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URIC-ACID LEUKOMAINS AS FACTORS IN THE ETIOLOGY OF MIGRAINE AND KINDRED NERVOUS DISEASES.

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URIC-ACID LEUKOMAINS AS FACTORS IN THE ETIOLOGY OF MIGRAINE AND KINDRED NERVOUS DISEASES.

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IN THE MEDICAL NEWS of May 26, 1894, I published a paper on "Paraxanthin as a Factor in the Etiology of Certain Obscure Nervous Conditions." That paper was based on the study of a patient who had had migraine all her life till she was past sixty years of age, at which time the migrainous attacks were superseded by epileptoid paroxysms, which came at about the same interval of time as the migrainous attacks had previously occurred, and produced no bad effect on the intellectual faculties. I showed, by a careful study of this case, that it belonged to the class of cases which were formerly thought to be due to an excess of uric acid in the blood, but which at the present time, since we know that uric acid is non-toxic, are left without any very definite pathology. I found that the urine of this patient passed during and just after a paroxysm contained not only an excess of uric acid, but also a *very great excess of paraxanthin*, a poisonous leukomain of the uric-acid group. I also found that the paraxanthin-solution taken from the urine of this patient, when injected into mice, produced

symptoms like those from which my patient suffered. From this study I drew the conclusion that paraxanthin-poisoning, rather than uric-acid poisoning, is an important etiologic factor in producing these epileptoid attacks.

A subsequent study of this and other so-called uric-acid cases not only confirms me in the foregoing conclusion, but it has led me to believe that the uric-acid leukomains, of which paraxanthin is the most poisonous, are important etiologic factors in producing the nervous symptoms which have heretofore been attributed to uric acid. I believe that classic migraine is a leukomain-poisoning, and that there is a form of so-called epilepsy coming on late in life, often taking the place of the migrainous attacks of previous years, which has as its most important etiologic factor the very poisonous leukomain, paraxanthin. The foregoing conclusions will, if correct, be of much clinical importance. I wish, therefore, to afford an opportunity of judging of their value by presenting herewith, in connection with my previous paper already referred to, the evidence upon which they are based.

In the beginning I must express my obligations to Mr. Otto F. Bange for the assistance he has given me in this work; the investigations by him were conducted in his private laboratory and at his own expense, his only incentive being his love of science and his desire to assist me in the study of a question that not only required a great deal of time, but also much technical knowledge.

I am also indebted to Mr. Stuart Wallingford for assisting me in my private laboratory in making a

number of urine-examinations. In my previous paper I gave the technique of the urinalysis and many other important facts which here have a direct bearing, but cannot be repeated.

Specimen No. 1. Two gallons of normal urine were obtained from soldiers at the Newport Barracks. This specimen was a portion of the morning urine passed by a large number of strong, healthy men. It may, therefore, be taken to represent an average normal urine. The examination was made by Mr. Bange. The final fluid was evaporated to 8 c.c. Result: Paraxanthin was not present in sufficient quantity to be detected, and the final fluid was not poisonous to mice.

Specimen No. 2. Two gallons of normal urine were obtained as noted, and were examined by Mr. Wallingford under my direction. The final fluid was evaporated to 8 c.c. Result: No paraxanthin or other leukomains could be detected, and the resulting fluid was not poisonous to mice.

Specimen No. 3. Normal urine obtained as noted. Boric acid was added, and the fluid allowed to stand three days, and then examined by myself. The final fluid was evaporated to 8 c.c. Result: No paraxanthin or other leukomains could be detected, and the resulting fluid was not poisonous to mice.

Specimen No. 4. One quart of urine was obtained from a case of epilepsy—*grand mal.* The secretion was passed between and just after a series of severe epileptic convulsions. The patient was a boy, fifteen years of age, with a tuberculous family history. His mother attributed his sickness to a fright which he received when five years of age. For some years he has had one or more severe epileptic convulsions a day, usually occurring at night. At short intervals

a large number of violent convulsions will occur during the same day, and following these severe attacks he will be quite unmanageable for several days. He cannot dress or undress himself, and his mind is hopelessly diseased. To be brief, I may say the boy is a typical case of very severe *grand mal.*

The urine was examined by Mr. Bange, the final fluid evaporated to 4 c.c. Result: No paraxanthin or other poisonous leukomains could be found, and the resulting fluid was not poisonous to mice.

