RACHFORD (B.K.)

PARAXANTHIN AS A FACTOR IN THE ETIOLOGY OF CERTAIN OBSCURE NERVOUS CONDITIONS.

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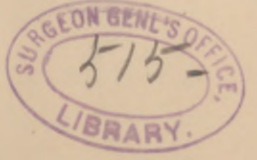
THIS paper narrates the history of a patient that, at irregular intervals, had paroxysmal nervous attacks, the etiology of which was very obscure. After several months of careful study of this case I thought it possible that paraxanthin, a poisonous leukomain of the uric-acid group, by occurring in excess in the blood of this patient, might be the cause of these peculiar nervous attacks. Acting upon this idea, I procured eight liters of urine passed by the patient the day before, the day of, and some days after, a severe attack. From this urine 8 c.c. of a solution of paraxanthin was separated. One minim of this solution injected into the peritoneal cavity of a mouse produced symptoms much like those from which my patient suffered. The inference is drawn that we may have in the poisonous leukomains of the uric-acid group important and heretofore altogether overlooked factors in the production of certain nervous diseases and conditions.

That the reader may judge of the correctness of this inference, I give here a detailed history of the



case and of the experiments upon which the inference is based.

Mrs. X., sixty-three years of age, is married, and the mother of six grown children. The family history is negative, except that "one sister had some nervous trouble of the heart." The patient was always a hard-working woman until a few years ago, when her grown daughters took charge of all the household affairs, and left her without occupation. She has always been rather stout, but of late years her hearty eating and inactive life have made her much stouter than before; she now weighs more than two hundred pounds, and spends most of the day in her easy chair; she has quite as capacious an appetite as she has ever had, and is now, as she has always been, especially fond of meat. From her earliest remembrance to September, 1892, she suffered from periodic attacks of "sick headache," but since this date she has not had a single characteristic sick headache; instead of sick headache she has had epileptoid attacks, which have continued to the present time at about the same interval as her previous attacks of migraine. It is the origin of these epileptoid attacks, and of the previous megrim, that will especially interest us in the study of this case.

In September, 1892, she fell in her first "spell," and was carried into the house in an unconscious condition; after about thirty minutes she regained consciousness, but did not know anything about what had happened. For twelve hours after the attack she had a severe headache, which passed away, leaving her as well as usual. The doctor who saw her in this and many of her subsequent attacks thought in the beginning that they were apoplectic. She continued to have attacks similar to this one at intervals of about three or four weeks.

In all of these "spells" she became unconscious, and remained so for from twenty to forty minutes, when she would regain consciousness, to find herself suffering from a severe headache, which would pass off in from twelve to twenty-four hours, leaving her quite well again. These attacks came on without apparent exciting cause, and with absolutely no warning; she feels as well, if not better, than usual just before the attack, and they not infrequently come on at night during sleep. A number of times the patient has been seized with an attack while on her feet, and has fallen heavily to the floor. On one occasion she bruised her face and shoulder by a fall of this kind. The after-headache became less and less severe as the time passed, until at the present time "there is almost no headache following a spell." After five or six months these epileptoid attacks were less frequent, so that five or six weeks would at times intervene between the attacks, but such a long interval was usually followed by an unusually severe attack, and not infrequently by two attacks within a few hours. In the interval between the spells the patient was quite well, except that she was somewhat mentally depressed with the certain knowledge that at the end of five or six weeks she was sure to have "another spell." On September 18, 1893, three days after a very severe "spell," she came to my office for the first time. At this visit I obtained her previous history, and I prescribed phosphate of soda, in teaspoonful doses after each meal. The next day I examined her urine and found no albumin, sugar, or casts.

