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 II.

(Continued from page 603.)

LET us now study more closely these two forms of renal calculus, and let us begin with the more simple kind. I will select one which is very minute indeed, a mere point of matter; this, when placed in a small cell under the microscope, presented an appearance which is exhibited in the enlarged drawing on the screen.

It is seen to be irregular on its surface, as if composed of a number of little beads or grains aggregated together. Let us now watch the result of putting into the cell a few drops of a solution of carbonate of lithium. After a few minutes, the superficial beads became more or less transparent, and exhibited, in many instances, the appearance of small cells which had been denuded of their contents. The little calculus soon has a translucent ring around it, which becomes broader and broader as the action of the carbonate of lithium spreads, the opacity of the calculus remaining in the centre only. Under the continued action of the lithia-salt, this last remnant of opacity also disappears, and the whole calculus is reduced to a translucent substance, which has the appearance of being made up of a great number of little vesicles. If polarised light be employed, this is seen to contain matter having a crystalline structure; but the still further continued action of the alkaline fluid ultimately removes this too, and the calculus is then seen as a mass apparently made up of colloidal matter in a more or less membranous shape.

In these experiments, as well as in those made on the spheroidal cells of the urinary excretion of the lower animals, I have always employed a solution of carbonate of lithium, which has the advantage of not injuring the membranous structure of the substance; whereas Dr. Carter, in his examination of calculi, appears to have used the solution of potash of the *Pharmacopœia*—a preparation which tends to destroy that structure, and to mask, to a great extent, the character of the changes that occur. In the drawing on the screen are depicted the various appearances exhibited by one of the very minute seed-calculi during the progress of its solution by the lithium-carbonate.

Before proceeding to the examination of the more complex renal calculi, I wish again to draw your attention to the spherules from the excretion of the serpent and the bird, that you may see how they behave under like circumstances. Of course, the largest of these is very much smaller than the minutest calculus that we can make use of; but this fact in no way interferes with the observation of such spherules.

Let us first imagine that we put a particle of the white excretion on a microscopic slide, in a drop of alcohol, which does not alter the spherules; and, after covering it with a thin glass disc, examine it carefully. Then the appearance depicted on the screen is seen; some spherules being large, some smaller, and some smaller still, till at length a size is reached which seems to be the smallest which they are capable of assuming. Next, let us place a moistened finger upon the thin upper glass, and rub it upon the powder for a few seconds, using a fair pressure; then, on re-examination under the microscope, the whole of the spherules have disappeared, and in their place are seen innumerable irregularly-rounded particles of a pretty uniform size.

If, instead of using pressure, we allow the alcohol on the slide to evaporate, and introduce a drop of a solution of carbonate of lithium, and then watch what follows, we shall see that the outlying spherules in the field are usually the first to be acted upon, and exhibit the following appearances. After a few minutes, some of the spherules show a transparent line around them, which, on close examination, is seen to be composed of transparent beads; this ring grows larger and larger, so that, in a short time, no opacity

remains, save in the centre of the spherule. As time goes on, with renewed application of the alkaline solution, the dark central mass gets smaller and smaller, and at last altogether disappears, our original spherule being changed into a round membranous mass, without definite structure, containing crystalline matter which powerfully polarises light, which matter also in turn gives way under long-continued action of the lithia solution.

If we compare this description of what I may call the "dissolving view" presented to us by the changes in the normal spherule of the bird or reptile, with that before given of those which occur in the small or rudimentary calculus, we cannot help being struck by their close resemblance; in fact, whatever differences there may be, seem to be little more than differences of degree. Surely this must make us reflect on the possibility of there being a close relationship between the two, and may fairly suggest to us the question whether the rudimentary uric calculi found in man may not be merely aggregations of spherules—the product of the original cell-formation of the uric acid. In the case of the bird and reptile, we are sure that the spherule cannot have been deposited from uric acid previously dissolved in the urine, seeing that there is no such fluid to dissolve it; and it may be that, in the case of man also, the individual components of these calculi are simply the original cell-formations of uric acid, which have become somewhat altered in chemical composition, and rendered less soluble. If this be true, and if we can show that these rudimentary calculi are not produced by the precipitation of uric acid from the urine, we must at once remove them from that class of deposits which are called sand or gravel, seeing that these latter, whatever their size, have an altogether different structure. It is to the spherular grains and the more complex structures that I shall confine the name of renal calculi.

Dr. Prout, in his description of an uric acid calculus, speaks of the centre of uric calculi as non-crystalline in character.

