in urates to give a free deposit of uric acid crystals when acidulated. With this I filled two tubes to about one fourth of their capacity. To the first of these I added the urine of a horse, so as almost to fill the tube; to the second I added the same quantity of distilled water, in order that the amount of dilution of the human urine should be the same in each tube. After the tubes had been kept for some two or three hours at about 100° Fahr., their contents were examined. A few drops of hydrochloric acid added to the second tube—where water had been used as the diluent—caused a slow crystallisation of uric acid, but the acidification of the first, in which the urine had been diluted with that of the horse, failed to exhibit any precipitation; nor, when it was evaporated to a small bulk, could uric acid be detected either by the murexide or any other test. The experiment was repeated with the substitution of the urine of the lion for that of the horse. This failed to cause the disappearance of the uric acid.

If these observations are correct, we have arrived at a remarkable conclusion, for we have found, not only that the horse's urine is itself free from uric acid, but that it possesses the power of destroying, at least to some extent, the uric acid contained in the urine of man. It struck me that this conclusion was one which might be fraught with weighty consequences, and deserved, or rather demanded, much further and stricter investigation to corroborate it. Such proof, you will find, is not wanting.

I next took eight very small uric acid calculi, none of them larger than a pin's head, and, by the aid of a solution of carbonate of lithium, dissolved them in a little water. To this solution I added about eight ounces of the urine of the horse. After the mixed fluids had been kept some few hours at the temperature of the body, no uric acid could be detected.

This experiment shows that uric acid, in the form of calculi, when first dissolved in an alkaline solution, is destroyed by the influence of some ingredient which is present in the urine of the horse. After reflecting upon these phenomena, I endeavoured to find out what was the principle contained in these urines of the herbivora which imparted to them this peculiar power; and, seeing that they are rich in hippuric acid—a substance absent from the urine of the carnivora—I instituted a very numerous set of experiments upon the action of this acid on uric acid.

First, a strong solution of hippurate of potassium was mixed in equal quantities with a cold solution of the urate of the same metal, and kept for some few hours at the temperature of the body. On subsequent examination for uric acid by the microscopic test, none could be found, nor could any be detected by the murexide test. Another recorded observation is as follows. A cold concentrated solution of urate of ammonia was mixed with a strong solution of hippurate of sodium, made slightly alkaline with the carbonate; after being kept for a few hours at 100° Fahr., no uric acid could be found.

As it might be urged that the uric acid, though existing, was masked by the presence of other matters, the following observations were made, and have been frequently repeated. A cold solution on urate of ammonium was added to one of hippurate of sodium, and the solution made slightly alkaline with the carbonate, so as to imitate as nearly as possible the conditions which exist in the urine of the herbivora. On immediately placing a drop on a microscopic slide, and acidulating it with hydrochloric acid, numerous long crystals of hippuric acid were soon formed, and afterwards rhombic crystals of uric acid were seen, these latter being readily distinguished by their characteristic shape, and by their intense polarising power for light. After about half an hour, the solution having been previously warmed up to the temperature of the body, a second drop was examined, and the uric acid crystals were found to be much less numerous, and, in another hour or so, they were not to be detected at all. The solution was afterwards evaporated, and no evidence of uric acid could be discovered either by the microscope or the murexide test. By this observation, the fact that a change slowly takes place in the solution of the mixed salts is demonstrated; and it is also proved that the uric acid is not simply masked by the presence of other salts, for it is readily exhibited when the solutions are first mixed, and only slowly disappears under the influence of time and warmth.

In the earlier experiments which I made, which were qualitative only, it was found essential that the hippuric acid should be in large excess, in order that the results should be conclusive; but I was soon led to make quantitative experiments, so numerous that their enumeration would be tedious. I shall, therefore, only give you the results obtained and leave the details to be studied elsewhere, if desired.