On January 14, 1894, the attacks had continued at intervals of from three to six weeks, but I had not been fortunate enough until this day to witness one of these attacks. On this day she had two attacks, the first one mild, the second one severe. I saw her in the

second. The first attack was at 8 in the morning, and occurred as usual without warning. It lasted from twenty to thirty minutes, and she had just regained consciousness when I reached the house. At this time she was restless, somewhat confused in mind, and complained of pain in the left shoulder; the respiration was normal, the pulse 90, strong and regular. By this time I knew enough of the case to suspect that this mild attack would be followed by another and more severe during the day. I therefore arranged matters so that I could reach the patient within a few minutes should she have another attack during the day. At 7 P.M. the second attack occurred, and I had the good fortune to be present. This attack came on while the patient was in bed. She had remained in bed all day as a precautionary measure against a second attack, and all day she had seemed as well as usual, even up to the moment of her second attack. In the beginning of the attack the attention of the family was attracted by her peculiar, noisy breathing. She became unconscious at once, and her breathing very *labored*, her lips blue, the face congested; the arms and legs were straightened and stiffened, and remained rigid for eight or ten minutes, and then became relaxed and remained so during the remainder of the attack; the congestion of the face soon passed off, and the lips became red again, but the heavy, noisy, irregular breathing continued for twenty or twenty-five minutes, and did not become quiet and regular till just before the patient regained consciousness. The pulse in the beginning of the attack was strong, regular, and about 85 or 90 per minute; it gradually increased in frequency until at the close of the attack, which lasted forty minutes, it was 120 per minute; all the time, however, it was strong and regular. After the attack the pulse gradually re-

turned to the normal. The pupils were the same on both sides; they reacted to light and were contracted till near the close of the attack, when they became normal. There were no muscular twitchings except in her right upper eyelid, and here they occurred for a short time only during the most severe part of the paroxysm. After the heavy breathing subsided the woman lay for about ten minutes apparently in a normal sleep; she then began to move, opened her eyes, was much confused, and was not able to understand what had happened to her. She was now very restless, complained of pain in her left shoulder and wished to be moved frequently; she also complained of being sick at the stomach (this has been a common symptom in her recent attacks, but she has never vomited in any of them). About one hour later she went to sleep and slept the greater portion of the night. The next day she did not feel sick, but remained in bed, and on the second day she was up and about as usual.

This attack was "just like all of her previous spells," and as for a special purpose I have described this attack in detail, I would call particular attention to the following points, which were characteristic of all her attacks:

1. Sudden onset of attack, no warning.
2. Muscles rigid, but not convulsed.
3. Labored, gasping, irregular breathing.
4. Unconsciousness from beginning to end of the attack.
5. Heart-action rapid, but regular and strong.

In the study of this case it seemed to me that the peculiar attacks described had taken the place of the sick headaches of former years, and were therefore possibly of like origin. The case seemed to

me to correspond in every particular to that class of cases which Alexander Haig[1] describes as being due to that very indefinite condition "the uric-acid diathesis." My patient was stout, inactive, a great meat-eater, had suffered from sick-headache all her life till these headaches were substituted by the explosive attacks described. Surely this was a typical "uric-acid case," and I decided to put her on the treatment recommened by Haig. I asked her to stop eating meat, to eat sparingly of eggs, and to take no wine or malt liquors. All other food, such as milk, bread, and all kinds of fruit and vegetables she might have *ad libitum*. The medical treatment consisted of a dose of Carlsbad salts each morning and 5 grains of piperazin three times a day. I placed her upon this treatment, not because I believed her symptoms due to "uricemia," but because whatever might be the cause of the symptoms, I hoped to get the same good results from treatment that Haig had reported. I also directed that all the urine should be saved and sent each morning to Mr. Otto F. Bange, a competent chemist, who very kindly took great interest in making a quantitative estimate of the urea and uric acid in this urine from day to day.

On February 25th the woman had two attacks, one mild and one very severe. I again had the good fortune to witness one of these attacks, and it was quite as severe as and in every way similar to the attack described. The treatment as outlined had been faithfully carried out, and the piperazin had been given a fair trial without apparent influence in

[1] "Uric Acid."

either warding off or in modifying the severity of the attacks. The influence of the piperazin on the excretion of urea and uric acid is shown in the following table. In all of these examinations the specimen of urine examined was a part of the whole twenty-four hours' urine, except in the examinations made on the 24th, 25th, and 26th of February. The amount is calculated to 1000 c.c. of urine, which was the average amount passed by this patient in twenty-four hours.

