The formation and excretion of uric acid : considered with reference to gout and allied diseases / by A. Haig.

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The Formation and Excretion of Uric Acid

CONSIDERED

With Reference to Gout and Allied Diseases.

BY

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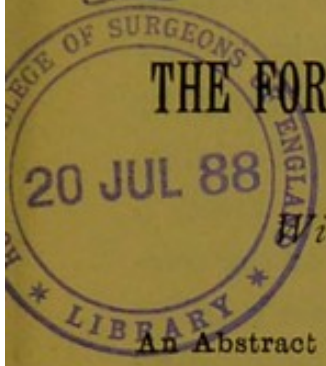
BEING A THESIS FOR THE DEGREE OF M.D. IN THE UNIVERSITY OF OXFORD.

JOHN BALE & SONS, 87-89, GREAT TITCHFIELD STREET,
OXFORD STREET, W.

1888.



THE FORMATION AND EXCRETION OF URIC ACID

CONSIDERED

With reference to Gout and Allied Diseases.

An Abstract of this Thesis appeared in the British Medical Journal, of July 7th, 1888.

NOTE.—The indented paragraphs are those which have been added since the thesis was submitted to the Examiners.

MY object in this paper is to point out that certain researches on the excretion of uric acid, on which I have now been engaged for several years, seem likely to throw new light on the part played by this substance in the causation of disease.

The paper naturally divides itself into two parts; 1st, the experimental, in which I shall give, as far as possible, a consecutive account of my experiments on uric acid excretion; and 2nd, the part in which the results obtained are used to elucidate the pathology of disease.

The diseases to which I shall attempt to apply my results are gout, the connection of which with uric acid is distinct and well proved, a certain form of[1] headache and some cases of epilepsy,[2] between which and the excretion of uric acid I have shown a very definite and, I believe, causative relation; and lastly, rheumatism, either acute or chronic, the connection of which with uric acid, though in many ways extremely probable, is not yet so definite as in the case of the above-mentioned diseases.

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[1] *Medico-Chirurgical Transactions*, vol. lxx.

[2] *Neurologesches Centralblatt.* March 1st, 1888.

Shortly stated, my results show, 1st, that the excretion of uric acid can be controlled by drugs and food in a way and to an extent not previously known, so that if a patient excrete say 10 grains of uric acid to-day (other things remaining the same) he may be made to excrete either 9 grains or 11 grains to-morrow by drugs given for the purpose; and further, if his uric acid to-day bears a relation to the urea excreted along with it, of 1-33 (*i.e.*, suppose he passed 330 grains of urea) it may be made to-morrow to bear a relation to it of say 1-27 on the one side, or 1-39 on the other.

2ndly. My researches make it probable that when the excretion of uric acid is diminished, relatively to the urea, its diminution is due to its retention and storage[1] in certain organs, as the liver and spleen, and perhaps other tissues; and conversely when it is increased relatively to the urea, its increase is due to a washing out of some part of the store previously deposited in these organs.

3rdly. That the formation of uric acid bears an almost constant relation to that of urea; but that its excretion may be varied, as I have just said, by drugs or food to a considerable extent.

4thly. That uric acid is probably never in excess in the blood, except when from continued retention of small quantities, there has been an accumulation of several grains in the liver and spleen, which is all at once swept out into the blood by a reversal of the process which previously caused the retention.

5thly. That the excess of uric acid in the blood, resulting from the sudden washing out of a previous accumulation in the liver and spleen, is a sufficient cause of many of the phenomena of uric acid diseases.

6thly. That all drugs and foods which diminish the

[1] *Journal of Physiology*, vol. viii. Nos. 3 and 4.

solubility of uric acid diminishes its excretion, and lead to retention and accumulation; and conversely all foods and drugs which increase its solubility facilitate its excretion and prevent retention.

7thly. That drugs which diminish the solubility and excretion of uric acid are harmful in diseases connected with it, while drugs which increase its solubility and so prevent retention and accumulation, are useful in the same diseases.

And first of all, I may perhaps say a few words as to the way in which I came to undertake this research without having originally the least idea of the importance which now appears to attach to it.

Some six or seven years ago, being a regular sufferer from a severe form of migraine, and obtaining only very inadequate relief from much advice and many drugs, I began to make careful notes of the circumstances of my trouble, and to note especially all food, drugs, exercise and other conditions which had any real or supposed connection with it. For a long time there was little result, till on giving up meat I at once found the intervals between attacks prolonged, and persistence in this change of diet gradually produced almost complete immunity; an immunity which continues to the present time, but only so long as the diet is adhered to, and I have now been for four or five years an almost total abstainer from butcher's meat, beer, wine and cheese, though I have, to some extent, replaced the meat by an increased quantity of milk and fish; but even now any serious infringement of these diet rules is pretty sure to be followed by a headache.

The results I obtained by leaving off meat and the relationship noticed by many observers between this[1] headache and gout, led me to examine the urinary ex-

[1] *Practitioner*, August, 1884, and March, 1886.

creta, and my paper in the *Medico-Chirurgical Transactions*, on "The relation of a certain form of headache to the excretion of uric acid,"[1] was the result of this investigation.

And having found out in this way the remarkable fluctuation in uric acid excretion corresponding to the headache, I began to speculate as to its cause, and was then led, by observing the strong acid reaction of ales, and their important connection with gout, to try the effects of acids on myself, and from that I went on to try alkalies and numerous other drugs.[2]

My urinary analyses have extended now over a period of more than two years, and have for a large part of the time been practically continuous, at least with regard to my own urine, which was often kept for periods of six weeks to two months, and more recently for a period of four months without any interval, the analyses being performed every day and records kept of general health, and presence or absence of headache, with notes of the exercise, drugs and food taken, and I have tested on myself, and occasionally on others, the actions as regards the urinary excreta of all the most important drugs used in the treatment of gout, rheumatism and headache, as also the effects of various modifications of diet so that in the records of these I have now a considerable accumulation of results bearing on the question.

And these results I have, both as tables of figures and as curves, the latter showing the daily excretion of uric acid, urea and acidity at a glance, so that their relative variations can be easily realised.

The processes I have used in my experiments are as follows:—For urea the hypobromite test with the apparatus of Dupré, temperature and pressure being always

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[1] *Medico-Chirurgical Transactions*, vol. lxx.

[2] *Journal of Physiology*, vol. viii., Nos. 3 and 4.

noted, and variations of volume due to them, as far as possible allowed for. For uric acid Prof. Haycraft's process as described in the *British Medical Journal*, vol. ii., 1885, p. 1100, and for acidity a solution of phenol-phthaleine with a graduated solution of soda.

