

RELATION OF URIC ACID TO MIGRAINE.*

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It is not strange that the causal relation of uric acid to migraine has repeatedly suggested itself to the minds of physicians, for the etiology of migraine has always been to the clinician what the origin and significance of uric acid has been to the physiologic chemist—a matter of speculation.

The enthusiasm which has arisen in the past decade or more in the study of the secretions and excretions of the living organism, has again awakened investigations referring to the effect of uric acid on the human body, and its relations to disease. So thorough has been this awakening that the foundation principles of pathology and therapeutics seem to have been threatened. Diseases, the etiology and pathology of which were thought to be beyond question, are now considered with reference to uric acid formation. Remedies which were formerly given because they overcame disease, are now given because they counteract the formation, and increase the elimination of uric acid.

Among the many diseases which have been etiologically considered with reference to uric acid, may be mentioned rheumatism, gout, migraine, epilepsy, asthma, and melancholia. Some investigators have become so impressed with the effect of uric acid on the human system that they have attempted to account for a man's disposition, his emotions, and even his character, by referring to the amount of uric acid which he retains in his system. It would seem from the writings of some that philosophy and religion, as well as medicine, would have to be considered anew from the standpoint of the uric acid diathesis.

The study of the relation of uric acid to migraine has, probably, received the most attention. Migraine has been called "the uric acid headache," because examinations of the urine, during and after the attack, seemed to show that the normal relation of uric acid to urea had been disturbed. That is, the amount of uric acid excreted, relative to the urea, is increased during the attack, while after the attack it is normal in quantity for a time, or diminished. "The greater the relative excess of uric acid, and the greater its absolute excretion per hour, the more severe the headache." (Haig.) From this it is concluded that uric acid is the cause of migraine.

With this theory in mind, I have for the past three years turned my attention to the study of the urine with special reference to the relation of uric acid and urea, in the cases of migraine which have come under my observation. In order that there may be no misunderstanding in reference to the results obtained, it will be necessary for me to describe briefly the methods employed in this study.

For the estimation of urea, Liebig's method was employed, which, though not as reliable as Kjeldahl's, for clinical purposes is deemed sufficiently accurate. The uric acid was estimated according to Hopkin's method, described by Von Jaksch, in his "Clinical Diagnosis," with this modification, however. Instead of titrating with the unstable potassium permanganate solution, a decinormal solution of sulphuric acid was used, with methyl orange as the indicator. This was suggested to me by a private student from the laboratory of physiologic chemistry, directed by Dr. E. C. Herter, of the

University of Berlin, and has been found to be reliable.

The urine was collected at the severest period of the headache, and quantitative estimates were made for uric acid and urea. After the headache had entirely disappeared, the urine was collected for the same length of time as before, and subjected to the same analysis. Comparisons were then made between the relation of the uric acid and urea of these two analyses.

The patient was instructed when the headache began, to save the urine of each urination in separate vessels during the entire period of the attack. From these numerous specimens, the one which was voided at the time of the greatest intensity of the headache, was selected for chemical investigation. After the headache had entirely disappeared, the second specimen was collected.

It was thought that if these headaches were due to a uric acid disturbance, it ought to be manifest in the urine at the height of the attack; and, on the other hand, that if the uric acid disturbance which so many investigators have found associated with the headaches, was a result of the attack, it ought to be manifest immediately after the headache had disappeared.

Of the investigations conducted in this way the report of three cases will be sufficient.

CASE 1.—Miss H., aged 40, a bookkeeper, has had dull, constant headache from childhood, which, at about 20 years of age, developed into paroxysms beginning over the right eye. The headaches, which are very severe, seem to be induced by overwork, or by slight colds. They are likely to occur during the menstrual periods, which have been frequent and profuse for the past ten years, but occur also at other times. Aside from the headaches, she gives symptoms of neurasthenia, but more of digestive disturbance. She has never had a serious illness. Her mother was subject to headaches, though not of the same nature, and had rheumatoid arthritis, slightly. She is pale, and sallow and weighs 138 pounds, but has no physical signs other than relaxed abdominal walls, and a right movable kidney. Blood examination: hemoglobin, 45 per cent., red blood-corpuscles, 4,600,000, numerous poikilocytes.

URINE ANALYSES.