From the table (page 8) one sees that the amount of uric acid was somewhat increased during the first ten days of the treatment, and was somewhat diminished during the last days of the treatment. But the increased excretion of uric acid under this treatment did not in any way influence the frequency or severity of the attacks. I would call special attention to the amounts of urea and uric acid in the specimens of urine examined on the 25th and 26th of February, just before and just after the severe attacks of February 25th.

Urine, February 25th, 6 A.M. Just before attack, urea, 6.00; uric acid, 0.25.

Urine, February 25th, 9 A.M. Just after first attack, urea, 7.00; uric acid, 0.55.

Urine, February 25th, 5 P.M. Just before second attack, urea, 8.00; uric acid, 0.40.

Urine, February 26th, 9 P.M. Just after second attack, urea, 5.00; uric acid, 0.15.

Urine, February 26th, 8 A.M. Next morning after attack, urea 12.00; uric acid, 0.25.

The study of the figures given is of considerable interest, as they clearly show that the excretion of urea is diminished and the excretion of uric acid increased during these attacks. The proportion of uric acid to urea is therefore greatly increased.

Date.	Urea in 24 hours.	Uric acid in 24 hours.	Medicine.
January 19	12.23	0.57	Piperazin
" 20	13.10	0.55	15 grains.
" 21	10.23	0.35	"
" 22	14.00	0.50	"
" 23	15.00	0.65	"
" 24			
" 25	14.00	0.65	"
" 26	13.50	0.53	"
" 27	12.50	0.50	"
" 28	15.00	0.67	"
" 29	13.9	0.82	"
" 30	14.25	0.45	"
February 1	10.00	0.25	"
" 2	12.00	0.36	"
" 3	9.00	0.30	"
" 4	8.00	0.40	"
" 5	9.00	0.36	"
" 6	10.00	0.50	"
" 7	14.00	0.50	"
" 11	10.00	0.25	"
" 13	12.00	0.35	"
" 15	11.00	0.33	"
" 16	10.00	0.25	"
" 25, 6 A.M.	6.00	0.25	"
" 25, 9 A.M.	7.00	0.55	"
" 25, 5 P.M.	8.00	0.40	"
" 25, 9 P.M.	5.00	0.15	"
" 26, 8 A.M.	12.00	0.25	"

Haig believes that the symptoms in just such cases as this may be explained upon the hypothesis that the uric acid occurs in excess in the blood and causes these symptoms by its action on the nervous centers, and that with the rapid elimination of the uric acid the blood is relieved of this excess and the symptoms subside. But Haig's hypothesis seems to me quite inadequate to explain the symptoms in the case reported, for the simple reason that *uric acid* and *its compounds are non-toxic.*

Bouchard[1] injected "experimentally into the

[1] "Auto-intoxication in Disease," 1894.

blood thirty centigrams of uric acid for each kilogram of the animal without apparent accident." In one instance he injected sixty-four centigrams for each kilogram without injury to the animal. When death did occur, following excessive quantities of uric acid, he was convinced by his observations that death was alone due to the excess of the vehicle. Roberts[1] says that "uric acid and its compounds are deleterious simply because of their sparing solubility in the bodily media." As all experimental evidence is opposed to the idea that uric acid could produce such a group of symptoms as were presented in this case, I was impelled to search elsewhere for the cause of these attacks, and in doing so I was led to inquire into the possibility of leukomain-poisoning as a cause of the nervous paroxysms. The reasons that determined the research, in spite of the fact that the uric acid leukomains had been found in normal and many pathologic urines, in such very minute quantities as to make it highly improbable that they could enter as etiologic factors in the production of disease, were as follows :

1. In this case there was an increase in the excretion of uric acid during the attack, and Haig[2] has shown that this increased excretion of uric acid is a constant accompaniment of certain forms of sick-headache and epileptoid attacks. It therefore seemed possible that along with the increased excretion of uric acid there might be an increased excretion of uric-acid leukomains, as these bodies

[1] "Uric Acid, Gravel and Gout," 1892.

