THE CROONIAN LECTURES ON THE CHEMISTRY AND THERAPEUTICS OF URIC ACID GRAVEL AND GOUT.

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LECTURE II.—CHEMISTRY OF URIC ACID GRAVEL: PROPHYLACTIC TREATMENT.

In the preceding lecture I gave an account of those points in the chemistry of uric acid and the urates which seemed to have a bearing on the subject matter of these lectures. I showed that there were three orders of uric acid salts, that in addition to the neutral urates and biurates, which had long been recognised, there existed a third order, namely, the quadriurates, which in reactions and chemical constitution differed widely from the other two. It was pointed out that the neutral urates, from their mode of origin and reactions, could not, with our present knowledge, be regarded as having any possible concern in the vital history of uric acid. It was also pointed out that the biurates, although known to us pathologically as constituents of gouty concretions, were not really known to us with certainty as physiological constituents, either of the blood or of the urine. On the other hand, it was shown that the quadriurates existed normally in human urine and in the urine of birds and serpents; and it will be demonstrated later on that when uric acid is brought into relation with the bodily fluids—with the blood, lymph, and synovia—it enters into solution in the first instance, not as neutral urate, nor as biurate, but as quadriurate. From all these considerations it would appear that whenever and wherever uric acid exists in the healthy organism it exists exclusively as a quadriurate. The quadriurates may therefore be regarded as being in a special sense the physiological salts of uric acid, and as constituting the only form in which uric acid subsists in the living body in the normal state.

I now proceed to consider more particularly the state of uric acid in human urine—the conditions which surround it, and the factors which tend to determine its precipitation or to prevent its precipitation in that fluid.

Inherent Tendency of Urine to the Spontaneous Liberation and Precipitation of its Uric Acid.—The chemical reactions and physical conditions which are concerned in the production of uric acid concretions are both varied and complex. Uric acid exists in the urine in combination with the alkaline bases. In perfect health these combinations maintain their integrity, not only while the urine is detained in the urinary channels, but even for some considerable time after it has been discharged. This, however, is not always the case. In certain contingencies these combinations are prematurely decomposed, their uric acid is set free, and is precipitated from the urine in the crystalline form. In calculous subjects this event takes place in the kidneys or bladder, and gives rise to the incidents of gravel. In less urgent instances, the precipitation takes place soon after the urine is voided, in the form of copious urinary deposits; but, apart from these pathological cases, and cases which hover on the pathological borderland, it may be shown that perfectly normal urines betray the same tendency. A considerable series of observations were made on this point with the urines of persons who were entirely free from any proclivity to calculous disorders. It was found that all acid urines, provided they were guarded against septic changes, invariably deposited their uric acid sooner or later. The time of the occurrence of the precipitation varied greatly: it usually began within twenty-four hours after the urine was voided, sometimes in a day or two, and sometimes it was delayed for a week or even longer. When the process was at length completed, whether that was early or late, all the uric acid had disappeared from solution; the filtered supernatant urine gave not the slightest

precipitate with hydrochloric acid, nor could there be detected in it, on evaporation to a small bulk and with careful search, any trace of uric acid. We must therefore recognise in normal acid urines an inherent tendency to the liberation and precipitation of their uric acid. This tendency only assumes a morbid significance when the event occurs prematurely, while the urine is still sojourning in the kidneys or bladder. Viewed in this light, pathological gravel may be regarded as due to an exaggeration of conditions which prevail, in a less pronounced degree, in the normal state; and an elucidation of these conditions may be reasonably expected to throw a light on the etiology of gravel and calculus, and perhaps furnish hints which may be turned to therapeutical uses.

Chemical Explanation of the Spontaneous Precipitation of Uric Acid in Urine.—The chemical reactions which are concerned in the spontaneous precipitation of uric acid in acid urines are very interesting to trace out. It is certain that uric acid always subsists in the unchanged urine as a quadriurate. The urine in which this substance is dissolved is a watery solution which contains a number of mineral salts. Among the salts the most important, in regard to the point under consideration, are the alkaline phosphates. These regulate, in the main at least, the reaction of the urine. The phosphates easily oscillate between the monometallic forms, or superphosphates, which have an acid reaction, and the dimetallic forms, which have an alkaline reaction. When the former preponderate, as is usually the case, the urine is acid; when the latter preponderate, the urine is alkaline.

We have, therefore, in an acid urine the quadriurate existing in the presence of water and of superphosphates. These conditions ensure the ultimate complete liberation of the uric acid. The first step in the process is the splitting up of the quadriurate by the action of the water of the urine into free uric acid and biurate. By this reaction half the uric acid is set free. But the biurate resulting from this reaction is immediately retransformed in the presence of superphosphate, by a double decomposition, into quadriurate. Two atoms of biurate with one atom of superphosphate (monometallic phosphate) change into one atom of quadriurate and one atom of dimetallic phosphate, according to the subjoined equation:—

These alternating reactions—breaking up of quadriurate by water into biurate and free uric acid and recombination of quadriurate by double decomposition of biurate with monometallic phosphate—go on progressively until all the uric acid is set free.¹

THE INGREDIENTS WHICH RETARD THE DECOMPOSITION OF THE QUADRIURATES IN NORMAL URINE.

