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ON THE RELATION BETWEEN DISEASE OF THE KIDNEY AND EXCRETION OF THE ALLOXURIC BODIES.

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WITHIN recent years not a little interest has been created by the study of the xanthin bases, more especially with reference to their excretion in disease. The observations on their relation to the other nitrogenous elements of the urine, especially uric acid, have resulted in some noteworthy discoveries, and have led to the formulating of many new hypotheses.

Gout and the uric-acid diathesis have particularly attracted attention, and Kolisch, of Vienna, has propounded a theory in which the xanthin bases are made to explain much as to the causation and symptoms of these maladies. His theory is of not a little interest, though, as will be subsequently demonstrated, under the light of newer chemical methods it becomes wholly untenable. The basis of this theory implies the *formation* of uric acid normally in the kidneys, while any defect in these organs will result, not only in a defective elaboration and elimination of this substance, but in chemical processes by means of which certain poisons, namely, the xanthin bases, are manufactured in abnormal quantities instead.

The alloxuric bodies (*i. e.* uric acid + xanthin bases) form, as is generally now recognized, a very important

derivative of the nuclein of certain cells through the intermediate formation of nucleic acid, and probably some other mother-substance. Under normal conditions the proportion of uric acid and xanthin bases, though varying to a considerable extent, may be said to have a fairly constant ratio—the uric acid being always in vastly greater quantity, its amount in healthy persons being 10 to 27 times that of the xanthin bases. Such being the case under normal conditions, Kolisch finds that a very different result is obtained in gout and in uric-acid diathesis according to the condition existing in the kidneys.

With normal kidneys the greater part of the alloxuric bodies is eliminated as uric acid, but where renal disease occurs the relative proportions of these two constituent elements of the alloxuric bodies are altered, the uric acid being diminished in amount and the xanthin bases relatively increased. In other words, the renal cells are unable to transform the nuclein derivatives into the right proportions of uric acid and xanthin bases, although the total alloxuric bodies remain normal in amount. Where the amount of uric acid is diminished, and the xanthin bases increased, toxic symptoms develop, for these latter substances are regarded as poisons, and their excessive formation and retention is of grave pathologic significance.

In the series of changes which occurs in uric-acid diathesis and gout, much of the symptomatology then depends on the condition of the kidneys, for their morbid state implies the formation of the poisonous xanthin bases to which Kolisch ascribes the varying series of symptoms. In the uric-acid diathesis per se, the kidneys are usually normal, and have therefore no difficulty in converting the nuclein derivatives into due proportions of uric acid and xanthin bases. The total alloxuric bodies may be increased, but there is not a

very excessive alteration of their proportions. In gout, on the other hand, the kidneys are gradually diseased, the xanthin bases are formed in excess because the renal cells cannot convert the nucleic acid derivative into sufficient uric acid; hence are developed the toxic symptoms described in conditions of more or less advanced gout. In other words, three phases exist in uric-acid diathesis :

1. Simple lithæmia, the kidneys being normal and yielding merely excessive quantities of uric acid.

2. Mild gout, *i. e.*, prolonged lithæmia, in which the kidneys become gradually weakened so that, although there is no excess of uric acid formed, yet abnormal quantities of xanthin bases are being elaborated, producing in this way the milder symptoms of gout.

3. Marked gout with advanced renal disease, resulting in diminution of the uric acid, and very great increase of xanthin bases.

According then to this theory, uric acid in itself plays a comparatively unimportant part in the manifestations of pure gout, while the formation of xanthin bases is of paramount significance. Instead then of the oft-quoted axiom, "No uric acid, no gout," Kolisch would have us believe in a modification reading thus : "No xanthin bases, no gout."