[2] "Uric Acid."

belong to the same chemical group and are probably formed by the same or a like metabolism.

2. It seemed altogether possible that a perverted metabolism or a defective elimination might result in these leukomains being present in the blood in abnormal quantities not at all indicated by the amount of uric acid excreted.

3. Paraxanthin, the most poisonous leukomain of the group, when injected into mice, produces symptoms much like the epileptoid attacks which this patient has. According to Salomon,[1] it produces dyspnea and rigor mortis, or stiffening of the muscles.

For the foregoing reasons I thought it worth while to inquire whether or not paraxanthin was excreted in excess in the urine during these attacks. It was decided to make the experiment as clean as possible by separating from the urine only the paraxanthin; the other xanthin compounds, some of which are poisonous, were gotten rid of.

The eight liters of urine used for the investigation were passed just before, during, and following the severe attack of the 25th of February. Boric acid was added to the urine while it stood, to prevent fermentation. This urine was delivered to Mr. Otto Bange, the chemist, with the request that he would abstract from it the paraxanthin it contained; but as this process is tedious, requiring some weeks for its completion, the patient was in the meantime looked after in the following manner: The piper-

[1] Ber. d. Chem. Gesellsch., 1878, 1883, and 1888; Archiv f. Physiol., 1882, 1884; Zeitschr. f. klin. Med., 1884; Zeitschr. f. Physiol. Chem., 1887, 1889; Arch. f. Anat. u. Physiol., 1878, 1887; Verhandlung d. Phys. Gesellsch. zu Berlin, 1880–81.

azin and Carlsbad salts were discontinued, and the patient was advised to continue the same diet, abstaining from meat as before, and to take a teaspoonful of phosphate of sodium in a cup of hot water each morning, and ten grains of salicylate of sodium three times a day; this treatment was continued for one week. During the second week only two ten-grain doses of salicylate of sodium were given each day. During the third week only one dose per day was given, and during the fourth week no medicine was given except sodium phosphate. After this the patient again took two ten-grain doses of the salicylate per day.

(The amount is calculated to 1000 c .c. of urine, the average amount excreted in one day.)

Date.	Urea in 24 hrs.	Uric acid in 24 hrs.	Medicine, per day.
March 8	14.00	0.60	Acid sal., 30 grains.
" 9	11.00	0.35	" 30 "
" 10	10.00	0.25	" 30 "
" 11			" 30 "
" 12	9.00	0.35	" 30 "
" 13	7.00	0.23	" 30 "
" 14	6.00	0.25	" 20 "
" 15	7.00	0.40	" 20 "
" 16	8.00	0.20	" 20 "
" 17	6.00	0.10	" 20 "
" 18	9.00	0.12	" 20 "
" 19			" 20 "
" 20	7.00	0.20	" 10 "
" 21	6.00	0.25	" 10 "
" 22	11.00	0.40	" 10 "
" 23			" 10 "
" 24			" 10 "
" 25	7.00	0.10	" 10 "
" 26	8.00	0.15	no med.
" 27	7.50	0.23	"
" 28	10.50	0.40	"
" 29	9.50	0.36	"
" 30	9.00	0.28	"
" 31	8.00	0.34	"
April 1	6.50	0.14	Acid sal., 20 grains.
" 2	7.50	0.15	" 20 "

On April 4th the woman had another attack, but it was not nearly so severe as those of five weeks before.

The table given shows the amounts of urea and uric acid excreted from day to day during the preceding three weeks.