In several renal calculi which I have examined, I have found some spherular bodies—masses of irregular shape, resembling much the partially broken-up pyramids, into which the spherules of the excretion from reptiles and birds frequently split when carefully rubbed and only partially disintegrated. I have also found crystals of oxalate of calcium, many of them octahedral in shape. From these examinations, I have formed the opinion that the appearances in the nucleus may arise from a slow alteration taking place in the first-formed or spherular urates, by the action of the fluid urine upon them, causing the gradual decomposition of the original ammonia salt, and an increase of its insolubility, leading, also, to the subsequent production of oxalate of calcium, which, we know, is the result of the action of a ferment on uric acid.

I may here state that I have often found that the excretion of reptiles and birds, when acted on for a long time by weak solutions of carbonate of lithium, leave a residue consisting of the organic or colloidal matter, mixed with crystals of oxalate and carbonate of calcium, and that these are often in the spherical form.

If, instead of a very small and rudimentary calculus consisting merely of an aggregation of grains, we take one of a larger size and more complex structure—one, for example, one-eighth or one-sixth of an inch in diameter—we find that, around this granular central nucleus, layers are arranged in concentric order, that is, the calculus becomes laminated, the number of layers depending greatly on the length of time during which it has been exposed to the action of the urine. These layers vary much in thickness, and also in colour, and probably are most of them originally composed of some urate rather than uric acid itself. The subsequent action of an acid urine on a deposited layer of an urate would often slowly reduce the urates into a state of free uric acid. In examining renal calculi which have this laminate arrangement, I have frequently found the central nucleus almost devoid of colour, and very different in this respect from the surrounding layers, which are generally of a pale or dark fawn colour. What is the cause of this peculiarity of the nucleus? The only explanation which at all satisfies my mind is, that the nucleus-granules have never been in a state of solution since they were formed in the kidney-cells, and, therefore, have never become re-crystallised with the colouring matter of the urine; in fact, that they are in a condition very much like that of the renal spherules of the lower animals. The colour of the layers is not at all difficult to explain; for, whenever uric acid or urates are deposited from solution, they invariably take with them the colouring matter of such solution, which becomes intimately united with the crystalloid, giving it an altered shape. Thus it appears to me that we have a rational explanation, both of the pale appearance or absence of colour in the nucleus and of the colour of the different layers which surround it.

I have now given my ideas on the subject of the formation of uric renal calculi, but I would wish them to be looked upon as such only—not as demonstrated facts. My object will be accomplished if they cause pathologists to reconsider their preconceived views, and if they become a starting-point for new investigations. It must, I think, be confessed that, up to the present time, the explanations of the origin of calculi have been either, on the one hand, most erroneous, or, on the other, most unsatisfactory.

Influence of Diet.—There can be little doubt that the occurrence of gravel and calculus is largely influenced by the diet; but on this subject I feel sure that the opinions frequently held are not altogether correct, and require to be reconsidered. As we shall find in our next lecture, that a gouty diathesis is so potent in the production of the diseases under review, it will be quite safe, in so far as the discussion of food is concerned, to assume that what tends to produce gout tends also to develop calculus, and that the diet which is of avail in the treatment of the one disease is equally so in the management of the other. It will be desirable to turn our attention to the principal groups of aliments, and ascertain what influence they have, not only upon the formation of uric acid, but also upon its condition with respect to solubility.

1. *Sugar.*—Much has been said about sugar as an article of diet in uric acid affections; and, of what has been said, much is certainly devoid of foundation. Nothing is more common than for a patient to tell one that he always avoids sugar, and looks upon it as a poison to the system, and a principle to be altogether shunned.

How do the facts stand with regard to sugar?

There are three kinds, which are commonly met with in different articles of food: (a) *Cane-sugar*, which, although it is most commonly seen and most largely cultivated as a separate article of diet, is yet much less common than (b) *Glucose*, or grape-sugar, which so extensively pervades the vegetable kingdom; and (c) *Lactose*, or milk-sugar, is a third kind, which gives the slight sweetness to the milk of different animals. These three forms of sugar are very closely allied to each other, both in physical properties and in chemical constitution. Cane-sugar, when warmed with a trace of mineral acid, is resolved into glucose, and undergoes the same change when taken into the stomach. Grape-sugar is also closely allied to starch; and the latter, under the influence of many chemical agents, and when taken into the alimentary canal, passes through the stage of dextrine into that of glucose. Both cane and grape-sugar are prone to undergo the alcoholic fermentation, and to be resolved, chiefly into carbonic acid and alcohol. Milk-sugar, or lactose, undergoes the alcoholic fermentation only indirectly, and much less quickly than glucose; still, milk does ferment with yeast. On the other hand, lactose is apt to undergo another change, and to be directly converted into lactic acid, with the production of some butyric acid. Besides these three, there are some other sugars existing in small quantities in the animal body; but these need not occupy our time.

