THE RELATION
OF A
CERTAIN FORM OF HEADACHE TO THE
EXCRETION OF URIC ACID.

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IN a paper which appeared in the 'Practitioner'¹ in 1884, on the "Influence of Diet on Headache," I made some observations on the great improvement that occurred in a case of paroxysmal headache on the total abstention from butcher's meat, beer, wine, &c. I considered that the history of the case and its treatment tended to show "that the headache and other phenomena are the result of a poison circulating in the blood, that that poison is a product of the process of digestion of certain foods, especially butcher's meat, &c.," and this opinion I have found no reason to alter, but, on the contrary, my further investigations have greatly strengthened it.

With regard to the exact chemical nature of the poison, however, I was apparently not so fortunate; for I first of

¹ 'Practitioner,' 1884, vol. xxxiii, No. 2.

all suggested that it might be an alkaloid produced, by bacteria in the intestines, out of nitrogenous food taken in excess of the individual powers of digestion; but a subsequent careful investigation of the history and symptoms brought out such a strong relationship to certain modified cases of gout that in a second paper to the 'Practitioner,'¹ I put forward this view of the subject, and at the same time I began to turn my attention to the nitrogenous excreta of the urine, as the question seemed to be almost certainly one of nitrogenous metabolism. It is the result of these urinary investigations that I now wish to bring to your notice.

The headache in question is a very well-defined one, and as a rule easily separable from the very numerous headaches due to other causes; it has been written about by Dr. Liveing,² Professors Latham³ and Trousseau,⁴ and has been noticed more or less shortly by other well-known writers, some of whose remarks are quoted in my second paper to the 'Practitioner.' It has been called megrim, sick headache, nervous headache, bilious headache, &c.

That the headache is not necessarily hemicranial is now, I believe, generally admitted, nor are special optical phenomena a necessary part of the picture.

It may affect the whole head, but when at its worst there is generally one spot more affected than the rest, and in the case that forms the subject of this paper this spot is the centre of the occiput. The pain when severe is throbbing, a throb corresponding to each arterial pulsation; it is greatly increased by movement, or by stooping down.

Among concomitant symptoms are mental dulness and inability to fix the attention, extreme and persistent coldness of the extremities, and other vaso-motor phenomena, as slight rigors, and irregular local perspirations; appetite is uncertain but not altogether lost, the bowels are often

¹ Ibid., March, 1886.

² 'Megrim and Sick Headache,' Churchill, 1873.

³ 'On Nervous or Sick Headache,' Cambridge, 1873.

⁴ 'Lectures on Clinical Med.,' New Syd. Soc., vol. iv.

irregular, and there may be a feeling of pain, heat, or fulness in the right hypochondrium; the tongue is clean, pulse slow and of high tension and the temperature normal or slightly subnormal, these latter symptoms serving to distinguish it from the frontal headache of constipation. There may be sensory phenomena, as the well-known optical ones, or I have sometimes noticed the hearing altered so that sounds seemed greatly intensified; there is often a family history of headache, or gout, or both (see my second paper to the 'Practitioner').

It is brought on by any relative excess in the meat food, especially in butcher's meat, and I have seen numerous cases both in private and among out-patients where, though meat seemed to be taken in great moderation, the headache has been markedly better when it has been entirely left off; and in the case which forms the subject of these investigations the headaches were reduced by diet treatment from one in a week to one in a month, and gradually down to one in eighteen months, and as I shall show, can be brought back at any time by a change of diet.

Excessive exercise is a predisposing cause of headache, and it must be remembered that it (exercise) has as its result a large excretion of urea and uric acid.

After trying various methods of estimating urea I finally settled down to use the hypobromite process with the precautions and corrections recommended by Dr. Noel Paton;¹ with regard to uric acid, there was not much choice, and Professor Haycraft's method, also recommended by Dr. Paton, was adopted. These two processes I used throughout my experiment and have every reason to be satisfied with the apparent accuracy of the results obtained.

It will save further explanation if I say at once that I am myself a sufferer from this form of headache and its concomitant symptoms, and that these experiments were made on my own urine. They were therefore carried out with a regularity and continuity which it would, I think, have been very difficult to attain to with even the most

¹ 'Practitioner,' March, 1886.

obliging of patients. Thus from the 24th of October last to the beginning of January my urine was collected, and the urea and uric acid, and sometimes other constituents, estimated almost without a break. I also made a daily note as to weather, exercise, food, drugs (if any), and health, especially the presence or absence of headache, or threatenings of it. I also weighed myself from time to time. I always took special care to write down my notes about health and headache before beginning the analysis of the urine for the twenty-four hours in question, so that the result of this could not influence my statements.