I have every reason to think that my results are fairly accurate, but in any case being all obtained by the same processes they may be safely compared *inter se.*

Having found, as detailed in the *Journal of Physiology*, that acids always diminished the excretion of uric acid, and caused it to be retained and accumulate (as supposed) in the liver, spleen, &c., and also that alkalies always increased its excretion by washing it out from these organs, and afterwards preventing its retention, it became at once easy to explain why my headaches had been less frequent and severe when I left off meat, beer, cheese, &c., and this was further elucidated by some experiments with meat, taken for the purpose, which showed that while it increased the formation of both urea and uric acid in their natural proportions, its[1] phosphates and sulphates increased acidity, and so caused retention and accumulation of uric acid in the liver and spleen, and when on some future occasion, from an accidental diminution of acidity, or excess of alkali in the food, this store was swept out into the blood, a headache was the result. The acid in beer and wine, and I suppose the salts in cheese, acted in the same way.

And I soon found that by causing retention of uric acid for a few days, and then rushing it all out into the blood with an alkali, I could produce the headache at will.

Also that when uric acid was in excess in the blood, and causing a headache, I could drive it out of the blood back into the liver and spleen, and stop the headache by taking an acid,[2] and I have repeated this experiment many times

[1] *Ziemssen*, vol. xvi. pp. 126-7.

[2] *British Medical Journal*, vol. i., 1888, p. 73.

both on myself and others, and have also numerous records of cases treated by myself or others where diet[1] and acids have acted in precisely the same way as in my case, so that I have come to regard this uric acid headache as a good starting point, from which we may reason to other diseases connected with uric acid.

The first thing that directed my attention to acids was, as I have said, the relation of four-penny ale to gout, as seen among out-patients, and I have given notes[2] in my paper on headache of the amount of acid in several kinds of ale and stout, and anyone may convince himself of the presence of considerable amounts of acids in all wines and similar beverages, and generally the cheaper kinds are more acid than those that are dearer. So that there can be no sort of doubt that these beverages will cause retention of uric acid in those who take them, and this will be great in proportion to the amount of acid in the beverage and the quantity consumed. See Sir T. Watson's Lectures, vol. ii., p. 823, where good instances are given of the different effects of malt liquors and distilled spirits in causing gout.

As Sir A. Garrod has discussed the question of the causation of gout by beer, wine, &c., it will be necessary to give some of his remarks, and my reasons for thinking that he has not estimated their true importance as causes of this disease.

After remarking[3] that distilled spirits do not cause gout, even when mixed with sugar, he goes on to say that with wines the case is different; that drinkers of *light wines* suffer least, as these contain a small amount of alcohol,

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[1] See "Some Clinical Features of the Uric Acid Headache," St. Bartholomew's Hospital Reports, 1887, p. 201.

[2] *Medico-Chirurgical Transactions*, vol. lxx.

[3] "Lumleian Lectures," *British Medical Journal*, vol. 1, 1883, p. 653.

no unfermented matter, *but a considerable quantity of acid vegetable salts.* He then says that fresh fruits diminish acidity through the conversion of their vegetable salts into carbonates; and I would here ask why should not the vegetable salts of the light wines be similarly converted? He then goes on to the *heavier wines*, as those of Spain and others, and says they contain more alcohol, much unfermented matter, *are almost devoid of vegetable salts*, and have great gout producing power. And treating of the cause of this gout production, he says "it cannot be the acidity alone, for the wines, which are most harmless, are quite as acid, or even more so than malt liquors and the Peninsular wines." I would remark in this connection that the large quantity of malt liquor often taken is an important factor. See Sir T. Watson (previous reference) for cases where three gallons of stout were taken in a day. He (Sir A. Garrod) finally sums up in favour of the unfermented matter in these beverages as the cause of their gout producing power, but he does not seem very clear as to the exact nature of this matter.

Now I think that anyone who has followed my reasoning thus far, will not have much difficulty in seeing that the action, which I have shown, that acids have on the excretion of uric acid, is sufficient to account for all the phenomena here involved. And, from my point of view, wines, ales and porter may be all regarded as solutions containing a very small amount of albuminoids, a certain amount of alkali or alkaline salts, and a certain amount of acids either free or combined; and it is obvious that if the alkalies, or the vegetable salts which can be converted into alkaline carbonates predominate, the beverages will act as doses of alkali, while if the acids and acid salts incapable of conversion, predominate, they will act as doses of acid. And this consideration explains the dif-

ference. Sir A. Garrod has noticed between the light and heavy wines, and also why wines that act as diuretics (probably from their containing an extra quantity of potash or its salts)[1] are less harmful than others; also why old and expensive wines are less harmful than new and cheap ones, for one of the effects of keeping wine is a loss of acidity by ætherification.[2]

As will have been seen from previous papers I had worked at diet for a long time before I began to study drugs, but the effects of all varieties of diet on uric acid excretion may be summed up by saying that all foods that increase acidity diminish uric acid excretion, and all foods that diminish acidity increase uric acid excretion. I have not been able to satisfy myself that any food increases the formation of uric acid above its normal relation to urea (1-33) (see *Journal of Physiology*). A highly nitrogenous diet of course increases the formation, both of uric acid and urea, but only in their natural proportions.

Foods may increase acidity directly by the acids or acid salts they contain, or indirectly by causing dyspepsia and acid fermentation processes in the stomach or intestines (see dyspepsia later on). They may diminish acidity by the alkali they contain,[3] as Sir W. Roberts says that the alkalescence of the blood is probably due to the preponderance of alkaline bases in our food.

While speaking of this subject I must not forget to mention a very interesting table of Lehmann's results, which is given by Sir A. Garrod in his Lumleian[4] Lectures, showing uric acid and urea excretion under different diets, thus:—

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[1] Dr. B. Yeo, *British Medical Journal*, vol. i., 1888, p. 18.
[2] See Mr. W. Blyth's "Foods, Composition, and Analysis," p. 439.
[3] Urinary and Renal Diseases. Ed. IV., p. 56 and others.
[4] *British Medical Journal*, vol. 1, 1883, p. 704.

	Urea.	Uric Acid.
On mixed diet	32.4 ...	1.1
On animal diet	53.1 ...	1.4
On vegetable diet...	22.4 ...	1.0
On non-nitrogenous diet... ...	15.4 ...	0.7

Sir A. Garrod concludes from this that the amount of uric acid excreted is not nearly so much affected by the nature of the food as the urea is, and that therefore there is no reason why a moderate amount of meat should not be given. But I have shown above that meat increases formation of both urea and uric acid, and that as its salts increase acidity, it further causes retention of uric acid. So that I believe that there is very considerable harm in giving meat in these diseases (see statements at beginning of paper), and I am able to prove that this is so, at least in the case of headache, and I feel pretty confident of being able to prove the same for other members of the group.