The most common of the non-nitrogenised principles contained in food is starch, seeing that it forms seventy per cent. of wheaten flour; and almost the whole of many of the simple amylaceous articles of food, as rice, maize, arrowroot, tapioca, sago, etc.; also of the potato, turnip, carrot, and so on, when these latter are dried. It can be shown that, when taken into the alimentary canal, starch is soon changed into glucose-sugar by the action of the saliva and pancreatic juices; and, when cane-sugar is taken, the same change ensues—so that, however carefully sugar is avoided as an article of food, it is still abundantly formed in the canal when amylaceous matters are eaten; and the result is the same whether a pound of starch in any of its dietetic forms, or a pound of cane-sugar, be taken, glucose-sugar being formed in both instances.

There is a very popular idea that sugar causes what is termed acidity, and hence it is scrupulously avoided by many. Is this true? Between two and three years ago I was much struck at seeing an American surgeon of great repute, putting lump after lump of white sugar into his tea, and I asked him why he did so. He told me that, in the States, it is a common habit to take sugar thus as a preventative of heartburn, and that he took it for that purpose. His answer made a strong impression on my mind, and since then I have often questioned dyspeptic patients as to their experience on this point. At first nearly all exclaim, "Of course sugar causes acidity," but as yet I have failed to find anyone who could assure me, from personal experience, that the eating of lumps of ordinary white sugar produces more so-called acidity than taking any other article of diet. Many of us probably know that the eating of a dry biscuit is often followed by the same symptoms in a severe degree. It must be borne in mind that I do not for a moment include sweetened

fruits, and such-like substances in the same category as simple sugar. One can hardly believe that the eating of a lump of cane sugar would seriously add to the glucose which is daily produced in the alimentary canal of an individual living on an ordinary mixed diet. Let us see what has been found experimentally with regard to the influence of sugar on the production of uric acid. Böcker says that the effect, in man, is to lessen the quantity of that principle, and Bischoff and Voit have proved that, in dogs, starch produces the same effect on the urinary excretion as sugar, so I think we may say that there is no increase in the uric acid when sugar is taken. When, however, sugar is given to an animal along with a fixed amount of nitrogenised food, it causes a marked diminution of the eliminated nitrogen and, at the same time, a great augmentation of the weight of the animal; so that there is no doubt as to the influence of sugar and amylaceous matters in fattening; they act in fact by preserving the protein compounds from undergoing such rapid metabolism as otherwise would take place.

Although the uric acid is not increased but rather diminished by sugar, may not the taking of sugar cause that principle in the urine to assume a less soluble form? May it not develop a greater amount of free acid in the urine? Dr. W. Roberts asserts that the acidity is not increased either by cane sugar or by honey, which chiefly consists of glucose, and I know of no observations which indicate that the urine is rendered more acid by the taking of this extensively diffused article of food. The same negative result, as to the acidity of the urine, has been observed in the case of fresh fruits, nay more, Wöhler has found that cherries, apples, and strawberries either diminish the acidity or even cause alkalinity, through the conversion of the vegetable salts which they contain into the carbonates of the same bases. As we proceed we shall meet with other proofs that sugar does not necessarily influence the production of the diseases under consideration.

I must devote a few minutes to the discussion of a most important subject, viz., the influence of different alcoholic beverages on the production of uric gravel and renal calculi. We must remember that all such beverages contain alcohol united with different proportions of water; some little more than this, others, however, contain sugar, together with colouring and so-called extractive matters, also salts of potash and lime, united with vegetable or mineral acids. Many wines, also, contain a certain amount of some free organic acid. It is necessary to investigate the influence of the most important of the constituents of these beverages upon the urinary secretion, and first let us take alcohol itself.

1. *Alcohol.*—According to the experiments of Böcker and Hammond, the uric acid appeared to be slightly increased in quantity by the taking of alcohol, and even this is matter of doubt, and, on the whole, its influence on the production of that principle may be regarded as inconsiderable, nor is there any reason to suppose that it sensibly affects the acidity of the urine.