Uric acid, as I have said, exists in the urine in the form of quadriurate, and when the urine is secreted with an acid reaction, that is to say, for some 16 or 20 hours out of the 24, this compound exists amid conditions which, if they stood alone and uncontrolled, would lead to speedy precipitation of uric acid in the free state. But in the normal course no such speedy precipitation occurs, it only occurs as a remote and postponed event after the urine has been voided. It is obvious, therefore, that the urine contains certain ingredients which inhibit or greatly retard the water of it from breaking up the quadriurates. Were it not for the presence of these inhibitory ingredients uric acid would be thrown out daily in the urinary passages and everyone would be subject to gravel. Hence an inquiry into the nature of these inhibitory agents has a pathological as well as a physiological interest, and bears directly on the etiology of calculous disorders. The inquiry is not a simple one. The urine is a very complex fluid. It contains besides urea a number of saline constituents, together with pigmentary and other extractives. Where, among all these, are the inhibitory agents to be found?

Attention was first directed to the saline constituents. It was found that when urine was dialysed, whereby its crystalline ingredients were for the most part removed, it lost to a considerable extent its power of retarding the decomposition

¹ For full proof of this reaction I must refer the reader to my paper "On the History of Uric Acid in the Urine."—*Med.-Chir. Trans.*, vol. 73, p. 238

of the quadriurates. This observation indicated that the inhibitory power resided, partly at least, in the crystalloids of the urine. The chief crystalloids of the urine are urea, and the chlorides, phosphates, and sulphates of potash, soda, ammonia, lime, and magnesia. Solutions of these several substances in distilled water were prepared, and their effect on the quadriurate was tested in the following manner. A speck of a purified specimen of the amorphous urate deposit was placed on a glass slide, and intimately mixed with a drop of the solution to be tested. The covering glass was then applied, and the result watched under the microscope. The time at which crystals of uric acid began to make their appearance was taken as a measure of the activity of the tested solution in decomposing the quadriurate. The standard of comparison was distilled water, which usually caused crystals to appear in five minutes. Solutions of urea of various strengths acted precisely with the same speed as distilled water. It was obvious that urea had no share in the power resident in urine of retarding the decomposition of the quadriurate. The chlorides and sulphates, in the proportion of 1 per cent. and upwards, imparted to water a considerable power of delaying the appearance of crystals. The potash salts were found to have more effect in this respect than the corresponding salts of ammonia and soda. The common disodic phosphate (rendered perfectly neutral to test paper by the addition of phosphoric acid) showed about the same inhibitory power as sodium chloride. None of these solutions, nor any admixture of them approached the natural urine in power of postponing the decomposition of the amorphous urate. More pronounced effects were obtained with the dipotassic phosphate. A solution of this salt containing only 0.2 per cent., and, perfectly neutralised, appeared to act almost as slowly on the deposit as a normal acid urine. Urines which were alkaline from fixed alkali had absolutely no decomposing effect on the amorphous urate.

Attention was next turned to the colouring matters of the urine. The amorphous urates have an intense affinity for urinary pigment; the pigment cannot be removed from them by any solvent which does not at the same time destroy their integrity. I had noticed that deeply-tinted urates were more slowly decomposed by water than pale-coloured urates. It had also been noticed that artificially-prepared quadriurates, and the quadriurates which constitute the urinary secretion of birds and serpents, all of which are devoid of colouring matters, are much more quickly broken up by water than the natural amorphous urate, which is always more or less tinted. Moreover, it was found that a urine which had been filtered through animal charcoal, and thus deprived of its pigment, acted very much more rapidly on the amorphous urate than the same urine before it had been filtered through charcoal.

It can, therefore, scarcely be doubted that the pigments of the urine play an important part among the ingredients which impart to normal urine its remarkable power of retarding the decomposition of the amorphous urate. In the febrile state, and in other wasting disorders, the urine is sharply acid and rich in urates, and yet such urines are not prone to deposit free uric acid, though very prone to deposit amorphous urates. In these cases the urine is always deeply coloured, and the pigments are probably the chief agents which prevent the precipitation of free uric acid under these circumstances.

CHEMICAL ETIOLOGY OF URIC ACID GRAVEL.

The more remote and predisposing causes of gravel do not come within the scope of the present inquiry. Whatever these causes may be, they must be translated into changes in the composition of the urine before they can determine the occurrence of calculous accidents. No amount of morbid proclivity to uric acid gravel can take effect if the urine be alkaline, nor if the proportion of uric acid in it fall below a certain point. The causes which will be here considered are those which lie exclusively in the chemical constitution of the urine itself.

I have just given proof that the salines and pigments of the urine exercise a protective influence against premature precipitation of uric acid; and it may hence be inferred that a diminution of these salines and pigments may sometimes act, in a negative manner, as a determining factor in the production of gravel and stone.