In these observations I have used the urates of ammonium, sodium, potassium, and lithium, and acted upon them with the hippurates of the same bases, and I have uniformly found that when hippurates and urates are together in solution a change ensues, the urate becoming gradually destroyed, and probably a part of the hippurate also. It has required, under the conditions which have been present in most of the experiments, nearly fifty times as much hippurate as urate for the complete destruction of the urate; but, when the dilution was much increased, the quantity of hippurate required seemed to be lessened, as little as twenty-five parts of hippurate being sufficient. Possibly in the animal body the action takes place more rapidly than in the flasks of the laboratory.

Although my experiments have been numerous, and have occupied a very long time, still I feel that more are required in order that we may arrive at definite conclusions as to the relative power of the different hippurates and urates over each other, and the quantity of

dilution which gives rise to the maximum amount of action—besides which, the nature of the change which ensues requires to be thoroughly investigated. The details of my experiments on the subject are contained in the appendix to a paper recently read to the Royal Society.

Having established the fact that hippuric acid reacts upon uric acid, we can, I think, at once make use of it to explain a difficulty which we left unsolved in our first lecture in relation to the urine of the sucking-calf. We have only to take our original assumption that there are cells in the kidneys of all herbivorous mammals capable of forming uric acid—then, this principle would be always present in the urine unless it was subsequently removed; and having now shown that hippuric acid has a destructive power over uric acid, it follows that, when the urine of a herbivorous mammal contains but little hippuric acid, then uric acid is present. This is the case in the sucking-calf. When, however, the young animal ceases to take milk and lives on a diet of grass, clover, and the like, then the urine becomes rich in hippuric acid, and the uric acid disappears, being removed by the destructive influence of the hippuric acid.

The explanation I consider to be satisfactory, though it is one which I could not, till recently, have imagined to be correct. It is generally supposed that hippuric acid replaces uric acid, that is, is formed in its stead in the system. It does indeed replace it, though not, as is usually thought, by being formed, under certain circumstances, instead of it, but on account of its possessing the power of removing the uric acid after it has been produced in the renal cells. The explanation holds good equally with reference to the occasional presence of uric acid in the urine of the adult herbivorous mammal. Under their ordinary diet a certain amount of uric acid is always formed. Hippuric acid is also present in large quantities, sometimes as much as 1—1.5 per cent., in which case no uric acid can be discovered in the urine; but, when these animals are made to eat food which fails to yield hippuric acid, the uric acid remains intact, and hence it is that, from time to time, we hear of the presence of this principle in the urine of herbivorous mammals.

Now it follows necessarily that what happens in the case of these lower animals, applies also to man. If the quantity of hippuric acid becomes increased, the uric acid becomes diminished, and we are in a position to explain an observation made by Heller, who, in conjunction with a friend, first ascertained the quantity of uric acid which each excreted daily when under an ordinary diet; they then changed the character of their food—Heller living for a week on wheat and rye bread—his friend on rye bread only, water being the sole drink of both. The uric acid soon began to diminish and to be replaced by hippuric acid, and, at the end of the week a mere trace of uric acid was found in Heller's urine—none in that of his friend. During the next week, on an ordinary diet, the hippuric acid gradually diminished and the uric acid reappeared in the former quantities. Doubtless the character of the food, in these experiments, had a direct influence on the formation as well as on the destruction of the uric acid, for the amount of the nitrogenised elements of the food must have been small.

We know that glycine or glycochol (gelatine sugar), which enters into the composition of the bile of many animals, is closely connected with hippuric acid, that this latter can be broken up into benzoic acid and glycine, when boiled with caustic alkali, and, in fact, benzoic acid, when absorbed from the stomach, takes up glycine and becomes converted in the system into hippuric acid and is thus thrown out in the urine. Such being the case, I thought it most desirable to try the influence of this body upon uric acid and to find out whether it plays any part in the change of the uric acid. I made numerous experiments, using glycine in place of hippuric acid, the other conditions remaining the same, and in no instance did I observe any change in the uric acid; even when days or weeks had elapsed. I then had to look to benzoic acid and ascertain whether the change in the uric acid was due to its influence, and for this purpose I completed a set of observations corresponding to those previously made with hippuric acid. The results were as follows:

I found that benzoic acid, in the form of a benzoate, when in contact with an urate in an alkaline solution, caused the same slow change in the uric acid which ensued when a hippurate was employed. This change, however, cannot be well observed under the microscope, because the crystallisation of the benzoic acid is so rapid that the presence of uric acid is obscured; but, when the solution is evaporated and the benzoic acid removed by alcohol, the murexide test can be readily employed. In the appendix to my recent communication to the Royal Society, I have detailed the various observations on this point, which appear to show that about the same

amount of a benzoate as of a hippurate is required in order fully to effect the change in the uric acid.

To us, as physicians, several questions naturally suggest themselves. Can we make any practical use of the facts before us? Will the administration of hippurates or benzoates prove of any practical value in the treatment of the different forms of diseases connected with the uric acid diathesis? Can a diet be devised which will assimilate to some extent the urine of man to that of the herbivorous mammal? These are questions of no little importance to us and to humanity at large.

Let us see how far they may be answered. In January 1842, when a young student, I read a paper before the Chemical Society, which was published in their *Transactions* and in the *Philosophical Magazine* for that year. It was entitled *On the Conversion of Benzoic Acid into Hippuric Acid in the Animal Economy*. In it, I fully confirmed Wöhler's then recent discovery of the conversion of the one acid into the other, but I proved that this change could not be effected by the benzoic acid uniting with the uric acid, as has been suggested; first, because the quantity of the latter was not sufficient; secondly, because the uric acid found in the urine excreted three or four hours after the taking of benzoic acid was not very appreciably diminished.

I also suggested in the paper the probable future synthesis of hippuric acid, and that, if benzoic acid be administered beyond a certain amount, the excess will pass into the urine in an unchanged condition. Both these suggestions have since then been realised.

Within the last few years, I have returned to the consideration of the subject, and have obtained a large amount of clinical experience.

If hippuric and benzoic acids in an alkaline solution possess the power of changing and removing uric acid, it is natural to suppose that, when the blood is in an abnormal state from its presence, the administration of the salts of these acids should prove valuable; for there is no doubt that, if hippurate of sodium be added to a blood-serum which shows the presence of an urate, the latter is soon removed from it. Clinically, I have derived great advantage from the administration of these salts, which I have used very largely in cases of gout; and patients have asked to be allowed to continue taking them, so much did they think they were benefited by them. To us at the present time, it is important to ascertain whether they are of value in cases where uric acid is liable to be deposited in any portion of the urinary tract. This I shall endeavour to do.

In the first place, these salts act advantageously on the mucous membrane of the bladder and its appendages; and, in cases where there is a disposition in the urine to become ammoniacal from decomposition, they are most useful in checking such tendency. You will, perhaps, remember that, in my first lecture, I said that I had found the urine of the horse much less liable to decomposition than that of man, a circumstance possibly due, in part, to its containing hippuric acid. This action on the membrane may influence much the secretion of the colloid matter, and thus prove valuable in cases of gravel and calculus, which are so intimately associated with this colloid; and lastly, it may have an effect upon the excretion of uric acid—a point which I must now endeavour to ascertain.

I have said that the usual absence of uric acid from the urine of the herbivorous mammal is due, not to its non-formation, in small quantities, in their kidneys, but to the presence of considerable quantities of hippuric acid in the urine; and that, provided that we remove this latter principle by an alteration in the food, assimilating it to that of the young sucking animal which takes milk only; or by giving vegetables which do not yield hippuric acid; that then uric acid appears in their urine. Ought we not, therefore, to conclude that the administration of benzoic or hippuric acid would influence the excretion of uric acid? Is this the case? In the herbivora, the urine is always alkaline in reaction; in man, it is acid. In my experiments on the destructive influence of hippuric or benzoic acid upon uric acid, I found it important to use solutions made alkaline with a carbonate, thus imitating, as nearly as possible, the condition of herbivorous urines. We do not get this in the case of man. Let us see the facts. In 1842, when, in a very limited number of experiments, I gave benzoic acid in the free state, I found but little alteration in the excreted uric acid, still it was lessened.