To establish so all-important a theory as this of Kolisch, it would be necessary to prove similar changes in the alloxuric bodies in all cases when the kidneys are the seat of disease. Kolisch himself has already endeavored to do so, and cites a number of cases of nephritis in which, although the total alloxuric bodies are eliminated in normal quantities, the uric acid is relatively diminished in amount. Like other observers, however, he has employed in his estimation of the xanthin bases the method of Krüger and Wulff, a method which has been shown by such authorities as

Huppert, Arnstein, and others, to give unsatisfactory and incorrect results, the estimates in nearly all the cases being far too great for the xanthin bases. Xanthin bases, according to this method, are first precipitated from the urine by copper, then subsequently the estimation is made in terms of nitrogen by the method of Kjeldahl. Now, such a method as this, which precipitates the nitrogen-containing xanthin bases, lets fall also the nitrogen from other elements in the urine, and when later the total nitrogen is estimated, it becomes an index, not of the xanthin bases alone, but of any other nitrogenous elements that may be present. The final estimates, then, would yield results far in excess of what actually exists.

It has been shown, for example, that certain albuminous bodies may be present in the urine, and yet not be recognized by the ordinary tests, and these with their nitrogen would be readily precipitated by the copper. Again, albumin, when recognized, is extremely difficult to eliminate totally from the urine before commencing such a test, and if any remain in the material to be tested, it would, of course, add to the total nitrogen estimated. The same applies, too, to the presence of potassium sulpho-cyanide, which exists in the urine in quantities equaling .5 to 1.6 mg. of nitrogen; and this, too, being precipitated by the copper-method, still further increases the amount of nitrogen estimated, which is supposed to indicate merely xanthin bases.

In order the more readily to avoid such sources of error (errors, too, which, though seemingly small, actually lead to astounding results when dealing with such minute portions), Salkowski has devised a method which has been proven by careful analysis to leave a minimal source of error in estimating quantities of the xanthin bases. This method, which consists in the preliminary precipitation by silver, avoids any danger

of including in the final estimates either the albumin or the potassium sulphocyanide, for the estimation of the bases is made directly, and not in terms of nitrogen. It has, moreover, been tested in comparison with that of Krüger and Wulff in Salkowski's own laboratory where the investigators (Flatow and Reitzenstein) have shown in tabulated form the results of numerous observations, and in practically every case the older method showed quantities of xanthin bases far in excess of those which the newer test manifested, in experiments where the identical specimens of urine were employed for the parallel test. This discovery of theirs has practically rendered unreliable all previous quantitative work on the alloxuric bodies, and among these must be included the work of Kolisch on gout and uric-acid diathesis.