What, then, is the explanation of this table? Simply, I think, that Sir A. Garrod has never noticed, as I have done, the relation of uric acid to urea in the excretions produced under each kind of diet, or he would have seen that it proved almost the reverse of his conclusions. I think if I put down the table again and along side of it my figures expressing the relation of uric acid to urea, this will be seen to be the case :—

	Urea.	Uric Acid.	Relation.
On mixed diet	32.4 ...	1.1 ...	1-29
On animal diet	53.1 ...	1.4 ...	1-38
On vegetable diet	22.4 ...	1.0 ...	1-22
On non-nitrogenous diet ...	15.4 ...	0.7 ...	1-22

It may now be seen that what really happened was that under the mixed diet, uric acid was slightly in excess of its normal relation to urea (taking that as 1-33); that on the animal diet it was decidedly diminished, *i.e.*, the rise of acidity on animal diet diminished the excretion (formation

going on steadily at 1-33); on the vegetable diet excretion was greatly increased, *i.e.*, uric acid previously formed and retained, was swept out by the excess of alkali in the diet, and the non-nitrogenous diet (whatever that consisted of) the same.

I will further point out that if the animal diet had been continued, the person experimented upon would soon have had a very considerable store of uric acid in his liver, spleen or other organs, either doing them harm, or ready to be swept out in the "Alkaline tide" (Sir W. Roberts) into the blood, and when there to cause headache, hypochondriasis, epilepsy, gout, or any other disease of this group to which he happened to be liable. So that I am quite unable to believe that in this class of diseases, meat, especially strong butcher's meat with its large amount of salts,[1] can be taken with impunity. I may say also that the results in the above table, correspond in every particular with my own obtained with similar changes of diet, and the relations of uric acid to urea are just such as I meet with in my every day work. It will be noticed that I say above, that the patient will be affected by that disease of the group to which he happens to be liable, and taking headache for example, though I have shown that in one form of headache the poison is almost certainly uric acid, we are still obliged to suppose that the individual who suffers from it, has his nervous system or some part of it in a weak and irritable condition, so as to be easily affected by the irritant, for every one has uric acid retention to some extent, dependent as regards amount on his food and habits; but everybody does not suffer from headache. The same reasoning applies to epilepsy, and there is some reason to suppose that the centre (vaso-motor) which is weak and

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[1] See table of Diets. Parkes' "Practical Hygiene," Ed. VII. p. 243.

irritable in this disease, is very closely related to that which is affected in headache.[1]

Further, I am quite aware in the case of headache, with which I have had most experience, that there are two ways of treating the trouble, either by strengthening the nerve centre, or by removing the irritant; but the latter way is the most certain, and acts in the worst cases; while remedies directed to the centre (Strychnia, Bromides) act slowly, and are only of use in slight attacks. I have said above that I am able at pleasure to increase or diminish the excretion of uric acid; but only within certain limits. And the reason of this is, that in none of my work or experiments with drugs or food have I ever been able to produce an absolutely excessive formation of uric acid (*i.e.*, in excess of its normal relation to urea), nor in myself or any other persons have I met with anything to show that such excessive *formation* occurs.

To come to facts, more than a year ago I calculated the relation of uric acid to urea, on a period of some six weeks results, and I found that 1 grain of uric acid corresponded to 33 grains of urea, and I took this relation as the basis of my curves, and have used it in all my subsequent work; and more recent results tend to show that this calculation was not far from the mark, for in my longer periods of urinary estimation I have got very nearly the same proportion between those two substances; thus in a period of four months in which the urine was kept, and its urea, uric acid and acidity estimated every day; there was a total urea excretion of 41,804 grains, and a uric acid excretion of 1,281 grains giving a relation of 1-32.6. Or to take the months separately, the 1st month gives a relation of 1-34.6, the 2nd 1-31.7, the 3rd 1-31.5, and the 4th 1-32.7, but the

[1] See Prof. Du Bois Reymond quoted by Dr. Liveing, "Megrim and Sick Headache," p. 300.

relations of uric acid to urea from day to day vary to a much larger extent, being sometimes as high as 1-19 or as low as 1-45, but taken over a long period, as we have seen above, the variations on each side of the normal nearly balance each other, and we get a resulting relation somewhere about 1-33.

From these facts I should be inclined to conclude that for every 33 grains of urea or thereabouts, 1 grain of uric acid is regularly and punctually formed, but, as I have shown above, the excretion of uric acid can be altered in various ways by diet or drugs, and it does not necessarily pass out along with the urea corresponding to it, but may be to some extent retained and kept back for several days; and then, at some future period uric acid excretion will be in excess of the urea to a corresponding extent. And when such a sweeping out of retained uric acid occurs, *i.e.*, when any drug or food is taken, which increases its solubility and washes out the accumulation in the liver and spleen, some 5-6 or more grains of uric acid may be present for a time (during the plus excretion) in the blood, and this is quite sufficient to account for the headache I have spoken of, for the fits in some cases of epilepsy, for hypochondriasis and melancholia, and for various amounts of arthritic pain up to an acute attack of gout. So that all these troubles may be caused by continued retention of uric acid without the formation of a single grain of it in excess of its normal relation to urea 1-33. And this relation 1-33 gives the key to the whole situation, and enables me to say on any given day whether uric acid is being retained, or excreted in excess, and also gives me the means of estimating roughly how many grains have been retained during a given period, and therefore how many grains it is in my power to sweep out if I please, by giving a food or drug which will increase its solubility; and in this way it is in my power to cause or prevent the

above form of headache at any time, and I believe the same applies to some cases of epilepsy ; but I cannot cause the headache without also causing plus excretion of uric acid, or cure the headache without at the same time diminishing or stopping the plus excretion ; and I argue from this that the uric acid is in excess in the blood at the time it is passing in excess in the urine, and that its excess in the blood is the cause of the headache, the epileptic fit, and the arthritic pains, and I have shown in the papers previously mentioned that uric acid is in excess in the urine at the time of the headache and of the epileptic fit.

And now bearing in mind that it has been shown (see *Journal of Physiology*, vol viii. p. 211) that acids probably by diminishing the solubility of uric acid cause it to be retained in the body, while alkalies, by increasing its solubility, prevent retention and sweep out any of it that has been previously retained ; we will pass on to examine the action of other drugs.

Iodide of Potassium.—This is a drug which is of much value in uric acid disease, but my experiments with it fail to prove that it has any action on the excretion of uric acid, other than that of an alkali ; thus taken in five grain doses three times a day it has little or no effect on the excretion of uric acid, though this tends to run up in the alkaline tide parts of the day, and to cause slight headache ; in larger doses (as ten grains three times a day, and upwards) it distinctly diminishes acidity, and uric acid runs up in excess of urea as it would under any other alkali.