2. *Distilled Spirits.*—In the various distilled spirits, as brandy, rum, gin, and whisky, there are found very small quantities of different ethers and essential oils, which, doubtless, modify to some extent the action of the alcohol on the different functions, but cause no essential alteration in the constitution of the urine.

3. *Wines.*—The various kinds of wines, although they possess one character in common, viz., the presence of oenanthic ether, still differ from each other in many important particulars, so that, to ascertain their properties and their influence upon the production of calculus and gout, we must group them into at least two classes.

In the first division we have the natural light wines, in which the alcohol is small in quantity, not more than 10 per cent., and in which the fermentation has been allowed to proceed till the whole of the sugar has become destroyed. These wines are rich also in acid tartrates, and in racemates.

In the second division we may place the Peninsular wines of Spain and Portugal, the wines of Sicily and Madeira, and Champagne and the other sparkling wines. These all contain a considerable quantity of sugar, owing to the arrest of fermentation which has been induced by the addition of distilled spirit, for it must be remembered that the process of fermentation is stopped when 12 per cent. of alcohol is developed. In this class of wines there is a marked absence of the vegetable salts, which become insoluble on the addition of the spirit, forming the well-known crust deposited on wine casks, which is known in commerce under the name of argol.

Besides these two divisions, there are many wines which are more or less of an intermediate character; some, in their properties, approaching to our first, others to our second group.

In each class of wines we also find some which are white and

some which are red, the difference depending on the presence or absence of the colouring matter derived from the inner surface of the grape-coat. In many of the inferior wines there also exists much free acid, arising from the setting-in of the acetic fermentation.

The question now arises, have we any facts with regard to the special effects of different wines in the diseases which we are now considering? I think we have many, and much information which we can use to guide us in the prevention of such diseases. With regard to gout, our knowledge under this head is considerable, and this may serve as a pretty accurate guide in the case of calculus, seeing how close is the connection between that disease and gout, though I must not for a moment be supposed to say that all the causes which lead to the one form of disease must necessarily produce the other.

It may, as I believe, be confidently asserted, with respect to gout, that, with an absence of alcohol in any shape, coupled with an absence of hereditary predisposition derived from alcohol-drinking ancestors, the disease would be practically unknown; and that Noah, in planting his vineyard and drinking the wine thereof, laid the foundations of much misery for his descendants.

It is most essential to separate the different kinds of alcoholic beverages from each other in estimating their tendency to produce disease. Thus alcohol in the form of distilled spirits, although, when taken in excess, it causes serious mischief, injuring the liver, kidneys, heart, and other organs, still has little or no power of producing the uric acid diathesis, or, at any rate, the gouty development of it. In spirit-drinking countries, or among spirit-drinking families, gout is unknown. Look at Scotland and its whisky-drinking classes—and they are said not to be too sparing in their potations—the disease is practically absent; hardly ever seen in the hospitals. Look at Poland, where they drink a kind of arrack; the same holds good. A physician from Warsaw, to whom I was once showing some cases of gout in my hospital wards, said that he was peculiarly interested in them, as it was the first time he had ever seen examples of this disease; and, in connection with this, I may mention that, not only does spirit by itself fail to cause gout, but the combination of spirit and sugar is harmless in that direction; for toddy, I am told, is usually a sweet beverage.

When, however, we investigate the influence of wines, we shall find a different result. Drinkers of the common light wines, such as the red Bordeaux and the Rhine wines, suffer but little; while, among the same nations, those who indulge freely in beer, as do the inhabitants of Berlin and Munich, for example, are by no means free from evil results to their health.

Experience shows, with respect to the influence of the different kinds of wines, that the natural light wines, in which the alcohol is small in amount, while there is an almost complete absence of unfermented matter, which contain also a considerable quantity of acid vegetable salts, are little liable either to produce gout, or to lead to the formation of calculus or gravel.

On the other hand, the Peninsular wines, and those which resemble them, which are stronger in alcohol, contain much unfermented matter, and are almost devoid of the vegetable salts, have great gout-producing power, and, at the same time, lead readily to a condition of urine favourable to the production of gravel and calculus.

4. *Malt Liquors*—Ale, Beer, Stout, and Porter.—We come, lastly, to the malt liquors—ale, beer, stout, and porter. In the manufacture of all of these, the fermentation is arrested at a particular period, so as to leave what is called a "body"; in that they are but partially fermented, they resemble, therefore, the Peninsular wines. Now, from my own experience, and I believe it is also the experience of all who have attended to the subject, I can confidently assert that these beverages have a great tendency to produce the uric acid diathesis. Compare the hospitals of Edinburgh and Glasgow with those of London. In the former, gout is scarcely known; in the latter, the disease is common, the difference, as I believe, being chiefly due to the different beverages drunk by the working classes of the two countries; it is, in fact, the difference between whisky and malt liquors.