Specimen No. 5. Two quarts of urine were obtained from a case of epilepsy—*petit mal.* This case was under observation at my clinic at the Medical College of Ohio for some months. The patient, a boy of ten years, had a bad tuberculous and nervous history; he was anemic and poorly nourished, and had had epilepsy for "four or five years." When he came to the clinic for treatment he was having on an average one attack a day. In these attacks the boy would lose consciousness for a few moments, and then complain of being sleepy. His mother said that at all times he was nervous and irritable, and much changed in his disposition. This boy was very much improved by treatment; so much so that when I sent him to the country (in June) he had had only one attack during the previous month. The improvement in his epilepsy was no doubt due to the improvement in his general health and strength. The treatment consisted in systematic exercise in the open air, good food, including one quart of milk each day, and syrup of iron iodid and cod-liver oil. The specimen of urine examined was obtained from this boy between and after two nervous attacks, and was examined by Mr. Wallingford under my direction. The final fluid was evaporated to 6 c.c. Result: No paraxanthin or other leukomain was

found, and the resulting fluid was not poisonous to mice.

Specimen No. 6. Four quarts of urine were obtained from a case of acute mania following influenza. This patient was an overworked business man, fifty years of age. He had had a very severe attack of mania following influenza. The maniacal symptoms lasted some weeks, and then passed off. During the eighteen months following this first attack he had a number of attacks of acute mania; they would be accompanied by intense pain in the back, and would always follow symptoms of influenza. The last attack of this kind lasted two days, and it was during this time that the specimen of urine was obtained.

The urine was examined by myself. The final fluid was evaporated to 6 c.c. Result: No paraxanthin or other leukomains of the xanthin-group could be found. The resulting fluid was not poisonous to mice.

Specimen No. 7. Four quarts of urine passed by a patient during and after a severe attack of migraine. This patient was a German woman, thirty-three years of age, whom I had known for many years as a sick-headache sufferer. Her mother and one of her sisters also have the same disease. During the many years that I have known her she has often come to me hoping to get relief from these migrainous attacks, which came every two or three weeks and utterly prostrated her, confining her to bed for from twelve to twenty-four hours. At these times her stomach would reject all food, and she would suffer from intense headache. She was a great meat-eater and beer-drinker. A number of times I succeeded in making her quite comfortable and free from headaches for months at a time. The treatment at these times consisted in stopping the beer

and fresh meat, giving her instead vegetables, fruit, eggs, and milk, *ad libitum*. The medicinal treatment was a dose of Carlsbad salts each morning and five drops of tincture of veratrum viride when the patient suspected an attack was coming on. When she would adhere to this treatment she suffered very much less from migraine. But always after some months of caretaking she would lapse into her old habits of eating and drinking, and the migrainous attacks would take on their former severity.

The urine was examined by Mr. Bange, and the final fluid evaporated to 10 c.c. Results: Paraxanthin and other leukomains of the xanthin-group were found in considerable quantities. The resulting fluid responded to the chemic tests for paraxanthin, and a drop of the fluid evaporated on a glass slide showed under the microscope paraxanthin-crystals, and when injected into mice this fluid produced poisonous symptoms resembling paraxanthin-poisoning. In this way the resulting fluid was shown to contain a substance which responded to the chemic, microscopic, and physiologic tests for paraxanthin. In the evaporation, other xanthin-leukomains crystallized out, but the fluid was not sufficiently evaporated to get rid of these leukomains and give a pure solution of paraxanthin, as was done in the case reported in my previous paper. The resulting fluid in this case was, therefore, a solution of the leukomains of the xanthin-group, the most important of which is paraxanthin.

First experiment. Five minims of this fluid were injected into a full-grown house-mouse. In five minutes the mouse was very nervous, its breathing very rapid, its muscles twitching. The muscular twitching gave way to convulsive movements, and the mouse died fifteen minutes after the injection.

Second experiment. A second mouse was injected

with two and a half minims of the same fluid. In fifteen minutes it did not resist handling, was apathetic, and its breathing rapid and labored. After the mouse had remained in this condition for a half-hour a second injection of two-and-one-half minims was given; three minutes later convulsive movements came on and continued till the mouse died, fifteen minutes after the last injection.