It is interesting here to remember that in chronic gout or rheumatism, it is often necessary to give doses of ten grains and upwards to get any appreciable results, and that other salts of potash are often given with the iodide. A recent article[1] on the treatment of psoriasis by very large doses of

[1] *British Medical Journal*, vol. 1, 1888, p. 27

iodide of potassium is also interesting; for if, as some suppose,[1] this skin disease is connected with uric acid, the result might, I think, be due to the large dose of alkali.

I have also experimented with iodine in the form of tincture; but it caused intestinal irritation with minus absorption of food, and consequent fall of urea and acidity, so that too many factors were brought in for me to be able to judge of its action, apart from that on the intestines. I think also that probably very little iodine was absorbed as there was little or none in the urine, but when taken as the potash salt it is plentifully excreted in the urine.

I have followed up this view that the iodide of potassium acts merely as an alkali by putting cases of chronic gout and rheumatism among my out-patients on the citrate of potash, and the results, as regards relief of pains, have seemed to me to be fully as good as those previously obtained with the iodide.

Phosphate of Sodium.—This is a well-known solvent of uric acid, and it is interesting to note that it increases the excretion of uric acid, in spite of the fact that it increases the acidity of the urine; so that all substances that increase urinary acidity do not cause retention of uric acid, but only those that increase acidity without themselves aiding in the solution of uric acid, so that our ultimate factor is the solubility of uric acid, or of the compound which any salt in question forms with uric acid; further, there is here shown the indirect action that food or drugs may have by adding to or taking away from the natural solvents (phosphate of soda) of uric acid in the body, in addition to their more direct action as alkalies and acids.

The above mentioned extra acidity with phosphate of sodium may be more marked in the urine than in the blood and tissue fluids; still, if acids retain uric acid by diminish-

[1] Sir A Garrod, "Gout and Rheumatic Gout," p. 454.

ing its solubility, their action would probably be prevented by the presence in the blood of a plentiful supply of a solvent.

Salicylates.—We now come to a very important group of drugs, viz., salicylic acid and its salts, important because their action on uric acid excretion is so peculiar, and important also because their value in many of the diseases of which I shall speak presently is so well proved.

I have shown in a paper read at the Royal Medical and Chirurgical Society on the 10th of last January,[1] that salicylates increase the excretion of uric acid, and further, that they increase it in spite of a high and rising acidity; we have just seen that phosphate of soda increases the excretion of uric acid in spite of a rising acidity, but then it was itself the cause of that acidity; but salicylates increase the solubility of uric acid and wash all accumulations out of the liver and spleen at once, so that uric acid may be from 5-8 grains in excess of the urea on one day; and, further, no amount of acids that I have been able to give along with the salicylates have had any effect in preventing this flushing out of uric acid, if anything they seemed to increase it. Further, I have pointed out that the flushing out of uric acid into the blood under salicylates is not accompanied by any headache, as it would almost certainly be, if it had taken place under an alkali. And if the uric acid which causes many of the diseases with which we are now concerned comes from a store which has gradually accumulated from the continued retention of small quantities by acids, then, if salicylates do, as I have shown, prevent acids from causing retention, we come at once into possession of a fact which is capable of explaining a large part of their value in these diseases.

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[1] *British Medical Journal*, vol. 1, 1888, p. 77, and Proceedings of Society, January to March, 1888, p. 325.

Salol appears to me to act like a salicylate, only less powerfully and less quickly.

In a paper read at the Royal Medical and Chirurgical Society on the 24th of last April,[1] I have shown that lead and iron cause retention of uric acid, and have said that this is probably due to the fact pointed out by Sir A Garrod,[2] that the urates of these metals are insoluble.

Phosphates and sulphates have been mentioned above as increasing acidity, and when they do not (as in the case of sodii phosph.), specially increase the solubility of uric acid, they cause retention just as acids do; chloride of sodium acts in the same way, and it is interesting to note that it has been given with success in a case of migraine,[3] no doubt curing it just as the acids which I have recommended (see previous reference to action of acids in headache).

Though phosphates, sulphates and chlorides increase acidity, they have not seemed to me to increase it so quickly as an acid does, and I should not therefore expect to get as quick and satisfactory results with these salts in the treatment of headache, as I have been able to obtain with acids.

Colchicum.—This is a drug about the value of which in acute gout I have never had any doubt, and I always give it to my patients at first. In my own experiments with it, which have not been repeated on account of the intestinal trouble it caused, it diminished acidity and slightly increased the excretion of uric acid, and this I suppose was the effect of the intestinal irritation and griping pain, which caused diminished absorption of food and consequent diminished formation of urea and acid; and for the present

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[1] Reported in *British Medical Journal* and *Lancet*, of April 28th.

[2] *British Medical Journal*, vol. i., 1883, p. 495.
British Medical Journal, vol. ii., 1887, p, 528.

I do not see how to find out the real action on uric acid excretion of such drugs as colchicum and iodine, which cause intestinal irritation. It is possible, however, that colchicum may do some good through causing intestinal irritation, for this would diminish absorption and lessen urea and acidity, and so promote the excretion of uric acid, which several observers have noted that it does.[1] It has been long known that it makes the urine less acid, and I believe that it does this by causing intestinal irritation.

If this be not its mode of relieving podogra, colchicum may have a direct action on the nerves;[2] or it may tend to lessen inflammatory action, and so give ease.

Dr. Noel Paton has observed[3] that colchicum increases water and urea moderately, and uric acid to a much greater extent, and he infers that this is an increased production of uric acid, because the excretion merely falls to normal when the drug is stopped.

I have given my reasons above for thinking that it is not an easy thing to prove increased production of uric acid, and I should certainly not be inclined to draw the same inference that Dr. Noel Paton has from his results; for if we may suppose that colchicum acts in the way I have suggested and by interfering with nutrition reduces acidity, the natural result of this is an increased *excretion* of uric acid from the store in the liver, spleen and elsewhere, and if now the colchicum is stopped, the excretion of uric acid may go on as usual, for the colchicum has swept out an accumulation which is only gradually replaced, but this proves nothing with regard to uric acid formation which has really not altered in its relation to urea one jot the whole time.

Before passing on to apply these results to the explana-

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[1] Watson's *Lectures on Physic*, vol. ii., p. 833.

[2] Dr. Brunton's *Pharmocology and Therapeutics*, p. 968.