Poverty of the urine in saline matters is probably an influen-

tial factor in the disproportionate frequency of stone among the children of the poor as compared with the children of the easier classes. The prevalence of stone among the natives of India is also probably to be explained in the same way. The children of the poor are fed largely on farinaceous articles—bread, gruel, oatmeal, and potatoes, with but a scanty allowance of milk, meat and fish. Wheat flour contains only 0.51 per cent. of mineral matter in proportion to the totality of the dry substance; oatmeal only 2.50 per cent.; potatoes only 2.50 per cent.; whereas milk contains 5.50 per cent., and the various forms of meat and fish 5 to 5.50 per cent. Rice, which forms so large a part of the diet of the natives of India, only contains 0.39 per cent. of mineral matter in proportion to the totality of the dry substance of the grain. These enormous differences in the amount of saline ingredients in the articles of food must, of course, make a corresponding difference in the proportion of the saline constituents of the urine, because saline matters pass out of the body almost exclusively through the kidneys. On the other hand, the well-known immunity enjoyed by sailors from stone and gravel depends, no doubt, as Mr. Plowright has shown, on the prodigious quantity of salt which seafaring men habitually consume with their food. The same observer has pointed out that the dwellers in a district of Norfolk called Marshland, where the drinking water is brackish, are singularly free from stone, as compared with their less fortunate neighbours in the adjacent districts of that county.²

Deficiency of Pigment in the Urine.—In chronic Bright's disease, with contracting kidneys, the urine is conspicuously pale, and is often, indeed, almost entirely devoid of pigment. There is no excess, but rather a diminution, of uric acid in the urine in these cases; nevertheless, deposits of uric acid are by no means uncommon, and sometimes actual renal gravel occurs. The percentage of salines is also low, and this doubtless contributes to the result; but probably the prepotent factor in the precipitation of uric acid in these cases is the deficiency of pigment in the urine.

Poverty of the urine in salines and pigments, however, only accounts for certain limited groups of calculous cases. There are other and larger groups, in which the urine is neither defective in salts nor in colouring matters. The subjects of calculous disorders among the easy classes—especially those of a gouty type—usually void a urine which is full coloured and abundantly rich in salts, and we must seek in some other direction for the cause of the morbid tendency. In these cases the chief determining factors are, I believe, to be found in the proportion of uric acid in the urine, and in the degree of acidity of the urine.

The influence of these two factors was investigated by a method which approximates pretty closely to the conditions of the actual clinical problem. In the earlier part of the lecture I showed that normal acid urines tended to deposit uric acid sooner or later, and the inference was drawn that this inherent tendency was the same in kind, though less pronounced in degree, as the tendency existing in pathological gravel. If this inference be well founded, it follows that the controlling factors in the two cases are similar, and that the conditions which hasten or retard the precipitation of uric acid in a sample of urine preserved in a test tube, would, if they could be made applicable, hasten or retard the precipitation of uric acid in the urinary passages. The mode of experimentation was as follows: A series of test tubes were each charged with 10 cubic centimetres of a normal acid urine. One of them was a control tube, and had no addition made to it. To the others additions were made of known quantities of various substances, of which it was desired to know the effects on the time of onset of uric acid precipitation. The contents of the tubes were protected against decomposing changes by the inclusion of a few drops of chloroform. The tubes were then corked and placed in the warm chamber at blood heat. The tubes were frequently examined, and the time when uric acid began to be deposited was noted. When the experiment was finished, the acceleration or postponement of precipitation in the several tubes, as compared with the control tube, was computed.

Proportion of Uric Acid in the Urine.—A sharp distinction must be drawn between the proportion, or percentage, of uric acid in the urine and its rate of secretion, that is, the total quantity excreted per hour or per day. The proportion of uric acid in the urine bears no constant relation to the rate of its excretion by the kidneys. During the digestion and absorption of food the hourly discharge of uric acid reaches its highest level, but its percentage in the urine is usually not high, owing to the fuller volume of the urine at this time. On the other hand, after prolonged fasting and during sleep, the hourly discharge of uric acid sinks to its lowest point,

² See a paper by Mr. C. Plowright, of King's Lynn, in the *Medical Times* for October 10th, 1885.

but its percentage in the urine touches its highest pitch. Again the occurrence of uric acid gravel is not a reliable proof of an excessive output of uric acid; and it is certain that individuals may habitually discharge a daily amount of uric acid considerably beyond the average, and yet be quite free from the symptoms of gravel. Nor is such an occurrence even a sure indication that the urine contains an undue percentage of uric acid. Cases are sometimes encountered in which the urine is caught, as it were, in the very act of depositing uric acid gravel; cases in which the urine, as it is voided, sparkles with crystals of uric acid. On four occasions I have been able to estimate the uric acid in such urines. The results are shown in the following table:

TABLE VIII.—*Showing the Percentage of Uric Acid in Four Urines which were in the Act of Depositing Uric Acid at the Moment of Emission.*

No. 1 contained	0.084 per cent.	of uric acid.
" 2 "	0.076 "	" "
" 3 "	0.032 "	" "
" 4 "	0.022 "	" "

In the first and second cases the percentage of uric acid greatly exceeded the average; in the third case it was slightly below the average; and in the fourth case it was very much below the average.