Specimen No. 8. Two gallons of urine were obtained from a patient in whom migrainous attacks were superseded by epileptoid attacks after she was sixty years of age. This is the same case so fully described in my previous paper, already referred to. The urine was passed between and for some days after two very severe attacks which occurred the same day. The urine was examined by Mr. Bange, and the final fluid evaporated to 8 c.c. Result: Paraxanthin and other leukomains of the xanthin-group were found in considerable quantities, and the resulting fluid was very poisonous to mice. From the resulting fluid hypoxanthin, xanthin, and other leukomains were eliminated, so as to have as pure a solution of paraxanthin as possible; this solution responded to the chemic, microscopic, and physiologic tests for paraxanthin.

The concentration and strength of this 8 c.c. of paraxanthin-solution is shown by its very poisonous effects on mice. If one minim of this solution was injected into the peritoneal cavity of a mouse it produced increased nervous excitability and convulsions, followed by general tetanic muscular contractions, which always terminated in death. The small quantity of the paraxanthin-solution (one minim) required to produce this effect, when compared with the non-poisonous effect of ten or twenty minims of the "resultant fluid" from normal urine, shows that in this case paraxanthin was enormously increased

in quantity in the urine passed by this patient during or just after an epileptoid attack.

From the foregoing examinations and experiments the following summary may be made:

1. Two gallons of normal urine do not, by the method used, yield an appreciable quantity of paraxanthin or other leukomains of the xanthin-group.

2. One quart of *grand mal* epileptic urine passed between and after severe epileptic convulsions did not yield an appreciable quantity of paraxanthin or other leukomains of the xanthin-group.

3. Two quarts of *petit mal* epileptic urine, passed just before and after an attack, did not yield an appreciable quantity of paraxanthin or other leukomains of the xanthin-group.

4. Four quarts of urine from a case of influenza-mania, passed during the attack, did not contain an appreciable quantity of paraxanthin or other leukomains of the xanthin-group.

5. Four quarts of urine, passed during and after a severe migrainous attack, yielded considerable quantities of paraxanthin and other leukomains of the xanthin-group.

6. Eight quarts of urine, passed during and after a migrainous epileptoid attack, yielded comparatively large quantities of paraxanthin and other leukomains of the xanthin-group.

Upon the above investigations here summarized I base the following conclusions:

1. Normal urine contains such a small quantity of uric-acid leukomains that they cannot be detected in such quantities of urine as can conveniently be obtained from one person for urinalysis.

2. Many pathologic urines, including the urines in *grand mal, petit mal,* and influenza-mania, contain so small a quantity of the poisonous uric-acid leukomains that it is highly improbable that they act as etiologic factors in the production of these diseases.

3. Urine passed during an attack of migraine or migrainous epilepsy contains such comparatively large quantities of paraxanthin and other leukomains of the xanthin-group as to make it highly probable that they act as important etiologic factors in the production of these diseases.

At the present time there is probably no fallacy more deeply rooted in the medical mind than that uric acid and its compounds are toxic, and that they produce by their direct action on the nervous system a number of nervous diseases. The uric-acid theory of nervous disorders has never been supported by chemic or physiologic experiment. But it has been such a convenient theory to cloak our ignorance concerning the etiology of so many diseased conditions, that now we are loath to give it up, even in the light of the experiments which in recent years have demonstrated that it is non-toxic, and that it can only produce disease in a mechanical or reflex way by reason of its insolubility in the body-media. But the time has now come for us to discard, once and for all, the idea that uric acid and its compounds, by their presence in solution in the blood, can produce nervous symptoms. In accepting the non-toxicity of uric acid and its compounds we are compelled to seek another explanation for the nervous disorders which have heretofore been thought to

be due to the toxicity of these substances. But in doing so we must not forget that uric acid and its compounds, by reason of their insolubility, may be pathologic factors in gravel, gout, and other diseased conditions, and that the term uric-acid diathesis is rightfully used to describe the condition in which, either from increased production or deficient elimination, there is an excess of uric acid or its compounds either in the blood or in the tissues.