[3] *British Medical Journal*, vol. i., 1886, p. 377.

tion of uric acid diseases, I must mention one more interesting fact which Sir A. Garrod[1] has pointed out, viz., that suppression of perspiration is followed by an increase in the urinary acidity, so that we have here one more way in which the alkalescence of the blood and tissue fluids may be diminished and retention of uric acid brought about, and this fact provides us with an easy explanation of the causation of gout attacks by chill or exposure to cold winds. And with regard to the acids thus retained by deficient skin action, as also with regard to those formed in excess in dyspepsia, Sir A. Garrod notices only their comparatively unimportant rôle in precipitating uric acid in the urine, or leading to its deposit in the joints, but he says nothing of the more important action which I have shown[2] them to have in causing retention of uric acid in the liver and spleen, and there forming a store which must at some future time be swept into the blood.

PART II.

Headache.—I have shewn, as I believe, that[3] a certain form of headache (? migraine) is due to an excess of uric acid in the blood, and that, though there is no doubt some nervous centre implicated and irritated by the poison, the nerve centre may be neglected if the poison is removed from the blood, as may be done most conveniently and

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[1] "Gout and Rheumatic Gout," p. 258.

[2] *Journal of Physiology*, vol. viii., nos. 3 and 4.

[3] *Medico-Chirurgical Transactions*, vol. lxx., and St. Bartholomew's Hospital Reports, 1887.

quickly by acids,[1] and further, that the headache may be prevented by avoiding such food as causes increased formation of uric acid and urea, and by increasing acidity causes at the same time retention of uric acid (*e.g.*, butcher's meat). I have also shown in my paper on headache above referred to, that a large excretion of urea and uric acid in normal proportion often goes on without any headache, and the reason is that the uric acid comes direct from the kidney, it is excreted as fast as it is formed and is not in excess in the blood (see paper in *Journal of Physiology*), and from this we may gather that meat causing an excess of uric acid and urea would do no harm if its third result increased acidity, did not give rise to retention of uric acid.

There are some interesting points of connection between dyspepsia and uric acid diseases, for one effect of gastric troubles and fermentation processes may be the formation of (acetic, lactic and butyric) acids, and M. Bouchard "Leçons sur les Auto-intoxications," speaks of conditions in which the stomach may become a perfect manufactory of such acids, and if these are absorbed and diminished, the alkalinity of the blood and tissue fluids, they would undoubtedly cause retention of uric acid and lay up a store of material for a future attack of some uric acid disease. And this headache generally occurs in close connection with some amount of dyspepsia.

Epilepsy.—I have reason to think that the fits in some cases of this disease may be found to have just the same relationship to the excretion of uric acid as the headaches which I have previously described; and in the *Neurologesches Centralblatt*, of March 1st last, I have given a diagram of the uric acid curves got from a case which was under my care at the Royal Hospital for Children and Women. The urine was carefully drawn off, after several of

[1] *British Medical Journal*, vol. 1, 1888, p. 73.

the fits, by the resident medical officer (Dr. F. M. Johnson), and the urine of some thirty hours was collected and kept separate in reference to the fits with the greatest care; and it will be seen from the curves which resulted that the uric acid excretion was very low (retention) before the fits began (just as in headache), that it rose with each fit and fell between them, and that it reached its greatest height in a period corresponding to several very severe fits, and fell nearly to normal when the fits finally ceased.

Further, it will be seen that though the uric acid excretion was as low as 1-50 before the fits, and as high as 1-20 during the worst of them, in the excretion of the whole period the fluctuations balanced each other and the relation of uric acid to urea was 1-34 or nearly normal. And I should expect that cases of epilepsy which give similar uric acid reactions would yield to treatment by drugs or diet directed to the prevention of uric acid retention, just as the uric acid headache has been found to do, and that drugs which cause retention of uric acid would act unfavourably; and to some extent this is already known to be the case, for I have shown that iron and lead cause retention of uric acid, and iron is said to do harm[1] in very many cases of epilepsy, and I[2] know that it does so in this headache, and lead is known to cause[3] epilepsy in some of those who come in contact with it.[4]

The patient from whom the curves given in the *Neurologeshes Centralblatt* were obtained, had been under my care as an out-patient for some time, and when on bromides had only about one fit in a month; and I had several times examined the urine before and after these fits, and got

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[1] Brown Sequard Quain's "Dictionary of Medicine," p. 450.

[2] St. Bartholomew's Hospital Reports, pp. 204, 208.

[3] Dr. Ross, "Diseases of Nervous System," Ed. 1, vol. 2, p. 915.

[4] Mr. Pepper, L. Nov. 5th, 1887.

reactions similar to those given. I then took her into the hospital, gave her ordinary diet of which she ate heartily, and no medicine. On her fourth day in the hospital she had one fit, and on her seventh day the series of fits from which the uric acid curves were obtained.

The family history of this patient is as follows:—"Father's father rheumatism, mother's father rheumatic fever, mother and father both suffer with chronic rheumatism, a younger sister died at the age of three in a fit, and an elder sister æt. thirty, has suffered from fits since she was seven years old. Patient herself has had fits since she was ten years old; she is now thirteen, big for her age, is inclined to be stout and eats heartily. Her fits are severe with marked general convulsions, she is often insensible for half an hour, and then suffers from headache and drowsiness, she has often cut and injured her face, and sometimes passes her water in a fit.

I will now give a few notes of another case in contrast with the above, in which I got no uric acid reaction corresponding to the fits, and which differs from the previous case very markedly, both in history and in the character of the fits themselves; when seen as an out-patient I had taken the fits to be epileptic, but there is possibly some doubt on this point, at any rate the fits were very different from those of the previous case.

Harriet C——, æt. thirty-six, had her first fit at twenty-seven years of age; has obtained decided relief with bromides as an out-patient; salicylate of soda, which was then tried, seemed to have no effect on the fits. Fits generally come about the catamenial period, but bromides prevent them or make them slighter.

History.—F. and M., alive and old, have "rheumatics," no gout or rheumatic fever; has one brother and one sister who are well and have not suffered from rheumatism, gout,

headache or fits. Patient is not married, but has had one child, who died after a few months, no miscarriage, no history or symptoms of syphilis. She was then taken into hospital and the fits watched for, and the urine collected as in the previous case, and the results of its examination showed that there was not the smallest rise of uric acid excretion corresponding to the fits, if anything it was rather diminished as compared with that in the urine passed before them. The fits themselves (as observed by the resident medical officer, Dr. Johnson, to whom I am indebted for a description of them, as also for much care and trouble in collecting and separating the urine) had the following characters: she simply fell and lay on her side without struggling or convulsion, and unconsciousness did not last long, for on being placed on a bed she at once resisted an attempt to draw off her water. She did not injure herself in any way, and though she says she has sometimes bitten her tongue, we could find no marks on it. Dr. Johnson was of opinion that the fits were rather hysterical than epileptic, but I think it possible that they were of a reflex nature and due to utero-ovarian irritation.