It will be seen from this table and the previous one that the no-meat-diet very greatly diminished the amount of urea excreted. With the exception of occasional variations the amounts of urea in the urine progressively diminished after the patient, three months previously, had been advised to approach as nearly as practicable to a vegetable diet. The amount of uric acid in the urine also during this time progressively diminished. This was no doubt in part due to the action of the medicine, and it is also a noticeable fact that the amount of uric acid excreted fell more rapidly under the salicylate of soda than under the piperazin treatment. The patient was again advised to continue the same diet, and also to continue the sodium salicylate, ten grains twice a day, with a dose of Carlsbad salts each morning.

On April 25th the patient had one light attack, which was less severe than the one three weeks before.

On April 27th, the woman had recovered quickly from the slight attack on the 25th, and was as well as usual. It was the opinion of all who have observed the patient during the past few months that she was now better than she was four months before; the attacks were comparatively mild compared to what they were then. It seemed, therefore, altogether

probable that she had been improved by the treatment.

With this history of the case we can now return to the study of the etiology of these attacks, and to the inquiry whether or not this patient has an excess of paraxanthin in her urine, and, if so, could paraxanthin-poisoning account for the symptoms in her case?

Let us first inquire what is paraxanthin. Paraxanthin is one of the poisonous leukomains of the uric-acid group, and of all this group it is the most poisonous. According to Salomon, who was the first to isolate this substance, its physiologic action is as follows: In mice the reflexes are increased to a tetanus, followed by a rigor-mortis-like contraction of the muscles, and dyspnea is a constant symptom. The formula for paraxanthin is $C_7H_8N_4O_2$. It is a noticeable fact that paraxanthin, xanthin, and gerontin, the most poisonous leukomains of this group, all have two atoms of O, while uric acid ($C_5H_4N_4O_3$) has three atoms of O. Uric acid, it would seem, is therefore a more highly oxidized body than these poisonous leukomains.

Salomon also found that paraxanthin occurred in normal urine in such minute quantities that its poisonous properties were lost in dilution. From 1200 liters of normal urine he obtained only 1.2 grams—that is, one milligram of paraxanthin for every liter of urine. It would, therefore, take one-half a liter of urine to yield one-half a milligram of paraxanthin, which is the poisonous dose for mice.

From the 8 liters of urine previously spoken of,

Mr. O. F. Bange isolated the paraxanthin by the method of Salkowski and Salomon.[1]

By this method there was obtained 8 c.c. of a very concentrated solution of paraxanthin. From a drop of this solution on a glass slide characteristic

[1] The method in brief is as follows:

Method.—The phosphates are precipitated with ammonium hydrate; after twenty-four hours the urine is filtered or decanted from the precipitate, and a 3 per cent. solution of nitrate of silver is added to it, about 0.5 or 0.6 of silver being used for each 1000 c.c. of urine. It is, as a rule, necessary to add more ammonia to hasten precipitation; after precipitation the precipitate is washed six or eight times with distilled water by decantation; the silver compounds suspended in water are then decomposed with hydrogen sulphid, the current of H_2S is made to pass through the water in which the compounds are suspended for hours; the liquid is now decanted or filtered to separate it from the precipitate, and evaporated down to about 1000 c.c. if 6000 c.c. of urine have been used; the remaining uric acid is thereby separated; this liquid being filtered, ammonia is again added; after twenty-four hours it is again filtered and precipitated with silver nitrate, the silver being added as long as precipitation occurs; the supernatant liquid is removed by decantation, and the precipitate is transferred to a filter and allowed to stand for twenty-four hours in a dark place. It is then dissolved in hot nitric acid of 1.1 specific gravity to separate the hypoxanthin. If working with 4 liters of urine, from 60 to 70 c.c. of acid will be sufficient. After two hours, filter and carefully add ammonium hydrate to neutralization, and for the third time xanthin and paraxanthin are separated, the precipitate washed, suspended in water, and again decomposed with hydrogen sulphid. It is filtered while hot, and the filtrate evaporated to 50 c.c. and a little ammonium hydrate is added, and after twenty-four hours the last traces of phosphates and oxalates will be precipitated; the filtrate is again evaporated on a sand bath, and when the liquid begins to get turbid evaporation is suspended; the next day the xanthin will be found in a mass at the bottom of the beaker; filter the liquid and evaporate to a few c.c. —from 10 to 20—and one has a concentrated solution of paraxanthin. If the solution be very concentrated, paraxanthin will crystallize out.

paraxanthin-plates and needles crystallized out, and a drop of the solution in a solution of potassium hydrate gave the white precipitate which is characteristic of paraxanthin.