On the 2nd of November, I began, for the purpose of this experiment, to take butcher's meat and cheese, each once in the day, having previously (except when away from home) abstained from them for several years; and I continued to take them in very slowly increasing amounts (but only once a day) till the 2nd of January. At first they seemed to have little effect; but gradually the threatenings of headache got more frequent and severe till in the twenty-four hours ending 26th of December, I had a headache lasting more than eight hours, and on the 2nd of January (1887) I had a more severe headache than I had experienced since May, 1885; and that one was I believe due to my breaking through my diet rules with several too good dinners. On the 2nd of January I left off the meat and cheese again, and I have since (now more than four weeks) been practically free from headache, having on one occasion only a slight threatening.

I think, therefore, that there can be no reasonable doubt of the intimate relation of this form of headache to diet, at least in this particular case, and my observations lead me to believe that cases of it that are apparently similarly affected by diet are not by any means rare.

As to the relation of this headache to the excretion of uric acid, my results at first were very equivocal, and though it seemed to me that there was some relation between the two, I thought that the uric acid was, if anything, slightly diminished on the days on which

threatenings of headache occurred. When, however, on the 26th of December I got a decided headache, it occurred to me to separate the urine passed during the headache from that before and after, and I at once got definite results, which were not only exactly repeated in the more severe headache of the 2nd of January, but these latter

results showed clearly the diminished excretion before and after the headache, and so served to explain the equivocal results previously obtained. It would take too much space to give all the results of my urinary analysis, so that I shall confine myself to those from the 25th of December onwards, which include the more important of my positive results, and these I have entered in the accompanying table.

Date.	Twenty-four hours ending.	Amount of urine.	Sp. grav.	Total uric acid.	Relation of uric acid to urea.	Exercise.	Food.	Drugs.	Health and remarks. Weight 126-127 lbs. (without clothes).
1886. Dec. 25	9.50 a.m.	1620 cc.	1022	Grs. 499 12.5	1-39	Minus; a very little walking	Ordinary, plus Once meat, Once cheese	None	Slight headache on afternoon of 24th; bowels open.
"	a.m. p.m. hr. min. 26 9.50-6.40 = 8 50 on 25th		Not taken	186 5.7	1-32	—	—	"	Headache lasting most of the time.
"	p.m. a.m. 26 6.40-9.50 = 15 10 25th 26th		"	318 6.9 504 12.6	1-46	—	—	"	Headache passed off.
"	26 9.50 a.m.	1450 cc.	1030	514 12.7	1-40	Minus	Once meat, Once cheese, Christmas puddings	"	Headache as above. This was a separate analysis of the two parts mixed together.
"	27 9.50 a.m.	1590 cc.	1025	441 13.1	1-33	Wet day; no exercise	As on 26th	"	Threatening of headache off and on during day. Flatus, and bowels imperfectly open.
"	28 9.50 a.m.	1820 cc.	1024	561 16.0	1-35	Exercise plus, viz. 2-3 hours' work in the snow	Twice meat, Once cheese	Sodæ Salicyl., 2-3 doses of gr. iij	Headache continued to threaten. Sodæ Sal. greatly improved matters.
"	29 6.45 p.m.	1540 cc.	1025	499 12.7	1-39	Exercise minus; 5 hours' out-patient's work	Once meat, Once cheese	Sodæ Sal., gr. iij or iv	Well and bowels open. Some rheumatic pains in fingers.
"	30 6.45 p.m.	1500 cc.	1022	415 12.4	1-33	Exercise minus	"	Sodæ Sal., gr. iij-iv; Calomel, gr. ʒʒth	Slight sore-throat. Threatening of headache afternoon of 30th.