Since this account of her case was written, Harriet C—— has been attending as an out-patient, and on one occasion she had a fit in the waiting room, which I was fortunately able to see. It had all the characters of a severe epileptic attack, with general convulsions, dilated and insensible pupils, and face becoming dusky from stoppage of respiration. She lay on her left side, and it was fully twenty minutes before she recovered her senses sufficiently to sit up. About ten minutes later I got her to pass some urine, and this on examination gave a very distinct uric acid re-action (1-17). She had two or three more fits the same evening on her return

home. This seems to show that many cases of epilepsy, besides those in which there is a strong family history of gout, or in which the fits begin at an early age may be found to give uric acid re-actions. It also shows the importance of separating the urine of the fit very carefully from that excreted before and after it, more especially when the fits come singly and are slight; for I have very little doubt that insufficient attention to this point was the cause of my negative results in the previous slighter fits which this patient had, and it will be remembered that I had precisely the same experience in the case of headache. (See *Medico-Chirurgical Transactions*, 1887, p. 4 and 5 of paper.)

I may mention that in the previous case, which yielded uric acid re-actions, salicylate of soda did seem to have some effect in preventing the fits; but I shall not go into that matter here, as I am at present more concerned with the relation of some cases of epilepsy to the excretion of uric acid, than with the results to be obtained in such cases with drugs that influence the excretion of uric acid; the uric acid re-action is simple and conclusive, while the results with drugs, in a disease like epilepsy, which gives no warning of its approach, and in which the number of fits which would occur without any kind of treatment can not be even roughly estimated, are open to many sources of fallacy. But a vegetarian diet (which has long been known to be useful in many cases of epilepsy[1]) will, I believe, give the best results in all cases of epilepsy that give uric acid re-actions; and the finding of such re-action will be of value as indicating the cases in which this diet is most likely to succeed. My experience with headache,

[1] See reference in my paper on the "Uric Acid Headache," St. Bartholomew's Hospital Reports, 1887, p. 211.

however, tends to show that the diet will have to be continued for a long time as (eighteen months to two years) before the best results it is capable of giving are obtained. And cases of epilepsy, in which the frequency of fits is markedly increased by a drug which causes retention of uric acid (as iron), may be expected to yield uric acid re-actions.

It is interesting to remember in this connection that Sir A. Garrod has found uric acid to be in excess in the blood[1] during attacks of epilepsy, and as I have shown it to be in excess in the urine during these attacks in some cases, the connection between the blood and the urine seems to be pretty complete. Sir A. Garrod does not go on to make the deduction which my researches have led me to make, viz., that the headache and the epilepsy are both due to uric acid, and that their close relationship and frequent connection with gout, which he notices can be thus easily explained; he only says (p. 461) "the value of this fact (*i.e.*, the presence of excess of uric acid in the blood) cannot be estimated at present; but must be left to future observations and enquiry."

Hypochondriasis.—My researches have also brought out some interesting relations between this trouble, and the presence of uric acid in the blood, and I have pointed out in my paper on epilepsy that the joyous feelings that sometimes precede the fits, and have been noticed by several observers, as well as myself, as preceding the uric acid headache (migraine), are probably due to absence of uric acid from the blood, because retention of that substance is going on: (see minus excretion of uric acid before the fits in the case of epilepsy, and before the headache in my case in *Medico-Chirurgical Transactions*), and in my own case the presence of excess of uric acid in the blood, not

[1] "Gout and Rheumatic Gout," p. 459-61.

sufficient to cause a headache, is accompanied by an overpowering sleepiness, heaviness and disinclination for exertion,[1] and mentally by bad temper, depression and woe, and a feeling that everything is going wrong; all of which quickly give way to the opposite feelings when an acid, or anything that raises acidity, has been taken, and drives the uric acid out of the blood.

Why does the high-feeding and, possibly, gouty middle-aged man get into his carriage or his train after breakfast and promptly fall asleep over his paper? Because his "alkaline tide" (Sir W. Roberts) is beginning to run, and uric acid is being washed into his blood current in excess from his stores in the liver and spleen. Possibly a considerable part of the so-called tonic effects of acids as nitro-hydrochloric are really due to their driving uric acid out of the blood, and putting an end to the depression it causes. It may be said this is only a temporary cure, and the uric acid driven back into the liver and spleen will return into the blood at some future time; but I have given in the *Journal of Physiology* (vol viii., p. 215) some reasons for thinking that part of the uric acid driven back by an acid is converted into urea and got rid of, and as a matter of fact a headache thus cured by acids does not tend to return very soon.

There are many connections between gout and insanity, especially when it puts on the form of melancholia. And gout has been known to alternate with[2] or replace attacks of the last-named mental disease, just as it has been

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[1] See paper by Dr. Rockwell, *Medical Record*, March, 1888, p. 284, who says that irritability of temper is peculiar to lithæmia as distinguished from neurasthenia, and relates that he has been able to cure himself of excessive irritability by living mainly on a farinaceous diet; so that his experience of diet is the same as my own.

[2] *Manual of Psychological Medicine*, Bucknill and Tuke, p. 382.; also Sir A. Garrod "Gout and Rheumatic Gout," 3rd edition, p. 460.

observed to alternate with attacks of headache or epilepsy; and it is possible that there may be found every gradation of psychical abnormality from mere depression of spirits and bad temper up to melancholia and suidical, or other forms of mania produced by uric acid retention; and I am able, as I have said, either to cause or cure several of the slighter forms by influencing uric acid excretion, so that I have hopes that the knowledge of causation thus gained, may lead to a more successful treatment and prevention of the more serious developments of the trouble. It may also be remarked that the diet which is useful in headache and in epilepsy is of use in some forms of insanity; see (T. S. Clouston on "The Treatment of Insanity of Adolescence," *Practitioner*, vol. 1, 1881, annotation on p. 221.)

Dr. Broadbent in the Croonian Lectures, of 1887, makes some very interesting remarks on this subject. Thus, speaking of the pulse in melancholia, he says, "An unbroken series of gradations may be traced from the irritability and depression of spirits attending functional disorder of the liver up to complete melancholia with delusions"; and he further says that protracted high arterial tension is a very constant symptom of these cases, and he goes on to say "if it (high tension) is not itself the cause it is, at least, the index of the condition of the state of system on which the mental condition depends."

It would be hard to find any observations of greater interest from my point of view, for I have for a long time believed that a high tension pulse, in the absence of other obvious causes for it, may be a sign of excess of uric acid in the blood. Such a pulse is very often seen in the uric acid headache, and the tension is generally greater than usual at the time of the headache; when, as we have seen, there is reason

to expect the presence of excess of uric acid in the blood. I should believe therefore, for several reasons, that both the high tension pulse and the melancholia which Dr. Broadbent finds associated with it are due to excess of uric acid in the blood.