It has been shown, therefore, that alcohol, in the form of distilled spirit, although it is capable of producing the greatest mischief, does not cause calculus or gout, and that the lighter and more fully fermented wines are comparatively free from such power for harm; while, on the other hand, the imperfectly fermented wines, such as port, sherry, madeira, marsala, and champagne, as well as all malt liquors, are most prone to induce the different forms of disease which are the manifestations of the uric acid diathesis. It is now necessary that we should at least endeavour to ascertain what

principle or principles, present in some of these alcoholic beverages, absent from others, lead to the development of this diathesis, or aggravate it when it is already manifested, owing to hereditary or other causes.

It cannot be the alcohol alone. This, I believe, can be fully and satisfactorily proved, seeing that large groups of people whose custom is to drink freely of distilled spirits are yet free, instances are to hand in Scotland, Sweden and Norway, and Poland. It cannot be the sugar alone; for, although the partially fermented wines and malt liquors contain sugar, yet sugar, added to distilled spirit, does not appear to produce the uric acid diathesis. It cannot be the acidity alone, for the wines which are most harmless, are quite as acid, or even more so, than malt liquors and the Peninsular wines, and many people, who strongly object to the least acidity in wines, will, nevertheless, often take lemon-juice to an extravagant extent.

If, then, neither the alcohol, nor the sugar, nor the acidity, by itself is the cause of certain beverages proving so injurious, is it a combination of any of these that does the harm? We already know that the combination of alcohol with sugar, and that of alcohol with acid salts, are innocuous as far as the uric acid diathesis is concerned. What, then, is there left for us to fall back upon in explanation of the peculiar properties which some of these beverages possess, while others are devoid of them? The only conclusion that I can arrive at, with my present knowledge—and it is the result of much thought during many years—is that it is something which is a result of imperfect fermentation, and you will find that it is those beverages in which fermentation has commenced, and has been allowed to proceed to a certain extent and has then been checked, which, of a certainty, cause gout, and, probably, lead also to the production of gravel and calculus. If I am asked to state more exactly what this principle is, I cannot do so; it may be an influence only, a condition of matter, a ferment. At present it is a mystery to me.

In connection with this subject, however, I must return for a moment to that of sugar, which I told you had, as I thought, been regarded askance without due cause.

I would say that I do not, for a moment, classify with sugar either sweetened fruits or vegetables; for I am quite sure that such articles of diet will frequently produce heartburn and other dyspeptic annoyances in individuals who are not in the least inconvenienced by sugar itself. I cannot help thinking that these contain a *something* which is not simple sugar, but a substance which is the result of the long contact of the sugar with the fruit or vegetable juices—a kind of semifermented matter; in fact, that same something which exists in the stronger wines and the various malt liquors. Of this I feel confident, that in many cases where sugar, whether by itself, or in tea, coffee, and light puddings, does not disagree, and where fresh fruit, although sweet, produces no discomfort, the combination of sugar with these juices, if time has been given for them to act upon each other, will often cause well-marked dyspeptic symptoms.

But it may be said: If so, a ripe orange cannot be a good thing to eat, as it contains both sugar and acid juice, and these substances have been in contact with each other for a long time. I answer: Not necessarily so. So long as the orange exists as a fruit, with its botanical structure intact, so long there may be no change taking place between the different constituents. We have a striking analogy to this in the case of the bitter almond. When whole, this seed contains the crystalline amygdaline and an albuminous ferment. Separate one of these from the other, and each, by itself, is innocuous; crush and moisten the almond, prussic acid is immediately formed, and the union of the two principles is the production of a deadly poison.

VACCINATION.—Dr. Lionel A. Weatherly of Portishead, Somerset, has received a third grant from the Local Government Board for efficient vaccination.

PAPER labels may be removed from bottles by wetting the surface; then hold for an instant over any convenient flame. The steam penetrates the label at once, and softens the paste.

In the *Gazette Hebdomadaire*, M. Vigier states that camphor may be perfectly suspended, and become easily divisible, by the following formula:—Camphor, 15 grains; gum arabic, 30 grains; one yolk of an egg; and two ounces of decoction of linseed.

VACCINATION.—Mr. W. Blackburn of Uppermill, Saddleworth, has lately received a Government grant for successful vaccination in his district.