In some diseases, such, for example, as gout, which belong to the uric-acid diathesis, the distressing symptoms are no doubt due to the precipitation in the tissues or elsewhere of the comparatively insoluble urates; but in other diseases, such for example as migraine, which may also be classed as coming under the uric-acid diathesis, the uric acid, although it may occur in excess in the blood and urine of these cases, has nothing whatever to do with producing the constitutional symptoms. It is a sign, but not a cause of these diseases. The extensive and valuable studies of Haig and others have clearly demonstrated that there is a form of migraine and a form of epilepsy in which the excretion of uric acid and the proportion of uric acid to urea in the urine are greatly increased during the paroxysm of these diseases, but these carefully-made observations were misinterpreted to mean that uric acid in the blood was the cause of these diseases. My investigations show that in a case of migraine and in a case of migrainous epilepsy there was in the urine passed by these patients during their attacks, not only an increase of uric acid and an increase in the ratio of uric acid to urea, but there was also found a very great

increase of the poisonous leukomains of the uric-acid group, and the paraxanthin-solution from the migrainous-epilepsy case produced in mice symptoms very like those from which my patient suffered.

These obervations tempt me to offer the following substitute for the uric-acid hypothesis in explaining the etiology of migraine and kindred nervous disorders.

First. Typical migraine is due to the action on the nervous centers of soluble, poisonous uric-acid leukomains. The presence of an excess of these leukomains in the blood precipitates an attack of migrane, which is terminated by their elimination through the stomach and kidneys.

Second. Leukomain-epilepsy is a form of epilepsy etiologically quite distinct from the other forms of epilepsy. It is caused by the action on the nervous centers of paraxanthin and other poisonous leukomains of the uric-acid group, which by their presence in the blood precipitate an attack. Leukomain-epilepsy usually supersedes migraine; it commonly comes on after middle life, and does not, as a rule, impair the intellect.

The foregoing is offered only as a working hypothesis, to be confirmed or disproved by subsequent work in this field.

NOTES ON TREATMENT.

In the case of migraine I got, as noted, fairly good results from Haig's dietetic treatment. No wine or malt liquors and no fresh meat were allowed, but milk, eggs, fruits, and vegetables, *ad libitum.* But in the case of leukomain-epilepsy very little good

was accomplished by this treatment; however, when sodium phosphate, Carlsbad salts, or sodium salicylate was added to the treatment the patient was benefited. After some weeks without medicinal treatment this patient was placed upon potassium permanganate, one grain three times a day. At the present writing (August 12th) she has been taking the permanganate for two-and-one-half months, and has apparently derived more benefit from it than from the other medicines named. She passed a longer interval (seven weeks) without having an attack under the permanganate treatment than after any other. I am not at all sanguine about the therapeutic value of potassium permanganate in leukomain-poisoning, but only mention it here because it was suggested by the fact that I found it to be a good antidote for paraxanthin-poisoning in the mouse.

In my studies I was struck by the fact (as noted in my previous paper) that the most poisonous leukomains of the uric-acid group, viz., paraxanthin, xanthin, and gerontin, each have two atoms of O, while uric acid has three. Uric acid is, therefore, a more highly oxidized body than these poisonous leukomains. These facts suggested the use of potassium permanganate in leukomain-poisoning, because of its well-known oxidizing properties. I do not wish to offer the foregoing observations as an explanation of the action of the permanganate in paraxanthin-poisoning, but only mention them because they suggested its use in this condition. Before using the drug in the case of leukomain-epilepsy, as already narrated, the following experiments were made.

Experiment No. 1. One minim of the paraxanthin-solution obtained from the leukomain-epilepsy case + one minim of distilled water was injected into the peritoneal cavity of a house-mouse; the mouse died from paraxanthin-poisoning with the symptoms previously detailed (control-experiment).

Experiment No. 2. One minim of the same paraxanthin-solution + one minim of a one per cent. solution of potassium permanganate was injected into the peritoneal cavity of a mouse. This mouse, although quite sick, did not have the characteristic symptoms of paraxanthin-poisoning, and, after a time, entirely recovered.

These and other experiments convinced me that the permanganate is a fairly good antidote for paraxanthin-poisoning in the mouse, and led me to try its use in the case of leukomain-poisoning from which the paraxanthin-solution was obtained. But I must say that my experience thus far does not promise any great things from the use of the drug in this condition.

I believe that in this paper I have touched upon a field ripe for clinical research, and my only excuse for publishing observations so incomplete is that it is almost impossible for a busy practitioner to find the time to carry to anything like satisfactory completion a work that requires so much time and labor as this one does.

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