Notwithstanding all this, it would be an error to suppose that the quantum of uric acid excreted per day and its proportion in the urine are without influence on the formation of urinary concretions. It stands to reason that persons who daily void an excessive amount of uric acid must be more liable than those who only void the normal quantity to crises in which the percentage of that substance rises above the average, and it is susceptible of proof that, other conditions being favourable, a high percentage of uric acid in the urine becomes a potent factor in the determination of uric acid precipitation. The following observations may be taken as evidence on this point: A healthy urine which had deposited a copious sediment of amorphous urates in a urine glass was divided into two equal portions, A and B. A consisted of the lower portion, which contained the deposit; B consisted of the upper or supernatant portion. Both portions were warmed to blood heat, and became thereby perfectly transparent. Both portions were identical save in one respect, namely, that A contained a much larger percentage of uric acid—in the form of quadriurates—than B. The specimens were then tested by the method above described. Four test tubes were charged each with 10 c.c. of urine composed as follows:

Test tube No. 1 contained A alone; No. 2 contained equal volumes of A and B; No. 3 contained three volumes of A and seven volumes of B; and No. 4 contained B alone. The four test tubes were then corked and placed in the warm chamber at blood heat. The following table exhibits the times at which uric acid began to precipitate in the several test tubes:

TABLE IX.—*Showing the Influence of the Percentage of Uric Acid on the Time of Onset of Uric Acid Precipitation.*

Contents of the Test Tubes.	Time when Uric Acid began to be precipitated.
No. 1 contained A alone	2 hours
No. 2 " equal volumes of A and B	4 "
No. 3 " 3 vols. of A and 7 vols. of B	8 "
No. 4 " B alone	20 "

Grade of Acidity of the Urine.—The degree of acidity of the urine exercises, as might have been expected, a powerful influence on the time of precipitation of uric acid. In some cases of gravel I found the acidity of the urine fully twice as high as the normal average; in two such cases the urine was found to decompose the purified amorphous urate as rapidly as distilled water; but when its acidity was reduced to the normal level by the addition of sodium carbonate, it had then no more power in this respect than healthy urine, showing clearly that in these cases the determining factor in the disorder was solely excess of acidity. It was also found, experimenting on normal acid urines, that the addition of an

exceedingly minute quantity of an alkaline carbonate postponed the time of precipitation of uric acid very notably. The following table displays some of the results obtained by this mode of testing:

TABLE X.—*Showing Postponement of Precipitation of Uric Acid by the Addition of Minute Quantities of Alkaline Carbonates to the Urine.*

Additions made to the Urine.	Time when Uric Acid began to be Precipitated.	Postponement of Precipitation.
No. 1. Urine alone; control tube	2 hours	—
No. 2. Urine + 0.01 per cent., pot. bicarb.	4 "	2 hours
No. 3. " " " sod. bicarb.	5 "	3 "
No. 4. " " " lith. carb.	10 "	8 "

The quantities of the alkaline carbonates added in this experiment were so small, that the reaction of the urine, as tested by litmus paper, was not sensibly affected, and yet the postponement of precipitation was very considerable—considerable enough had the events occurred in the urinary passages to make the difference between the occurrence and non-occurrence of gravel. It will be observed that the sodium carbonate acted more powerfully as a retarder than the potassium carbonate, and that the lithium salt acted more powerfully than either. This, however, was solely due to the difference in their atomic weights. When these salts were used in quantities proportionate to their saturating power, no difference could be detected between them. It need scarcely be said that if the carbonates were added in sufficient quantity to render the urine neutral or alkaline, no precipitation of uric acid took place.

THERAPEUTICS OF URIC ACID GRAVEL.

The treatment of calculous disorders at the hands of the physician must always in the main be of a preventive character. When concretions are once formed in the kidneys or bladder and these are too large or too awkwardly lodged to be washed out by the flush of the urinary stream, there is little prospect that they can be dissolved away by imparting solvent qualities to the urine. In such circumstances we are constrained to have resort to surgical means; and it is a matter for congratulation that the recent brilliant advances in the surgery of the kidneys and bladder—advances largely due to the enterprise and skill of British surgeons—enable us now to face this alternative with greatly diminished anxiety. In the domain of prophylaxis, however, there remains to the physician a fruitful field of activity. Nowhere, perhaps, is the aphorism that "prevention is better than cure" more pertinent than in the case of calculous concretions. The force—the chemical force—which is requisite to prevent the precipitation of uric acid in the urinary channels is almost infinitely small as compared with the force which is requisite to redissolve a concretion already formed.

In considering the medical treatment of uric acid gravel it is important to fix our eyes on the urine itself. There is perhaps too ready a disposition to look for the determining causes of gravel elsewhere than in the urinary function—in the stomach, or in the liver, or in some general constitutional vice. It should be borne in mind that uric acid gravel is constantly seen as an independent disorder, existing *per se*, in persons who are in all other respects perfectly healthy. And if gravel be, not infrequently, complicated or associated with other morbid conditions, it only conforms in this respect to the common rule applicable to most other disorders. There is, however, no doubt that there exists a special relation between uric acid gravel and gout; and the circumstance that uric acid figures as a common factor in both has led certain persons to the opinion that the two complaints are substantially one and the same. This notion is certainly not correct; and from a therapeutic point of view it is, I believe, a mischievous notion. It is a matter of common experience that many gouty people are never troubled with gravel, and, conversely, that many subjects of gravel are never troubled with gout. In both complaints there is an aberration of uric

acid; but the error is essentially different in the two cases both in regard to its site and in regard to its nature. In gout the error occurs on *this* side of the kidneys, in the blood and tissues, and the uric acid is precipitated in state of combination as a biurate; in gravel the error occurs on *that* side of the kidneys, and the uric acid is precipitated in the urine and in the free state. In the former the deposition takes place in the true interior of the economy, in the latter the deposition takes place in what is, strictly speaking, the exterior of the economy, that is to say, on the surface of a doubling of the external integument. These differences are, I believe, radical, and involve important distinctions both in regard to pathology and in regard to treatment.