Time.	Amt. c.c.	Sp. Grav.	React'n.	Color.	Urea gm.	Uric Acid. gm.	Ratio.
Dec. 28, 1896, between attacks.	100	1024	Acid.	Amber.	2.312	0.0327	1-70
Jan. 9, 1897, height of attack.	100	1002	Neutral.	Pale.	0.3316	0.005	1-66
Jan. 9, 1897, after attack . . .	100	1025	Alkaline.	Pale.	2.43	0.1512	1-16
Jan. 12, 1897, height of attack	100	1006	Alkaline.	Pale.	0.718	0.006	1-12
Jan. 12, 1897, after attack . .	100	1019	Acid.	Amber.	1.57	0.03	1-52
Jan. 29, 1897, height of attack.	100	1017	Acid.	1.61	0.0317	1-50
Jan. 29, 1897, after attack . .	100	1006	Acid.	0.68	0.0185	1-36

A mixed diet, and also nine glasses of milk a day, were prescribed, and phosphate of soda was given three times a day. At the end of a month there was no abatement of the headaches, and the anemia was increased: hemoglobin 40 per cent., red blood-corpuscles, 4,000,000. The milk was then discontinued and salicylate of soda and Bland's pills prescribed. At the end of three months the headaches were not as frequent, nor nearly so severe. The anemia had disappeared, hemoglobin, 87 per cent., red blood-corpuscles, 6,160,000.

The patient then took up her work as bookkeeper, and at the end of a year the headaches had increased in frequency and severity. The blood again showed a slight degree of anemia. A diet, consisting almost wholly of vegetables and cereals was then prescribed, and continued for four months, but the headaches were more frequent than before. A milk diet was then prescribed,

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with most disastrous effects, the headaches being more severe than ever.

URINE ANALYSES.

Time.	Amt. c.c.	Sp. Grav.	Reac- tion.	Color.	Urea. gm.	Uric Acid, gm.	Ratio.
Feb. 16, 1899, height of attack . .	100	1002	Acid.	Pale.	0.26	0.0584	1-30
Feb. 16, 1899, directly after attack	100	1002	Acid.	Amber.	0.48	0.0285	1-16
Feb. 17, 1899, 18 hrs. after attack.	100	1012	Acid.	Amber.	1.53	0.042	1-36

The patient was again given a wholly vegetable diet, and salicylate of soda was taken three times a day. This was continued for two months, during which time the headaches were as severe and as frequent as when first seen two years previously. The anemia also increased: hemoglobin, 68 per cent., red blood-corpuscles, 5,440,000. A mixed diet, meat two or three times a day, was then prescribed, when the headaches became decidedly less frequent, and the patient improved greatly in general health. This condition has continued up to the present time.

CASE 2.—Mrs. R., aged 54, a society woman, has had sick headaches all her life, coming on every week or ten days. The headache always begins on the right side, and is accompanied with nausea and vomiting; she gives a typical description of migraine. Ten years ago she had a double ovariectomy on account of a uterine fibroid, and has not menstruated since. The headaches have continued as before the operation. Her father had similar attacks of headache and a brother is also so afflicted. A physical examination of the patient showed no abnormal signs. Examination of blood: hemoglobin, 100 per cent., red blood-corpuscles, 5,920,000.

URINE ANALYSES.

Time.	Amt. c.c.	Sp. Grav.	Reac- tion.	Color.	Urea. gm.	Uric Acid gm.	Ratio.
Aug. 8, 1898, between attacks.	100	1018	Acid.	Pale.	2.058	0.0419	1-49
Aug. 23, 1898, height of attack.	100	1008	Acid.	Pale.	0.92	0.00672	1-136
Aug. 23, 1898, after attack.	100	1014	Acid.	Amber.	1.54	0.0436	1-35

This patient was allowed to take a vegetable diet. Salicylate of soda in 5-grain doses was given three times a day. At the end of two weeks a second headache occurred, which was mild; in two weeks more, a third attack, very mild; in two weeks again, only suggestion of a headache, and thereafter, no headache at all. At this time the blood examination was as follows: hemoglobin, 93 per cent., red blood-corpuscles, 5,840,000. This condition continued for six months. Social duties were again undertaken, and the headaches became almost as frequent as before, though not nearly as severe.

CASE 3.—Mrs. F., aged 40, complains of a frontal headache, accompanied with nausea and vomiting. The attacks occur every seven or ten days. She has had these headaches since early childhood, has always had obstinate constipation, but no hereditary history of migraine. The patient is pale, and very nervous; tongue, heavily coated; pulse, 96; no valvular heart disease; has hemorrhoids and retroversion of the uterus. Blood examination: hemoglobin, 83 per cent., red blood-corpuscles, 5,520,000.