"	31 6.45 p.m. 1860 cc.	1017	401	11.5	1-34	Exercise minus	"	Calomel, gr. ½th; Pot. Cit., Sp. Am. Aromatic, and Sp. Æth. Nit., 2-3 doses	Sore-throat continued. Stiff-neck from morning of 31st. No headache.
1887.									
Jan.	1 6.45 p.m. 1680 cc.	1020	362	10.4	1-34	Exercise minus; 5-6 hours' out-patient's work	"	Calomel, gr. ½th; Sodæ Sal., gr. iv-v	Sore-throat better. Stiff-neck getting better. Severe headache after 5 p.m. on the 1st.
"	p.m. a.m. 26.45-8.30 1st 2nd	1023	213	9.2	1-23	Exercise little or none	No meat or cheese	Sodæ Sal., first in small doses; 8.30-6.45.	Headache very bad evening of 1st and at night. Not gone in the morning, but better and worse on and off through the day of 2nd.
"	a.m. p.m. 8.30-6.45 1st 2nd	1029	155	6.9	1-22	"	"	gr. xx in 2-3 doses	<i>Note</i> .—Only the above two analyses were made on the 2nd.
			368	16.1	1-22				
"	8 6.45 p.m. 1650 cc.	1020	356	10.2	1-34	Walking 2½ miles	"	A few grs. of Sodæ Sal.; Quin. Sulph., gr. ij	Headache bad on night of 2nd. Threatening during day, but better on the whole.
"	4 6.45 p.m. 1360 cc.	1024	418	11.2	1-37	3-4 hours' walking and standing	"	Quin. Sulph., gr. ij, evening of 3rd	Well and bright, especially latter part of day.
									<i>Note</i> .—There were three separate analyses on Dec. 26th, and two on Jan. 2nd.

N.B.—Brackets include those figures that refer to parts of days only.

The only results that require notice with regard to my previous analyses are (1) That the uric acid seemed to bear a smaller proportion to the urea on the days when there was partial or slight headache (and see also the proportion 1 to 39 and 1 to 40 on the 25th and 26th of December respectively), and (2) that the average excretion of uric acid, was for a long period about 12 gr. per day. With regard to the accuracy of the processes used, I would draw special attention to the results of the three analyses of the 26th of December, where it will be seen that the total of the two part analyses is in the case of the uric acid almost exactly the same as the result of the separate analysis of the whole, and in the case of the urea there is only a variation of 10 gr. in a total of over 500 gr.

On reference to the table then it will be seen that on the 26th of December, during a period of headache lasting eight hours fifty minutes, 5·7 gr. of uric acid were passed, this being at the rate of ·64 gr. per hour (and I have said above that the average is about 12 gr. per day, or ·5 gr. per hour), and further on the same day during fifteen hours ten minutes free from headache 6·9 gr. were passed or ·46 gr. per hour (*i. e.* below the average) ; on the other hand, the urea varied but little, being for the first period about 22 gr. per hour, and for the second about 21 gr. per hour ; the uric acid variation was little short of $\frac{1}{3}$, while the urea varied less than $\frac{1}{30}$; but I shall come back again to this relation of uric acid to urea. On the 2nd of January we find precisely the same relation, only here the headache lasted the whole twenty four hours, and we have the large uric acid excretion of 16·1 gr. or ·67 gr. per hour, against a total excretion on the previous day, when there was only about one and a half hours of headache, of 10·4 gr., while the urea only varied from 362 gr. on the 1st to 368 gr. on the 2nd ; the uric acid was here increased by more than $\frac{1}{3}$, while the urea only increased $\frac{1}{30}$. Then I purposely divided the urine of the 2nd of January into two parts corresponding as nearly

as I could get them to the two parts of the 26th of December.

In the first part, 6.45 p.m. to 8.30 a.m., viz. thirteen hours forty-five minutes, 9.2 gr. of uric acid were passed, or .66 gr. per hour; and in the second part, ten hours fifteen minutes, 6.9 gr. or .67 gr. per hour, so that on this day, when the headache lasted the whole twenty-four hours, the uric acid excretion remained much above normal the whole time.

It appears then that on both these days when there was headache present, the uric acid excretion was above .6 gr. per hour; but when the headache was absent either before or after the paroxysm, it fell below the average as .46 gr. on the 26th of December, .43 gr. on the 1st of January, and .42 gr. on the 3rd.

There is thus shown to be a very definite relation between the uric acid and the headache, viz. that it (uric acid) is diminished before and increased during the paroxysm, and what is more remarkable, the increase and diminution very nearly balance one another. Thus it may be seen from the table, or the diagram of curves, that the uric acid falls below the urea on the five or six days before the headache by rather more than 4 gr., while on the day of headache uric acid is above urea by about 5 gr.; the difference being due, I suppose, to some retention of uric acid on some of the days previous to the beginning of this diagram. That the uric acid is below the urea on the two days after the headache shows, I conclude, that there is again some retention going on.