In the same lectures Dr. Broadbent narrates the history of a case of mental derangement in which, "It was found by observation that her mental condition was always worse when the pulse tension was high, and that the only way of keeping it down was to cut off all meat and feed the patient chiefly on milk. When the tension was high she was suspicious, abusive, violent and unmanageable. When it was normal she was cheerful and tractable." The above exactly resemble the mental states I can produce by influencing uric acid, and I have reason to believe the pulse tension would vary with the amount of uric acid in the blood; the diet also, which was found to be useful, is just that best calculated to prevent uric acid retention.

It would, I think, be impossible to find any statement more strongly and completely confirmatory of my views as to the causation of such mental trouble by uric acid.

Dr. Broadbent's remarks on the pulse in epilepsy are of great interest, and especially what he says about some cases of this disorder which are associated with chronic high tension of the pulse, and are found to be very amenable to a diet with a restricted amount of animal food.

It is now easy to see why an attack of mania, melancholia, or headache should sometimes come to a sudden termination in an attack of gout (and not a few such cases are recorded). For anything that

drives uric acid out of the blood (as a rise of acidity), will drive it into the liver and spleen, and, as will be seen later on, probably into the joints also, and when this takes place to any large extent, an attack of gout is the result ; and indeed it is easy to bring on an attack of joint pain and inflammation in a gouty patient by giving acids.

If, then, the above mental symptoms are due, as I have strong reasons for supposing, to excess of uric acid in the blood, any rise of acidity in driving the uric acid out of the blood and curing the melancholia or the headache, will drive it among other places into the joints and cause the podagra, and we have here a simple explanation of the observed sequence.

A high tension pulse is probably seen more often in connection with the chronic forms of Bright's disease, than in any other condition and on reading the works of the late Dr. Mahomed on the pre-albuminuric stages of Bright's disease, I was much struck with the great frequency with which many symptoms which my researches have led me to attribute to uric acid are met with among the cases he singles out, as doomed eventually to have chronic Bright's disease.

Thus he says, Guy's Hospital Reports, 1879, p. 382, "Persons with this condition (high tension) suffer from minor ailments often met with in the subjects of chronic Bright's disease, as malnutrition, cold hands and feet, short breath, palpitation on exertion, imperfect digestion, bronchitis and gastric catarrh. Headache especially hemicranial, sometimes tinnitus and dim vision. Another patient is said to have palpitation, headache, dyspepsia, constipation, loss

of memory, cloudiness of intellect, depression and subnormal temperature; another patient is depressed and hypochondriacal, and another suffers from general malaise, headache and weariness, and most of these symptoms have been spoken of above, as due to uric acid or are mentioned by me as frequent concomitants of the uric acid headache." See *Medico-Chirurgical Transactions*, 1887, p. 2, of paper.

Dr. Mahomed urges that they are the signs of a poison in the blood, and that unless the condition of the blood is improved, Bright's disease will follow in a few years, and to effect this improvement he gives a non-nitrogenous diet with no beer or wine. Here again we have a blood poison giving many of the signs and symptoms of uric acid, and removed by a diet which will as I have shown prevent its retention in the body.

In my own case a certain reduction of nitrogenous food has been enough to completely prevent the uric acid headache, but the high tension pulse has remained. I am now trying whether a further reduction of nitrogen will remove this also, and so prevent the chronic Bright's disease, to which I feel sure that the late Dr. Mahomed would have condemned me. The very common association of interstitial nephritis with gout is, I think, greatly in favour of this view of its causation, and Dr. Norman Moore, in an article on the morbid anatomy of gout[1] gives as one of his conclusions the following: "That chronic interstitial nephritis is found in a large proportion of those bodies in which urate of soda is to be seen in the joints."

Further in the recent Collective Investigation Report

[1] St. Bartholomew's Hospital Reports, 1887, p. 289.

on Intemperance (*British Medical Journal*, vol. 1, 1888, p. 1309), it is said of gout "it would appear that prolonged 'free' indulgence in alcoholic liquors carries the gouty tendency nearly to its height," and further on "it must be remembered that the effects of indulgence in alcoholic liquors are here shown, not the effects of indulgence in pure alcohol." That is to say, we have from my point of view, the prolonged free indulgence in acids which cause continued retention of uric acid in the system, and eventually produce gout.

In the summary of the same report it is said (conclusion 3), "That in the production of cirrhosis and gout, alcoholic excess plays the very marked part which it has long been recognised as doing, and that there is no other disease anything like so distinctly traceable to the effects of alcoholic liquors." I am aware of several facts of great interest, tending I think to show that there is an important (causative) connection between retention of uric acid in the body and cirrhosis of the liver; but as some of these facts relate to the action on uric acid excretion of at least one drug about which I have not yet written anything, and to some cases which require further investigation, I shall reserve what I have to say on this matter for a future occasion. Conclusion 5, of the above report is as follows:—"That in the etiology of chronic renal disease, alcoholic excess, or the gout which it induces, probably plays a special part," which confirms from the clinical side, Dr. Norman Moore's conclusions drawn from morbid anatomy.

All these facts seem to me to be full of interest and suggestion, and I think that many of the conditions

I have mentioned will well repay some further investigation into their relation to the excretion of uric acid.

Gout.—The relationship of this disease to uric acid is not, I believe, a matter of dispute. Sir A. Garrod has shown[1] that uric acid is in excess in the blood during attacks, and minus, or absent, during the intervals, also that at the time of an attack though uric acid is abundant in the blood, the day's excretion in the urine is often below the normal. And the parallel between these observations of Sir A. Garrod and my own observations on the uric acid headache is very close,[2] for though I found that uric acid is in excess in the urine at the time of the headache, and I conclude that it is in excess in the blood at the same time, I often found that the uric acid excretion for the whole day was rather diminished, and it was only on carefully separating the urine of the headache period that I found excess of uric acid; for the diminished excretion of uric acid before and after the headache often more than counterbalanced the plus excretion during the headache, so that the net result on the whole day was a minus excretion of uric acid; and the same applies to the uric acid excretion of epilepsy, for though during the worst of the fits (see cases previously mentioned, and woodcut in *Neurologisches Centralblatt*) the excretion was as high as 1-20, and I have no doubt that uric acid was in excess in the blood; yet on the whole period the excretion of uric acid was 1-34, which taking 1-33 as normal is slightly low.

With regard to the actual phenomena of podagra, Sir A. Garrod has called attention[3] to the probability of the cartilages and ligaments of joints being not only very slightly

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[1] "Gout and Rheumatic Gout," 3rd edition, p. 114 and 132.

[2] *Medico-Chirurgical Transactions*, vol. lxx., p. 4 and 5 of paper.