The fact that gout and gravel sometimes exhibit a kind of vicarious correspondence—that the one complaint alternates with the other at different periods in the lifetime of the same individual, or in successive generations of the same family—while indicating an undoubted relation, indicates also at the same time as essential distinction. Speaking from a somewhat long and large experience of these ailments, I cannot recall a single instance in which a paroxysm of gout and a paroxysm of uric acid gravel broke out synchronously. And Sir Alfred Garrod, with a longer and still larger experience, gives me his testimony to the same effect. Some pertinent evidence on the point we are debating has been brought forward by Mr. Plowright, of King's Lynn.³ He remarks that, residing as he does in Norfolk, the chief stone district in England, he has been struck by the comparatively small number of cases of gout which have come under his notice as compared with the number of stone cases. He further shows, by reference to the Registrar-General's reports, that there is no correspondence between the prevalence of gout and of stone in the several counties of England and Wales. Some of the counties which have a high death-rate from gout have a low death-rate from stone, and, conversely, counties with a high death-rate from stone have a low death-rate from gout. In Scotland, where gout is rare, stone is comparatively common.

These considerations lead to the conclusion that gravel should be regarded as a primary vice of the urinary function—that it requires to be studied by and for itself—and that the urine is the proper and natural field for the investigation of its etiology and therapeutics. We have just seen that the factors which chiefly control the precipitation of uric acid in the urine are: the degree of pigmentation, the proportion of salines, the percentages of uric acid, and, above all, the grade of acidity of the urine; and I shall consider the treatment solely with reference to the operation of these four factors.

With regard to the deficiency of pigments as a contributory factor in the promotion of uric acid gravel, I have no facts nor suggestions to offer which have a bearing on the therapeutical problem; and I doubt whether any help is to be got from further inquiry in this direction. The subjects of gravel among the well-fed population of this country, as far as my experience goes, present no deficiency of pigment in their urine.

With respect to the proportion of saline matters in the urine, it is worth bearing in mind that the evidence gathered by Mr. Plowright, as well as the experimental indications previously adduced by myself, point strongly to the suggestion that the subjects of gravel should be advised to take habitually with their meals as much culinary salt as their palates will tolerate. I may also remind those whose lot it is to practise among the children of the poor or among the rice-eating populations of tropical and subtropical countries that it would be well, in cases of gravel, to see that the patient's food should contain an adequate proportion of articles rich in saline materials, that is to say, of milk, meat, fish, eggs, and salads.

The proportion of uric acid in the urine as a controlling factor in uric acid precipitation demands somewhat more notice. It is a common notion that the occurrence of uric acid gravel depends simply on an excess of this substance in the urine (so-called uric acid diathesis). This assumption pervades the entire argument of most writers on gravel, and dominates all their plans of treatment. I have already shown that the assumption is only partially true, and that

the percentage of uric acid is only a subordinate factor in the determination of uric acid precipitation. During the alkaline tide after meals the percentage of uric acid in the urine reaches almost its highest level, and yet there is less risk of precipitation at this time than at any other period of the day. It has, moreover, been demonstrated (see Table VIII) that uric acid is sometimes thrown down in the urinary channels when its proportion in the urine does not exceed the normal average or even when it falls considerably below the average. At the same time it is true that, when other favouring conditions coincide, a high level of uric acid excretion with a high percentage of it in the urine is a valid factor in the production of gravel, and that a lowering of that level, if by any means attainable, is an important therapeutical indication.

Attempts have been made in this direction by modifications of the diet and regimen. The advice given on this head by various writers is however very contradictory. Some recommend that the subjects of uric acid gravel should avoid sugar, fruit, and fat; others that they should take fat in abundance, and avoid starchy matters; some advise a vegetarian diet, others a mixed diet. The most reliable investigations indicate that fat, sugar, and starchy matters have not the slightest direct influence on the production and excretion of uric acid; nor has any proof been given that albuminoid substances of vegetable origin differ in this respect from albuminoid substances of animal origin. The only point that has really been made out is this: that the excretion of uric acid is diminished by lessening the albuminoid ingredients of the food, and that it is heightened by increasing these ingredients. But this class of aliments is absolutely essential to nutrition, and you cannot diminish them to any serious extent without injuriously affecting the nutritive equilibrium. After a careful examination of all the evidence on this point it appeared to me that the practical outcome was only this: that persons who are subject to uric acid gravel, and who are also troubled with a large appetite, should seek to allay their cravings and to lessen the intake of nitrogenous material by the free use of farinaceous articles of food with salads, fruit, and garden vegetables, all of which are comparatively poor in albuminoid constituents. I shall again revert to this subject in my fourth lecture when speaking of the dietetic treatment of gout.