URINE ANALYSES.

Time.	Amt. c.c.	Sp. Grav.	Reac-ti'n.	Color.	Urea. gm.	Uric Acid, gm.	Ratio.
Oct. 19, 1898, between attacks.	100	1010	Acid.	Pale.	1.13	0.025	1-45
Nov. 7, 1898, height of attack.	100	1016	Alkaline	Pale.	1.22	0.028	1-42
Nov. 7, 1898, after attack.	100	1020	Acid. +	Amber.	2.28	0.201	1-11

The patient was allowed a vegetable diet, and salicylate of soda was prescribed in 5-grain doses three times a day. Owing to sickness in the family, which called the patient away, no further observations were made.

It will be seen from the study of these cases: 1, both uric acid and urea were diminished during the height of the headache, but their relation was not disturbed; 2, that after the headache, the urea increased to about what it was between the attacks, while the uric acid increased much more, thus changing the former ratio.

These results differ from those on which the uric acid theory of migraine has been founded, in that the urea has not been found so stable a quantity as the results of other investigators show; and that the uric acid has not been increased during the headache, but, on the other hand, greatly diminished. Immediately following the headache, however, there was a great increase of uric acid.

When in these cases, however, the urine was collected during the whole period of the headache, and after the headache the urine was again collected for the same length of time, and quantitative analyses made of these two collections, the results were found to correspond exactly with those on which the uric acid theory has been founded.

From this it was concluded that the uric acid wave which is immediately associated with migraine does not appear until the latter part of the attack, and is really at its height when the attack is passing off. In other words, the time of the greatest severity of the headache precedes the highest point of the uric acid wave by a period of from two to three or four hours, as the case may be.

If this be true, and all my investigations have confirmed it, then it would seem that the increase of uric acid which is associated with migraine, is the result and not the cause of the headache. This conclusion does not seem unreasonable, when one recalls the decided digestive disturbances which take place during an attack of migraine. Digestion seems to be stopped at once, and nausea and vomiting follow. There is a disgust for food, and the appetite does not return for several days.

The uric acid theory of migraine does not alone depend on what is believed to be an absolute fact; namely, that uric acid is excreted in larger amount, absolutely and relatively to urea, during an attack of headache than at other times, but it is supported by a number of hypotheses which recent research has proved to be untenable.

It is supposed that migraine, being the sensory equivalent of epilepsy, must be due to the same cause as epilepsy, and, partially from the results of chemical analyses, and partially from analogy, it is concluded that epilepsy is due to a uric acid condition. But those who have studied epilepsy more recently from this standpoint, have come to the conclusion that the idea that the epileptic seizure is in any way caused by uric acid poisoning is wholly incorrect, and that the increased uric acid is an entirely secondary phenomenon, dependent on disturbances of digestion and metabolism due to the seizure itself.

It is stated that during an attack of migraine there is an excess of uric acid in the blood, and, as the same condition exists in an attack of gout, therefore migraine and gout must be due to the same cause, uric acid. But recently in the study of sixteen cases of gout by Adolf Magnus-Levy¹, he found that while uric acid in the urine was distinctly increased in nearly all cases of

¹ Zeitsch. f. Klin. Med., B. xxxvi, H. 5-6.

gout, especially during the first day, there was no diminution of alkalinity of the blood, but, in some cases, there was a slight increase of alkalinity. Until such a careful study of the blood is made in migraine, it will be a mere guess to say that there is more uric acid in the blood during the attack than at other times.

Because there is a leucocytosis, similar to that in uric acid diathesis, often present in attacks of migraine, it is concluded, according to the theory of Neusser in reference to the perinuclear basophilic granules, that migraine belongs to that class of diseases commonly called the uric acid diathesis. But a study of fifty cases having the uric acid diathesis, by Charles E. Simon², showed that there is no constant relation between the presence of the basophilic granules, and the elimination of uric acid or even of xanthin bases.

In accord with the uric acid theory of migraine, the vasomotor phenomena, the angiopastic, and the angio-paretic conditions described by Mollendorf and Latham, have been attributed to a "blocking up of capillaries by colloid uric acid." This is certainly a very ingenious explanation, but failing to confirm it by ophthalmic studies, and by every means at one's command, it is as unsatisfactory an explanation of migraine as the vasomotor neurosis theory, itself.