Kerner, who appears to have made a careful set of experiments, came to the conclusion that neither the nitrogenised nor the other principles of the urine were influenced by benzoic acid.

I have recently made some observations on the action of benzoic acid on the urine, with the results which I will give you in a minute. I may tell you that great care must be taken not to form conclusions from one or two experiments, as the excretion of uric acid is always

fitful, little circumstances causing it to be greatly diminished; for a few hours, and then suddenly increased. If the uric acid is directly formed in the renal cells, it is natural to suppose that much of it would escape the action of the hippurates contained in the fluid portion of the urine, and especially if that fluid is in an acid condition; and experiments seem to confirm this idea.

I will here give you the results which I have obtained.

First Set.

The average of four days' urine passed at 12 noon; breakfast at 9 A.M.; specific gravity 1015; diet normal.

5 fluid ounces gave of uric acid 0.63 grains.

After benzoate had been taken 34 hours, and 95 grains taken in repeated doses.

5 fluid ounces gave of uric acid 0.126 grains.

After omitting benzoate 76 hours.

5 fluid ounces gave of uric acid 0.665 grains.

So that, in these experiments, the uric acid appeared to be much diminished by the influence of the benzoate.

Second Set.

Urine at 11 P.M.; dinner at 7 P.M.; no drug taken.

5 fluid ounces gave of uric acid 0.34 grains.

Urine at 11 P.M., after 55 grains of benzoate administered in divided doses.

5 fluid ounces gave of uric acid 0.03 grain.

So that, as far as these experiments go, the uric acid was reduced to one-tenth of its original amount by the action of the benzoate.

Third Set.

Benzoate of soda in 30-grain doses, three times a day. Urine from 11 A.M. to 11 P.M., after having taken benzoate for 12 hours.

Total quantity = 39 fluid ounces.

Uric acid in the 12 hours = 3.90 grains.

Urine before taking benzoate, from 11 A.M. to 11 P.M.

Quantity = 31 fluid ounces. Uric acid = 4.96 grains.

So that the quantity of uric acid was much diminished by the benzoate.

Fourth Set.

Benzoate of soda given in 20-grain doses three times a day. Urine passed from 11 A.M. to 2 P.M., after 60 grains had been taken. Quantity, 5½ fluid ounces; specific gravity 1020; evaporated to 5 fluid ounces.

Total uric acid = 0.17 grain.

Urine passed from 11 A.M. to 2 P.M., after 120 grains of benzoate had been taken. Quantity = 9½ fluid ounces; specific gravity 1016; evaporated to 5 fluid ounces.

Total uric acid = 0.57 grain.

When no benzoate had been taken for 27 hours. Urine from 11 A.M. to 2 P.M. Quantity = 8 fluid ounces; specific gravity 1018; evaporated to 5 fluid ounces.

Total uric acid = 1.00 grain.

When no benzoate had been taken for 51 hours. Urine from 11 A.M. to 2 P.M. Quantity = 12 fluid ounces; evaporated to 5 fluid ounces.

Total uric acid = 1.25 grains.

When no benzoate had been taken for 75 hours. Urine from 11 A.M. to 2 P.M. Quantity = 10 fluid ounces; evaporated to 5 fluid ounces.

Total uric acid = 1 grain.

In this last set of experiments, during the administration of the benzoate, the uric acid was diminished in a remarkable degree.