I am satisfied, from repeated observations, that in the immense majority of cases of uric acid gravel in this country the immediate determining cause of the precipitation is *excessive acidity of the urine*, and that the paramount indication of preventive treatment is to diminish this acidity. All other schemes of treatment sink into insignificance in comparison with this. The use of alkalinising agents for the prevention of uric acid gravel stands on a perfectly rational basis. It is chemically impossible for uric acid to be deposited from an alkaline urine; it may even be said that it is impossible for uric acid to be deposited prematurely—that is to say, within the urinary channels—from a neutral or feebly acid urine; and as we possess the means of harmlessly reducing the acidity of the urine at pleasure, we have in our hands—in principle at least—the absolute power of preventing uric acid gravel. There are, however, some practical difficulties to be overcome. The disposition to uric acid gravel has a certain persistency. It may last intermittently for months or years, and it would obviously be too great a strain on a treatment which is purely protective to require that a patient should take antacid medicines in sufficient doses and at sufficiently short intervals to maintain the urine continuously alkaline or neutral over so long a period of time; nor is any such effort necessary. A study of the normal oscillations of the urine at different periods of the day and night leads to the inference that the liability to uric acid gravel rises to a dangerous intensity only during certain limited portions of the twenty-four hours.

The risk in gravel is almost confined to precipitations which take place within the precincts of the kidneys. Precipitations which take place in the bladder are harmlessly swept out at the next act of micturition. These latter probably only do harm when there is already a stone in the bladder, to which the crystals can accrete, or when a pouch exists in the viscus to receive and detain the deposit. What most concerns us therefore is the state of the urine as secreted by the kidneys

³ On the Cause and Distribution of Calculous Disease, by Charles B. Plowright. London, 1886, p. 14.

rather than the state of the product accumulated in the bladder. For the sake of brevity and by way of distinction we may be allowed to speak of *renal urine* and *vesical urine*. These two products, no doubt, usually correspond sufficiently closely to enable us to judge from the urine of micturition what the character is of the urine secreted by the kidneys; but this is not always the case. Vesical urine represents the aggregate work of the kidneys for several consecutive hours. During this interval the renal urine may have undergone sharp oscillations—from acid to alkaline, from dilute to concentrated, from richness to poverty in uric acid—but the vesical accumulation which is at length discharged by micturition will have a mean or average composition which entirely masks these oscillations. To arrive at a correct knowledge of the state of the urine as it flows from the kidneys it is necessary to obtain the secretion and to examine it at short intervals. Some years ago I made an extended series of observations on these lines. The subject of experiment was a healthy man of 28. The urine was collected at hourly, or at most two-hourly intervals throughout the 24 hours, except during the period of sleep, which was taken as a single interval.

The inquiry embraced observations on thirty-two complete days, besides a good many more on portions of days. The results of the investigation were incorporated in two papers published in vol. xv of the *Memoirs of the Manchester Literary and Philosophical Society*⁴ and in the *Edinburgh Medical Journal* for 1880.⁵ Some of the conclusions arrived at have a direct bearing on the preventive treatment of urinary gravel. The character of the urine was shown to be most affected by the digestion of food, by prolonged fasting, and by sleep. It was found that a meal, whether it was composed of ordinary mixed food or of purely animal or purely vegetable substances, produced two constant effects. It depressed the acidity of the urine and increased its volume. And, conversely, prolonged fasting raised the acidity and diminished the flow of the urine. During the hours of sleep, which are also of course hours of fasting, the acidity of the urine reached its highest point and the flow of the urine reached its lowest point. The proportion of uric acid in the urine, that is to say, its percentage, was found highest during the time of sleep; but the hourly excretion was highest during the hours following a meal. Now, if we apply these facts, in the light of the evidence previously adduced in regard to the factors which determine the precipitation of uric acid in the urine, we arrive at the conclusion that the period when there is most risk of precipitation in the kidneys is during the time of sleep, and especially in the early morning during the two or three hours preceding breakfast.

The deposition of uric acid is most imminent when there is a conjunction of the several conditions—that is to say, when the flow of urine is very scanty, when the secretion is hyperacid, and when it is rich in urates. Such a conjunction is most fully developed during the period of sleep. Sleep is a time of fasting, and therefore a time of hyperacidity of the urine—a time of recumbency and bodily immobility, and therefore a time when the renal stream approaches nearest to stagnation, and loiters longest about the purlieus of the kidneys. On the other hand, during the day and the waking hours the recurrence of the meals keeps the urine at a low degree of acidity, or even renders it for a time neutral or alkaline—the renal stream is comparatively full and rapid, and its descent from the kidneys is favoured by the force of gravity. During these hours, therefore, the risk of uric acid precipitation is reduced to a minimum, even in persons who have a distinct tendency that way. For, as I have repeatedly had occasion to observe, the urine of calculous subjects exhibits precisely the same cyclical diurnal variations as that of healthy persons, though not always in so marked a degree.