It will be seen from the table that on the 28th of December, 16 gr. of uric acid were passed, though there was only a threatening of headache on that day, and in the analysis not given in this table I note, on the 29th of November, that 15.9 gr. were passed, with the note on health, "Quite well, bowels open;" and on the 26th of November 15.2 gr. without any note of a headache being present. What, then, is the explanation of this apparent contradiction? If we had nothing but the absolute amount

of the uric acid to go upon, its relation to the headache might be somewhat obscure ; but a glance at column 7 of the table, showing the relation of uric acid to urea, gives us, I think, a clue to the reason why there is a headache on one day with a uric acid excretion of 16·1 gr., and not on another day with 16 gr. excretion.

Throughout the whole of these analyses I have been careful to note the relation of the uric acid to the urea every day, and the result gives me an average in health of about 1 to 33 ; and it will be seen that on the 28th of December, on which day 16 gr. of uric acid were passed with only a threatening of headache, the relation of uric acid to urea was 1 to 35, while on the 2nd of January, with 16·1 gr. uric acid and a very severe headache, the relation to urea was 1 to 22, a relation which has never been met with before. On the 29th and 26th of November, the days mentioned above, the relations were 1 to 31 and 1 to 33 respectively, which are either normal or close to it. It may be objected that on the 26th of December during the headache the relation was 1 to 32, or nearly normal ; but I think that in all probability the urine of this headache was not sufficiently accurately separated from that *excreted* before and after it, so that we have an approximation here to the equivocal results I have before alluded to ; and in any case the difference between a relation of 1 to 32 during, and 1 to 46 after the headache, is sufficiently well marked.

On the days I have mentioned above, where there was excessive excretion of both urea and uric acid in something like the normal relation to each other, this excess was the direct result of more than ordinarily severe exercise, a result which is perfectly in accord with those obtained by North¹ in his experiments "On the Influence of Bodily Labour on the Discharge of Nitrogen ;" and as long as the relationship of the uric acid to the urea shows no great fluctuations there is no headache ; but, as I have previously pointed out in my second paper to the 'Practitioner,'²

¹ 'Proc. Roy. Soc.,' 1885.

² 'Practitioner,' March, 1886, p. 182.

over-fatigue appears to precipitate attacks both of gout and megrim, and there is no doubt that during these large excretions of urea and uric acid, headache is not far off ; and if from any cause the uric acid fluctuates considerably in its relation to the urea, headache will be present during its excess and absent during its diminution (especially the diminution that follows the excess), and the headache will vary in intensity directly with the excess of uric acid over the urea.

We must now inquire into the cause or causes which underlie this fluctuation in the excretion of uric acid. The cause, whatever it is, affects the uric acid, and not the urea, which is steadily excreted at about the same rate as if nothing had happened. There is probably no excess in the formation of uric acid, but merely an alteration in the time of its excretion.

What cause can we think of that affects the excretion of uric acid and not that of urea ? It can hardly be due to anything wrong with the kidneys, for that would probably affect both urea and uric acid ; besides the cause here is very transient in its effects, and therefore probably not organic. Moreover, we have proof that urates may accumulate while the kidneys are quite normal, for Ebstein¹ has called attention to the fact that extensive arthritis uratica may be found in the post-mortem room along with normal kidneys ; and on the whole it appears to me that the best explanation that has yet been given, and the one which appears to best fulfil the above requirements is that of diminished alkalescence of the blood, which is no new theory, but in one form or another has existed for a long time. Thus Sir W. Roberts mentions it in some previous editions of his work, and in the last edition (the fourth) he says,² "It may be regarded as probable that the defective power of the kidneys to eliminate uric acid in gout arises from a diminished alkalescence of the blood;" and I think also that the researches of Dr. A. Auer-

¹ 'Die Natur der Gicht,' p. 18.

² 'On Urinary and Renal Diseases,' ed. iv, p. 73.

bach,¹ "Ueber die Säurewirkung der Fleischnahrung," are very much to the point here, as he shows that vegetable and animal feeders differ considerably in their power of preserving the alkalinity of their blood against acids formed in their bodies, or introduced from without; and that even where, as in animal feeders and man, this power is greatest, it may be gradually diminished and finally overcome by continued excess of acids. If we may suppose then that the gouty somewhat resemble vegetable feeders, in having less than the normal power of forming ammonia to resist acids, and prevent their taking alkali from the blood, then there will eventually come a time when, on flesh diet and beer, the alkalinity of their blood and tissue fluids will be so far overcome that urates will be far less easily soluble in them than in the normal condition. I think that we have here, in a nutshell, a key to a large part of the pathology of gout, explaining at one glance the great benefit noticed to follow on abstention from meat and beer, and the value of alkalis in treatment. The same connection has been noticed, and the same explanation no doubt applies to the influence of diet and drugs on this form of headache; and I would specially draw attention here to the action of beer, for the relation between fourpenny ale and gouty deposits is a matter of every-day observation. Now, beer and ale are strongly acid in reaction, and I found in a pint bottle of Ind, Coope's pale ale, estimated by the same method as the acidity of the urine, the equivalent of about 14 gr. of oxalic acid. Dr. Garrod² says that the average acidity of the day's urine is equal to about 30 gr. of oxalic acid, so that a pint of this beer represents a very considerable dose of acid, and beer has often appeared to me to precipitate a headache. A pint of fourpenny ale, estimated in the same way, yielded the equivalent of 18 gr. oxalic acid, and a pint of stout 25 gr.; so that it appears that the cheaper beers are even more strongly acid. Mr. Wynter Blyth says that the chief acid in beer is acetic.