[3] "Gout and Rheumatic Gout," p. 292.

vascular, but also less alkaline than the blood and tissue fluids in general, so that the same reasoning which leads us to suppose a retention of uric acid in the liver and spleen will apply[1] to its retention in these tissues also. And the fact that they are very slightly vascular may help us to understand why a drug like salicylate of soda, which takes some twenty-four hours or more to clear the blood of uric acid, may not have a very marked effect in podagra; for even after the blood has been more or less cleared by it, there may still be enough urate in some remote and slightly vascular parts to keep going an inflammation which has once been started, and salicylates will not in my experience stop a headache if it is at all severe, or at best they take some time to do it, and act much more slowly than a dose of acid; (as nitro-hydrochloric) but given before hand, or very early in the attack, they will prevent it.

It may not be without interest to point out that in accordance with this explanation of its causation. Gout may be regarded as a self-curing disease, for just as it takes origin in the plus acidity of vigorous nutrition and some excess of food, resulting, as we have seen, in retention of uric acid; so when a severe and painful attack of podagra has lasted for several days, metabolism is reduced both from diminished exercise, and probably also from diminished ingestion and digestion of food; there is diminished formation of uric acid and urea, and, what is more important, diminished acidity, so that the stored uric acid can find its way out of the body and the circle of life gradually rights itself.

There is an important point with regard to the way in which exercise tends to prevent gout; thus Sir A. Garrod says,[2] "Cullen remarked that gout seldom attacked persons

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[1] *Journal of Physiology*, vol. viii., Nos. 3 and 4, p. 213-14.

[2] "Gout and Rheumatic Gout," p. 230.

employed in constant bodily labour, or those who live much upon vegetable diet," the way in which the diet acts is now, I hope, sufficiently clear; but I must say a few words about the bodily labour.

The effect of exercise is to increase the formation of uric acid and urea (in their normal relation to each other)[1] and of acid, and one would expect that the rise of acidity from this source would cause retention of uric acid and so lead to gout; and I have no doubt that it would do so, but for the fact that bodily labour is almost inseparably connected with increased skin action. Now we have seen above, that diminished skin action is immediately followed by a rise of urinary acidity, and I take it for granted that increased skin activity and free perspiration eliminates a large amount of acid and lowers acidity (and I can prove that it does so); so that in the case of exercise (the effect of which here stands in marked contrast to that of meat diet), the extra formation of uric acid does no harm, because there is no rise in the acidity to interfere with its free elimination; and I have plenty of facts bearing on this point.

And now to take a general survey of the action of food and drugs in gout, I think we may say that all substances which are known to be harmful prevent uric acid excretion and cause retention, as acids (including wine, beer, meat, &c.), lead and iron; while all which are known to be useful facilitate uric acid excretion and prevent retention, as colchicum, alkalies, salicylates and vegetarian diet.

Rheumatism.—The effects I have shown that salicylates have on the excretion of uric acid, and their marked and well-known curative effect in acute rheumatism, would lead me to infer that this disease also is due to uric acid, in spite of the fact that Sir A. Garrod[2] has not been able to find it

[1] North "Proceedings Royal Society," 1885.

[2] Reynold's "System of Medicine," vol. i., p. 897 (1st edition).

in the blood. There are several striking facts which point more or less strongly in this direction; thus it will be obvious that a large part of the general statement I have just made with regard to food and drugs in gout will apply also to rheumatism, for the value and importance in both diseases of salicylates, alkalies and a meatless diet are matters of common observation. The important action of excess in beer and meat, and of excessive labour or exposure to weather in causation, are pointed out in the recent Collective Investigation Report on Rheumatic Fever;[1] and I have already gone into the mode in which some of these factors bring about retention of uric acid. With regard to excessive bodily labour, it is obvious that something quite out of the usual course is here meant, and that this is a very different matter from sufficient bodily exercise well within the power of the individual, which I have discussed in relation to gout.

The reason why the same poison (uric acid) in the blood produces in one person gout, in another rheumatism, in a third headache or hypochondriasis, in a fourth epilepsy or mania, is no doubt to be found to some extent in the amonnt of uric acid that has been accumulated, and the length of time during which it is in excess in the blood; but beyond uric acid itself and the conditions affecting its excretion, there are no doubt many factors of formation or function peculiar to each individual, as differences in vessel and nerve distribution, or in formation, growth and nutrition of these and other structures, either inherited or acquired, which determine the point on which the poison shall act most quickly and most forcibly, and so to some extent the effects it produces. Thus, one patient may suffer early in

[1] *British Medical Journal*, vol. 1, 1888, p. 387, et seq.

life from headache or epilepsy, and being thus led to alter his diet and mode of life may escape gout or chronic nephritis, into which a patient with a less sensitive nervous system would have drifted without any warning.

And, finally, I must say a few words as to some of the statements at the beginning of this paper. With regard to the formation of uric acid and its constant relation to urea, though my estimated relation of 1-33 has often been met with in the urines of other people which I have tested, I am not prepared to say that there may not be considerable individual variations in the relative formation of these two substances; but my object has been to show that, be these variations what they may, they are probably of little importance as regards the causation of disease by uric acid in comparison with the variations in excretion which, as I have shown, occur daily to some extent, or can be caused at will by a variety of foods and drugs.

And with regard to the excess of uric acid excreted under the influence of such drugs as the salicylates or phosphate of sodium, the great rush comes on the first or second day the drug is used, and after that, even though the same dose is continued for five or six days, it will never rise so high again, and be often scarcely above normal the rest of the time; and further, if the store of uric acid in the liver and spleen be swept out by one drug, another which generally causes plus excretion will, if given just after it fail to act.

I conclude that such drugs have no power to cause an excessive formation of uric acid, but that the fluctuations they produce are the result of a sweeping out of such amount of uric acid as has been previously retained in the liver and spleen, *i.e.*, they can influence excretion only.

I have shown[1] that a large formation of uric acid (as sixteen grains for a man who usually forms ten grains), provided it is all excreted at once along with the urea formed at the same time, does not give rise to any functional troubles such as usually accompany excess of uric acid in the blood, and it is therefore, I believe, not in excess in the blood under these circumstances. And both these propositions drive us to the conclusion that it is not by excessive formation, but by the continued retention and accumulation of small quantities, that uric acid comes to be in excess in the blood; and I have shown that by such retention enough may gain entrance to the blood to cause very definite diseases, some of which I can produce at will.

The retention is generally the result of the action of acids taken in food or drink, formed internally (as in dyspepsia) or retained by defective skin action. It is a physiological process occurring to some extent in everybody, and it is only when exaggerated by long continued errors in diet, or in habits, perhaps conjoined with dyspepsia, that it becomes a factor in the causation of uric acid diseases.

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[1] *Medico-Chirurgical Transactions*, 1887, pp. 9-10, Paper on Headache.