A study of these facts indicates that if we safeguard the night, the day may be generally left to take care of itself. This theoretical deduction is fully in accordance with experience in the treatment of uric acid gravel. In the milder cases a single full dose of the alkalisng agent taken at bedtime suffices to prevent the recurrence of the colicky pains and the discharge of uric acid concretions. For this purpose the citrates and bicarbonates of potash and soda are the most effective. The citrate of potash is, perhaps, on the whole, the

best preparation to employ; it has very little taste, and it sits comfortably on the stomach. The dose for an adult should not be less than 40 to 60 grains, dissolved in 3 or 4 ounces of water. In severer cases a single dose is insufficient, and the early morning urine will still exhibit a morbid disposition to precipitate uric acid. In such cases a second but smaller dose should be taken about the middle period of the hours of sleep. This is less difficult to manage with the subjects of gravel than in healthy persons. There is commonly in calculous subjects a certain restlessness and a certain irritability of the urinary organs, which leads to an increased frequency of micturition, and such persons rarely pass the night without a call to empty the bladder. Advantage should, therefore, be taken of this break in the continuity of sleep to take the second antacid dose. In this way the entire night and early morning may be effectually guarded.

Cases of uric acid gravel, however, are not always to be got rid of on these easy terms. Now and then instances are met with in which the perversion is so great that the urine is disposed to deposit almost the day through, and in which the normal alkaline tide after meals seems to be well nigh abrogated. Under these circumstances additional doses of the antacid are required to afford the requisite protection; and the right times for these doses are two or three hours after breakfast, and two or three hours before dinner. But, so far as I have seen, these extreme conditions only a last a short time—a few days at most; and there is then a return to a less urgent state of things. It is, indeed, a marked character of uric acid gravel that it oscillates in intensity; it comes and goes in paroxysms, reminding one of the waviness of gouty phenomena. For this reason it is desirable to frequently note the state of the urine, and to ascertain its greater or less proneness to deposit uric acid, so that the administration of the antacid may be adjusted to the actual needs of the patient. There is no great difficulty about this. If a freshly-voided specimen of the urine of fasting—say the urine of the early morning or the urine secreted just before dinner—be set aside in a glass vessel in a warm place (so as to prevent the deposition of the amorphous urates) the imminence of precipitation can be easily observed. If precipitation be morbidly imminent, crystals of uric acid will appear perhaps at once, perhaps in an hour or a couple of hours. If precipitation be not morbidly imminent, crystals will not appear for several hours—perhaps not for two or three days. It is possible in this way to gauge pretty accurately the intensity of the morbid tendency, and to regulate thereby the amount and frequency of the antacid dose, or to decide on its discontinuance.

A matter of some importance in the management of cases of uric acid gravel is the *arrangement of meal times*. Each meal acts on the urine as a dose of alkali, and also as a diluent, and in both these ways operates as a protective against uric acid precipitation. After the meal is absorbed and assimilated the urine becomes again increasingly acid and concentrated, and, as a consequence, increasingly prone to precipitate uric acid. Subjects of gravel should therefore be warned not to allow too long an interval to elapse between their meals. This precaution is especially needed as regards the interval between breakfast and the midday meal. The first meal of the day is, with most persons, very quickly digested, and its effects on the urine are correspondingly transient. At no time during the waking hours does the acidity of the urine tend to rise so high, and the volume of the urine to fall so low, as during the later portion of the interval between the first and second meal of the day. This interval should, therefore, be abridged. In this connection the pleasant institution of afternoon tea may come in for a word of commendation as serving to break the sometimes too long interval between luncheon and a late dinner. Some people interpose an unconscionable interval of twelve or fourteen hours between their last meal at night and their breakfast next morning. This is a very risky proceeding on the part of calculous subjects.

The essential thing in the prophylactic treatment of uric acid gravel is to guard the urine from precipitating within the precincts of the kidney. And we shall, practically, have attained our object if we succeed, not in altogether preventing precipitation, but in postponing it until the urine have quitted the kidneys. A postponement for a short time, even half an hour, may make all the difference between a precipitation which is fraught with pain and peril, and a pre-

⁴ "A Contribution to Urology."

⁵ "On Some of the Daily Changes of the Urine."

cipitation which is practically harmless. Now, the protective effect of an antacid dose extends a good deal beyond the point at which the urine is rendered actually alkaline. For although all acid urines of medium density precipitate uric acid sooner or later, the time of the occurrence of that precipitation is immensely influenced by the degree of acidity of the urine. Other things being equal, the more acid the urine the earlier is the precipitation, and the less acid the urine the longer is the precipitation postponed. An antacid effect, therefore, which is too feeble to render the urine actually alkaline, may be quite sufficient to depress its acidity to such a degree as shall postpone the time of precipitation until the urine has escaped from the kidneys, and even from the bladder.

Mineral Springs.