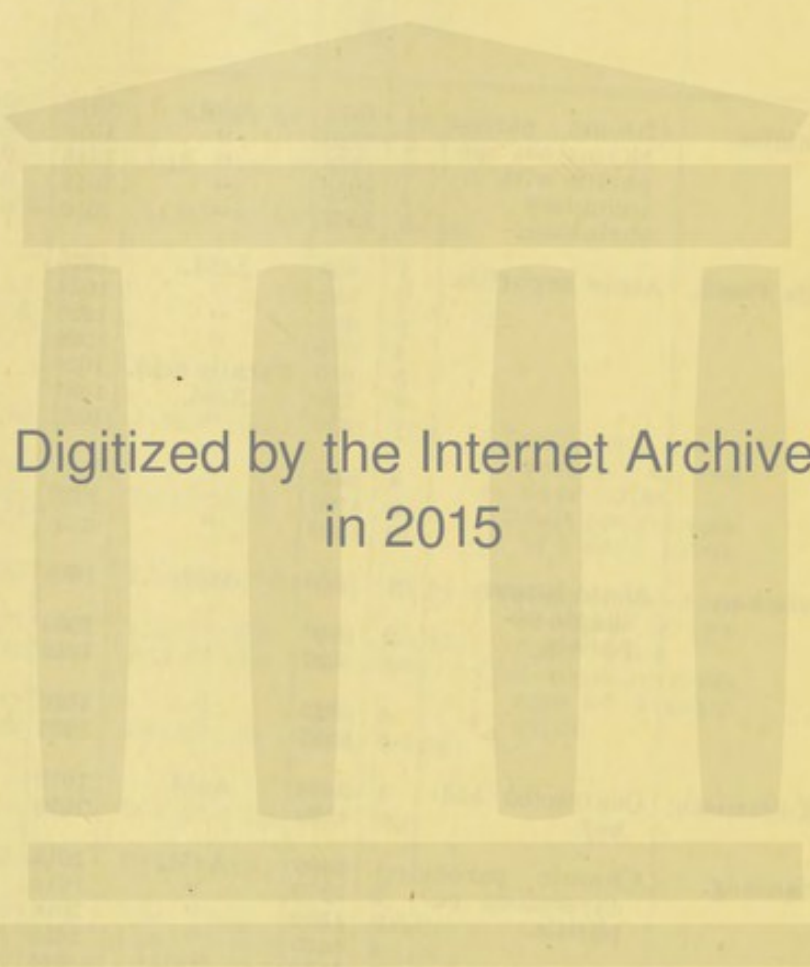
Realizing the importance of estimating accurately the excretion of alloxuric bodies in nephritis, on account of the supposed relation between renal disease and the various symptoms of gout, I have examined a number of cases of nephritis of different varieties (acute and chronic parenchymatous, contracted kidney, etc.), with this object in view. In the carrying out of these experiments the patients received each a diet which, while suitable to their condition, was given daily in the same variety and in exact quantity, until they had attained, before the experiments were started, a nitrogenous equilibrium (*i. e.*, in so far as this is at all possible in nephritis; vide v. Noorden-Ritter). In most instances 4 to 5 days were found necessary to obtain this result, and, as will be seen from the tables, excellent equilibrium was reached in several instances (Cases II, III, and IV). Medicinal or other therapeutic agents were, for the time, rejected, and everything scrupulously avoided which could in any way have an appreciable influence in altering the excretion of alloxuric bodies from day to day during the observations.

Following, then, the newer method of Salkowski, the xanthin bases were estimated by precipitating with silver, as recommended in modifications by Huppert; and from specimens of the same urine separate tests were made for uric acid by the Ludwig method, and the total nitrogen was estimated daily according to Kjeldahl. In every instance parallel estimates were made and averages taken; where the urine was insufficient, 48-hour specimens were employed and estimates made accordingly. For the quantitative analysis of the albumin from day to day, Esbach's instrument was employed.

An examination of the appended chart will explain the results of the investigations and it need be merely observed in passing that in gauging the physiological output of uric acid and xanthin bases, one is compelled mainly to rely upon the experiments made in Salkowski's laboratory, these being the only ones of importance yet made to determine the normal excretion of alloxuric bodies. Estimations there made show the daily excretion of xanthin bases to be from 27.2 to 56.1 mg. Similar experiments made under the direction of Professor Kraus in Graz have shown even somewhat higher values, though it has been further noted that even in health the variations are so considerable as to make one more than cautious before determining definitely as to what should be considered as pathological.

Again, normally, the relation between xanthin bases and uric acid, according to Salkowski, would be 1 to 10.2 up to 1 to 27.1. Hence the relation between their constituent nitrogens would be 1 to 8.8 up to 1 to 25; according to Flatow and Reitzenstein the ratios lie usually between 1 to 14 and 1 to 22.

Observing then the cases of nephritis I have examined (excepting No. IV), one finds the daily excretion of xanthin bases to vary between 13.6 and 47 mg.



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Average for each case taken from the total examinations made would be as follows :

I. 35.2 mg.	V. 17.2 mg.
II. 36.7 mg.	VI. 33.7 mg.
III. 22.7 mg.	VII. 33.7 mg.

These values then differ in the individual cases and even from day to day in the same case quite irrespective of the amount of urine secreted. Compared with physiological values given above, however, there is in no instance any abnormal quantity of xanthin bases excreted and the average would represent about 23.9 mg.