¹ 'Virchow's Archiv,' 98, p. 512.

² 'Brit. Med. Journ.,' i, 1883, p. 705.

I would suppose then that in the case of this headache, a considerable excretion of urea and uric acid is going forward, as on the 25th of December (see table); suddenly from some cause, either internal formation (dyspepsia and acid fermentation, &c.) or unwary introduction from without, a dose of acid is brought in, and for a time diminishes the alkalescence of the blood, and causes retention of uric acid. It will be seen by looking at the table that though 12·5 gr. of uric acid were passed on the 25th it was diminished with reference to the urea; then comes the headache, and with it, on the 26th (first part), a plus excretion of uric acid having its source in the previous retention.

With regard to the theory of diminished alkalinity of the blood, and the way in which it enables us to explain the effect of the diet treatment of this headache, I will quote what Sir W. Roberts¹ says of the "alkaline tide:"—"If as is believed, the normal alkalescence of the blood is due to the preponderance of alkaline bases in all our ordinary articles of food, a meal is *pro tanto* a dose of alkali, and must necessarily for a time add to the alkalescence of the blood." If an ordinary meal is a dose of alkali, a somewhat vegetarian meal, from which butcher's meat and beer are absent, must surely be a large dose of alkali; and here we have ready to hand a fairly good explanation of the effects of somewhat vegetarian diet in this form of headache, for there can be little doubt that it acts by keeping up the alkalescence of the blood, and preventing retention of uric acid from occurring.

The relation I have now shown to exist between the excretion of uric acid and this headache has been to some extent anticipated by those who have noticed the intimate relation of this headache to gout, and in my paper in the 'Practitioner' of March, 1886 (page 181), thinking over these relations, and referring to Prof. Latham's 'Lectures on Headache' I ask, "May not excess of uric acid in the blood cause such vaso-motor irritation, the excess being

¹ 'On Urinary and Renal Diseases,' ed. iv, p. 56.

only occasional and existing for a short time, so long as the kidneys remain undegenerated"? I should not now endorse the latter part of this, as I think we have at hand a better explanation of retention than any degeneration of the kidneys could afford; though no doubt where the kidneys eventually undergo degeneration this does not improve matters. And Prof. Latham,¹ in his "Lectures on the Pathology of Rheumatism, Gout, and Diabetes," kindly notices my question quoted above, and in reply to it says, "Certainly; and in persons whose sympathetic ganglia have this sensitive constitution the causes which lead to the formation of uric acid will develop an attack."

In conclusion, I think that this relation between the headache and the excretion of uric acid (*viz.* that there is diminished excretion of uric acid before and increased excretion during the headache; but that taking the two periods together there is no absolute increase in the excretion of uric acid, or alteration in its normal relation to the urea) will be found to hold good for all cases of headache which are influenced by diet in the way I have described; and further that the fluctuations in excretion here noticed may help us to clear up several important points in the pathology of gout and other diseases connected with uric acid; more especially by showing the way in which temporary retention of uric acid may be brought about, and in strengthening the hypothesis that in gout there may be more or less permanent diminution of the alkalescence of the blood, resulting in a chronic or constantly recurring retention of uric acid.

I must express my regret that I can only bring forward the results in a single case; but these results are so definite and complete in themselves that I think I have good ground for the deductions I have made from them; while the difficulty in obtaining anything like the same facilities for examining the urine of other people is obvious; and though several friends and fellow-sufferers have kindly promised me samples of urine collected with

¹ 'Brit. Med. Journ.,' i, 1886, p. 629, *et seq.*

the necessary care, I may still have to wait some time before I can get results fairly comparable to those obtained in my own case.

(For report of the discussion on this paper, see 'Proceedings of the Royal Medical and Chirurgical Society,' New Series, vol. ii p. 269.)