The results of the preceding observations made with the alkaline benzoates differ from those obtained by myself in 1842, and also from those of Kerner, in 1858, on which occasions benzoic acid itself was employed. Nor is it difficult to explain the discrepancy, for we know that benzoic acid, given by itself, increases the acidity of the urine, as is well shown when it is administered in cases of phosphatic urine; and, under these circumstances, it can possess little or no power of changing any urate it may meet with, in the renal cells or other parts of the urinary tract. I am still engaged in clinically investigating the value of the benzoates and hippurates, both in cases of gout and of gravel and calculus; and I hope ere long to bring the further results before the profession. I can confidently affirm that I have already obtained great advantage in the treatment of these diseases from their employment.

I frequently give the benzoic acid in the form of benzoate of sodium; but, if I wish at the same time to increase the quantity of the urinary excretion, then I give the benzoate of potassium or of lithium; and, if there be an abnormal acidity of the urine, some alkaline citrate.

Seeing that herbivorous animals excrete hippuric acid in a greater or lesser quantity according to the character of the food upon which they are fed, I cannot help thinking that some article of diet might be devised for those who suffer from the diseases above-mentioned, which might, at least to a great extent, keep in check the tendency to form and deposit uric acid.

THE GULSTONIAN LECTURES,

OR

THE STERILITY OF WOMEN.

Delivered at the Royal College of Physicians, February 1883.

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LECTURE III., PART II.—ITS PREVENTION AND CURE.

THE regulation of desire and pleasure cannot be passed over without some remarks. Of the moral condition of those in whom these feelings are absent, or in whom they are in excess, I shall say nothing; and this silence is not because the moral condition is either unimportant or without influence on bodily health and on sterility, but because there is little that requires to be said. The healthy performance of the function of childbearing is surely connected with a well-regulated condition of desire and pleasure; and a well-regulated condition is not a reduction to a minimum or total absence, neither is it excess. I have already said that both desire and pleasure may be, and not rarely are, entirely absent; and it is my opinion, founded partly on the distinct testimony or concurrence of married women who are examples of the evil, that an education, injudiciously ascetic, as it may be called, sometimes produces this deficiency, which is a source of much disappointment and disaster in married life; and this view is corroborated by what is quite certain—namely, that by indulgence the feelings may be, and not rarely are, produced or increased. Writing on sterility, Ambrose Paré gives directions how to increase desire with a view to conception. Equally important is excess of desire and pleasure, and its reduction within moderate limits is equally advantageous. Religion, morals, bodily health, and childbearing all combine to exalt the value and importance of moderation, and to show the evils of absence or of excess. The influence of separation of married people, or of living without cohabitation for a long time—a period, say, of several months—is very widely recognised; and it is probably dependent on the increase of desire and pleasure in those who have little of either, and on the restoration of them in those who have been rendered nearly impotent by excess. This power of separation has appeared to me to be far more frequently operative in women who have had a family than in those who are absolutely sterile; and remarkable examples are not rare.

I have heard and read of, but have not personally witnessed, the disappearance of sterility after recovery from a fever; and this result is ascribed to the prolonged separation caused by the illness. The explanation may be correct, but it does not appear to be the natural one, for fevers are powerfully injurious to general health, and are known to disorder the ovarian and uterine functions.

I have already spoken of sterility as caused by marriage, especially in the young, and we know the sterility of prostitutes and the sterility of confined animals who couple freely or excessively; and it is probable that all these infertilities may have a bond of union in their being due to excessive desire and pleasure, or to excessive sexual indulgence, or to both combined.

In animals, especially in cows and mares, the semen is described as being not rarely expelled from the vagina soon after coitus; and this failure to retain is said to be, in some cases, owing to the animal not being duly in heat. Attempts are made to cause retention by dashing cold water over the buttocks and external parts. A like failure to retain the semen is frequently complained of by women, who describe it as coming away immediately after coitus, and without leaving the horizontal position, or only on getting up. In either case, women often attribute sterility to this failure of retention, and seek a cure of it with a view to fertility. Further, I have repeatedly been distinctly informed by careful women who habitually have this disagreeable imperfection, that conception has