The effect of this solution on mice was next studied, mice being chosen for the experiment because they were known to be susceptible to paraxanthin poisoning, and because they were inexpensive and easily obtained.

The first experiment, on April 12, 1894, was with a full-grown house-mouse. *Time*, 5.35 P.M. Two minims of the solution were injected into the peritoneal cavity; after thirty seconds the mouse was very nervous, trembling, jerking when the sides of the can in which it was held were touched; this excitability increased almost to a tetanus, when, at the expiration of two minutes, the mouse jumped into the air and fell on its side, and after a few convulsive movements stiffened and died. The post-mortem examination showed no evidence of a needle-wound in the peritoneal cavity.

In this experiment the dose was so large that the paraxanthin proved so rapidly fatal that opportunity was not given to study the symptoms. For this reason I decided that in the next experiment I would introduce as small an amount of the solution as possible, and surely not more than one minim was used.

The second experiment was at 5.45 P.M. One minim of the same paraxanthin-solution was introduced into the peritoneal cavity of a full-grown, gray mouse. At 5.48 P.M. the mouse was very nervous, jumped spasmodically when the sides of the tin-can were touched; this reflex excitability con-

tinued until it was almost a tetanus. At 5.50 the mouse fell in convulsive movement, and almost immediately stiffened in a clonic tetanic contraction of all the muscles. This muscular tension was kept up almost uninterruptedly for three hours, when the mouse died. Toward the close of this period the muscles were relaxed, except at the onset of the attack there was no movement resembling a convulsive movement. From the beginning to the end of the attack there was dyspnea and a gasping respiration, which after a time was irregular. The heart's action was regular and apparently not affected by the poison.

By these, and many other experiments of which they are a type, it was proved that the substance separated from the urine, which responded to the chemical tests for paraxanthin, also when injected into mice produced the physiologic effects of paraxanthin.

The symptoms which are most characteristic of poisoning by this substance in the mouse are:

1. Nervousness, extreme reflex excitability — almost a tetanus.

2. Clonic, tetanic stiffening of the muscles, followed by muscular relaxation. (Convulsive movements usually absent.)

3. Dyspnea, orthopnea, asphyxia. The gasping respiration is probably the most characteristic symptom.

4. Heart unaffected.

According to Salomon one-half of a milligram will produce these symptoms in a mouse. As one minim of the 8 c.c. of concentrated solution of paraxanthin obtained from 8 liters of urine pro-

duced these symptoms, it is reasonable to conclude that this one minim contained one-half a milligram of paraxanthin, and that the 8 c.c., or 120 minims of solution contained 60 milligrams of the solution. As only one milligram of paraxanthin is found in one liter of urine, in the 8 liters of urine from this case the paraxanthin was increased as 60 to 8, or nearly eight times. From another specimen of urine, 8 liters, the paraxanthin was separated and evaporated to 8 c. c. That this solution contained paraxanthin was demonstrated by the chemical tests, and that it contained paraxanthin in very small quantities was shown by the experiment that 10 minims of the solution injected into the peritoneal cavity of a mouse did not produce the symptoms of paraxanthin-poisoning.

Upon the foregoing evidence I conclude that paraxanthin occurs in great excess in the urine passed by this patient during the epileptoid attacks already described, and that it is reasonable to believe that paraxanthin-poisoning is a potent factor in the production of these attacks.

117 Broadway.