From these refutations of the hypotheses, on the validity of which depends in a great degree the uric acid theory of migraine, it is concluded that whatever foundation there is for it, the theory must be based on the chemical investigation of the urine. But, as stated heretofore, in studying the urine closely through the attacks of migraine, it was always found that the highest period of the wave of uric acid excretion followed by several hours the period of greatest intensity of the headache. From this it seems evident that the increase of uric acid secretion which is associated with migraine must be the result of the headache, and not the cause of it. It can not be denied that through these studies of uric acid and certain by-products in the urine, we are coming to a closer knowledge of the causation of migraine, but Gower's statement is still applicable: "When all has been said that can be, mystery still envelops the mechanism of migraine."

MIGRAINE*.

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Migraine and headache are commonly considered synonymous terms. Migraine is, however, a distinct disease, the headache being its most pronounced and distressing symptom. In rare cases we may even have migraine without headache. It is undoubtedly the most frequent of all neuroses.

It is my desire to record some of the more striking manifestations of the disease as gathered from an unusually rich clinical experience. I shall base my remarks on the notes taken on fifty consecutive cases, the majority of which are taken from the neurologic clinics of Dr. H. T. Patrick, Chicago.

In looking over the notes, the first important item is the family history, the usual entry being "mother migrainous," "mother and two maternal aunts migrainous," "mother and mother's mother migrainous," "mother and father migrainous," "mother and two sisters migrainous," etc., the disease showing itself in six or seven mem-

bers of a family in some instances. To be exact there is a distinct history of direct heredity in 40 of the 50 cases. Of the 10 remaining cases, 8 knew little or nothing of parents and family; 2 explicitly said that neither mother nor father had headaches. Throwing out the 8 cases of uncertain history, we have 95.2 per cent. of the cases showing migraine in the family. Such figures are extremely significant. Thus we see that direct heredity easily plays the star rôle in the etiology of migraine. We might almost say that heredity was the *sine qua non* of the disease, the exceptions being only sufficient to prove the rule.

How the disease is transmitted, whether through the blood, or through instability of nerve-cells leads at once into the domain of theory, which has no place in this paper. The whole question of heredity is little understood and vague, and need not be touched on here. Suffice it to say that the pathology of the disease is unknown, no theory so far advanced being able to sufficiently explain all the phenomena of the disease. Moebius, in his monograph on migraine, says that 90 per cent. of his cases—87 in number—gave a history of migraine in the family. With such figures confronting me it is difficult to see how the other conditions so frequently ascribed as causes of migraine can assume any prominence, such as eye strain, deviations of septum, adenoids, pelvic disturbances, gout, rheumatism or lithemia. Because we sometimes see in the same patient adenoids and migraine, eye strain and migraine, indigestion and migraine, pelvic disturbances and migraine, hemorrhoids and migraine, etc., does not prove anything. They are simply coincident conditions. In England, where gout is very prevalent, much weight is ascribed to gout and lithemia as etiologic factors in migraine. In Germany, where there is little gout, Moebius states that he has never seen a case of migraine with gout, or with a family history of gout. Any of these coincident conditions may act as exciting causes, precipitating attacks, making them more severe and frequent.

It goes without saying that all such depraved conditions must be corrected as the first step in any plan of treatment. No modern medical man would to-day think of treating epilepsy, for instance, without first eliminating, so far as possible, all abnormal conditions, which might act as exciting causes of attacks. The best authorities, however, do not claim for an instant that the underlying cause of epilepsy is reflex in character.

With figures so overwhelmingly in favor of direct heredity as the etiologic factor of migraine, the so-called reflex causes assume insignificant proportions. I believe that these figures will assume even larger proportions, the more thoroughly and carefully family histories are elicited. A history of severe paroxysmal headache, extending over a number of years, is highly significant of migraine. Add to this a family history of migraine and the diagnosis is assured. Ophthalmic symptoms and vomiting are unnecessary for the diagnosis. It is always to be remembered, however, that brain tumor, chronic Bright's disease, glaucoma, or any organic lesion may develop in migrainous patients, and are to be excluded by the usual methods.

Authorities differ largely as to the part sex plays in the etiology of the disease. All agree, however, that females are more frequently affected. In Moebius' cases 60 per cent. were females. In Henschen's 140 cases 90 per cent. were females. In my series of 50 cases 80.4 per cent. are females. Of the 40 cases giving a distinct history of direct heredity, in 82 per cent. the inheritance is from the mother's side. Gowers says that in epilepsy

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² Am. Jour. Med. Sci.