It is evident then that one cannot speak here of an absolute increase of xanthin bases in the daily quantity passed.

The uric acid varies in daily quantities among the different cases between .2 g. (Case I) and .567 g. (Case II) (omitting Case No. IV, as above). Averages for each case from total observations made would be as follows :

I. .289 g.	V. .303 g.
II. .445 g.	VI. .395 g.
III. .286 g.	VII. .395 g.

Average of total is .358 g.

In short, the quantity of uric acid is either normal or slightly below it. Even, however, though in some cases it is present in abnormally small amount, its proportion to the xanthin bases remain unaltered, showing that just as in normal cases so in nephritis the proportions of the uric acid in the alloxuric bodies remain the same, viz.: about 91% ; and the total of alloxuric bodies excreted is, as a matter of fact, lower than the normal.

It should, however, be noted, that on certain days the ratio between the uric acid and xanthin bases did indeed appear altered, *e. g.*, 1 to 4.2 (Case I, first day) and again 1 to 7.3 (Case VII, second day). This was

most marked in Case No. IV, omitted in the remarks above, for the xanthin bases here reached, 81.1 mg., *i. e.*, nearly double of the normal average of Salkowski and far greater than any other physiological values obtained in all the observations made in the laboratory on healthy individuals. The proportions reached, too, nearly those of the uric acid—but inasmuch as for unavoidable reasons only one examination could be made, and as other cases show the variations from day to day occurring in these excretions, it can scarcely be justifiable to lay stress on the one observation made in that instance.

As illustrative of the variations that may occur one need but look at the chart opposite Case I, where on the first day this ratio was 1 to 4.2, while in the same case on the third day the ratio was 1 to 13; and again in Case V where, once it reached 1 to 11.4 and another time 1 to 26.

The important point remains, however, in all the cases, *viz.*: *that never was there an actual predominance of the nitrogen of the xanthin bases over that of the uric acid*, as Kolisch had found when making his own observations. Such a discrepancy as this can have but one cause, *viz.*, the error of the methods he employed, obtaining by the Krüger-Wulff method far too high values in favor of the xanthin bases.

Moreover, inasmuch as the causes of physiological variations in the excretion of the xanthin bases are by no means well understood, similar variations in cases of nephritis are equally difficult to explain. To draw any conclusions therefore on the power of the kidney to elaborate uric acid simply because there is an occasional increase in the excretion of xanthin bases and a narrowing in the quantitative ratio between these bases and the uric acid is certainly unjustifiable.

Another point, and one that is well worthy of notice,

has been observed in several cases of nephritis that we have examined, viz : that often the *percentage* of uric acid in cases of nephritis is very high. Were it a fact, as Kolisch insists, that the elaboration of uric acid in the kidneys is diminished on account of their diseased condition, and that the amount excreted is a direct measure of the disease present, one would expect that not only would the 24-hour urine show lessened uric acid, but so also each individual specimen. Such a condition is, however, by no means always found, for very often the percentage of uric acid in albuminous urine is on the contrary very high. The cases of *intermittent albuminuria* are particularly instructive in this connection and an examination of two such cases has been appended on the accompanying chart. The urine of these patients, while after resting, was almost entirely if not quite free from albumin ; after moderate exercise on the other hand, albumin was constantly present. The portions of the urine containing the albumin had nearly always a marked sediment of urates. In the one instance quantitative examination for uric acid showed in the morning urine (*i. e.*, after a night's rest) .0060 grs. in 100 cc., while in the same amount of urine passed later in the day, after a short walk, there was .0803 g. of uric acid. In the other case the difference in the urine before and after exercise showed the uric acid to be respectively, .0558 g. and .0698 g.

This fact then is sufficient to show that under conditions which distinctly injure the kidneys (judging at least from the amount of albumin present) the elaboration or rather the excretion of uric acid is in no way influenced—presumably the kidneys alone are not responsible for this function, and one must look elsewhere in the body for the source of uric-acid formation.

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