The use of mineral springs in the treatment of uric acid gravel demands a word of comment. A sharp distinction must be drawn between alkaline springs and non-alkaline springs. Alkaline waters, such as those of Vichy, which are largely impregnated with carbonate of soda, have the power of alkalisng the urine, and therefore absolutely protect against uric acid gravel during the period of their use. But the non-alkaline waters have no such power, and their beneficial action is due to the fact that they greatly increase the flush of the urinary stream, and thereby promote the carrying down of concretions already lodged in the precincts of the kidneys. Their efficacy in this direction is quite undoubted, but it is, I think, equally undoubted that the drinking of equivalent quantities of distilled water would be just as efficacious. A glance at the composition of the several non-alkaline springs which have acquired renown in the treatment of gravel supports this view, and indicates that the neutral salts contained in them have little or nothing to do with their efficacy. Some of these waters are impregnated with sulphate or chloride of sodium, others with salts of magnesia; others, again, only contain minute quantities of sulphate of lime, and are scarcely distinguishable, except for their warm temperature, from ordinary drinking water. Yet all these most diverse springs claim equal powers in cases of gravel. Is it not plain that what alone gives them efficiency is that which they all contain in common, namely, their watery constituent? Subjects of urinary gravel who pay, as many of them do, an annual visit to one or other of these springs imagine that such a visit clears them from their calculous tendency for the rest of the year. This, I believe, is a delusion. Such persons, on their return home, stand, in regard to their morbid proclivity, precisely where they stood before their visit.

It is obvious that a preventive treatment of uric acid gravel to be completely effective should be available all the year round, and be capable of timely application whenever the emergency arises. An adequate choice of substances which alkalis the urine is always at our disposal; their power of preventing uric acid precipitation amounts to a chemical certainty, and in even moderately prudent hands no harm can follow from their use. I see no reason, provided vigilant watch be kept on the imminence of uric acid precipitation in the fasting urine, in the manner before described, why sufferers from this kind of gravel should not, by a prompt resort to antacid remedies, be able at all times to protect themselves effectually against fresh formation of uric acid concretions, and thereby save themselves from a world of pain and danger.

THE *London Gazette* of the 17th inst. announces that the Queen has been pleased to give and grant unto James Patrick Andrew Wilson, Esq., L.R.C.P., L.R.C.S.Edin., Her Majesty's Royal Licence and Authority that he may accept and wear the insignia of the Order of the Crown of Johore of the Third Class, which His Highness the Sultan of Johore has been pleased to confer upon him, in recognition of his services while entirely employed in the service of His Highness beyond Her Majesty's dominions.

PROFESSOR KEKULÉ recently celebrated the twenty-fifth anniversary of his appointment to the Chair of Chemistry in the University of Bonn. A ceremonial "Act" in honour of the distinguished scientist was held in the Chemical Institute, and a torchlight procession of students took place in the evening.

ABSTRACTS OF LECTURES ON THE TREATMENT OF SURGICAL TUBERCULOUS DISEASES.

Delivered at the Royal College of Surgeons of England.

By W. WATSON CHEYNE, M.B., F.R.C.S.,

Hunterian Professor: Joint Professor of Surgery at King's College; Surgeon to King's College Hospital, etc.

LECTURE II.

I MAY, perhaps, best illustrate the value of extension in tuberculous bone disease by considering its effect in disease of the spine with paralysis. In tuberculous disease of the spine two factors are at work, in addition to the presence of the tubercle, in keeping up the chronic inflammation, namely: (1) the weight of the upper part of the body, and (2) the contraction of the muscles surrounding the diseased portion of the spine. The inflammation so kept up is apt to spread to the meninges, causing thickening of them, pachymeningitis, which may be either of a simple inflammatory nature, or may be combined with tuberculous infiltration. This pachymeningitis leads to pressure on the cord, and consequent paralysis. The other chief cause of paralysis is the extension of the tuberculous disease to the posterior part of the bodies of the vertebrae, and the subsequent formation of an abscess in the vertebral canal. The paralysis is hardly ever due to the pressure of the bone on the cord, for, owing to the destruction of the bodies, the canal is shortened, and there is no stretching of the cord nor want of room so long as no adventitious material is present; it is possible, however, that if the curve is very acute, the cord may become kinked, and its circulation and function thus interfered with. The chief factors being, then, the weight of the body and the muscular contraction, the first indication of treatment in a case of paralysis is to remove these factors. This is best done by complete recumbency to take off the weight of the upper part of the body, and extension to the head and feet to overcome the muscular contraction (see Fig. 1). This should certainly be

Fig. 1.

tried in all cases before proceeding to laminectomy, which is too much the fashion nowadays.

The importance of the second factor, the tonic contraction of the muscles around the spine, is not thoroughly realised, although Lannelongue, who is the highest authority on the pathology and treatment of spinal disease, has laid special stress on it, and has mentioned cases where, though the patient was kept absolutely recumbent, curvature has increased or developed. I have myself seen a similar case where a psoas abscess was opened in an adult, and where the patient was kept absolutely recumbent, and never allowed to sit up or raise his shoulders for any purpose whatever. When put to bed, there was no distinct evidence of curvature, but after some months an acute curvature was manifest. Some have, indeed, thought that the object of the double extension was to undo the curvature, an attempt which would probably do harm, whereas it is to prevent the pressure of the inflamed bones against each other by the surrounding muscles.

Three illustrative cases were mentioned:

CASE 1.—A boy, aged 4½, was admitted to Paddington Green Children's Hospital on April 6th, 1888. When 1 year of age he developed a tuberculous knee, which got well after three years' treatment. About two years and a-half before admission his back was noticed to be weak, and he was treated at another hospital by plaster-of-paris jackets, to which a jury mast was subsequently added. The curvature had been getting worse, and he was losing flesh. He had been unable to walk for nine months;