A POST-GRADUATE LECTURE ON FURTHER RESEARCHES ON THE CAUSATION OF ANÆMIA AND THE BLOOD CHANGES PRODUCED BY URIC ACID.

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I HAVE shown in my writings¹ that there is a large group of diseases, including paroxysmal hæmoglobinuria, splenic leucocythæmia, anæmia, and chlorosis, in which the blood changes occur in association with the passage of a large amount of uric acid in the urine.

On the other hand my results in myself and others also show that the value of the blood decimal² fluctuates from day to day with the amount of uric acid passing through the blood into the urine, and that the intentional increase of uric acid is always accompanied by a corresponding fall in the value of the blood decimal. And so constant are these results that I would undertake to make the blood decimal vary in anyone from day to day, according to a prearranged plan. On the other hand I would tell correctly from a 12 or 24 hourly examination of the blood what had been the changes in urate excretion during the same periods.

I now further proceed to show that iron cures anæmia by clearing the blood of uric acid, that the administration of uric acid will quickly undo its work, and that if in any case it fails to clear the blood of uric acid it also fails to cure the anæmia.

That when iron has failed to cure, other drugs that have more power over uric acid, or act in a slightly different way, may succeed; but that no drug of any kind will succeed if it fails to clear the blood of uric acid.

Lastly, I shall point out that this uric acid causation of chlorosis enables us to give an absolutely complete explanation of its occurrence in girls and young women; and, further, may enable us in the future to prevent it with an almost mathematical precision. And that similar reasoning enables us to account completely for the connection of this group of diseases with such factors of causation as rheumatism, dyspepsia, melancholia, headache, Bright's disease, hot climates, malarial and other fevers.

Fig. 1 shows the blood decimal of J. K., suffering from

chlorosis. From April 11th to May 8th she was on iron, and we see the rise it produced in the decimal. On May 11th iron was left off, and on May 15th the blood decimal was the same as on the 8th. On May 15th and two following days the

equivalent of 4 grains of uric acid were given, and on May 18th the blood decimal had fallen, but it rose again on the 22nd and 25th, after the uric acid had been left off. However, on the 17th and 18th, menstruation was present, and, as this might have caused a fall of the blood decimal (menstruation is nearly always accompanied by some dyspepsia, with fall of urea and acidity, and secondary uric acidæmia), I repeated the dose of uric acid on the 25th and two following days, and on the 29th the decimal had again fallen, to rise again on June 1st after the uric acid had been left off.

There seems, then, to be very little doubt that the administration of uric acid and its passage through the blood (for a similar administration to myself does cause it to pass in excess through the blood and into the urine³) causes a distinct fall of the blood decimal in spite of the presence of a considerable amount of iron in the body. But iron does not always succeed so well as it did in this case, and then, as we shall see in the following case, it fails because it is unable to clear the blood of uric acid, for other drugs which have more power in clearing the blood of uric acid succeed. Fig. 2

FIG. 2.

shows the blood decimal of A. P., aged 17, suffering from chlorosis, and below this for comparison I have placed the curve of the urine excretion in ounces.

I may say that she had been attending as an out-patient for more than three months, and taking iron the whole time, but on February 27th there was no improvement; the gums were very pale, and the face puffy and wax-like.

I took her in, examined the blood, and found the decimal at 0.34. I put her on pulv. ferri carb., and on March 6th the blood decimal was just the same; so that a week on iron and in bed produced no improvement. She suffered considerably from headache and dyspepsia, and I have little doubt that the dyspepsia kept the acidity low, and so prevented the iron from clearing the blood of uric acid, and hence, though given steadily for three and a-half months, it had practically done no good.

To test this point I began to examine the urine, and on March 8th there were 29 ounces containing 267 grains of urea and 15.2 grains of uric acid, a relation of uric acid to urea of 1 to 17. On March 9th there were 28 ounces of urine containing 206 grains of urea and 13 grains of uric acid, relation 1 to 15.

Here then, while the patient was on iron we have evidence of a great excess of uric acid in the urine, and no doubt also in the blood, which explained her headache and scanty urine (for the urinary water is, as I have shown, in everyone inversely as the uric acid excreted along with it⁴) and her œdematous, almost myœdematous, face from retention of fluids

in her tissues, and also completely explained why the iron had for so long failed to do good.

On March 10th, however, there was a slight improvement, and the blood decimal had risen to 0.37, but as I had found such an excess of uric acid in the urine in spite of the iron, I decided to stop it and give a drug which I knew had more power of clearing uric acid out of the blood and urine⁶. I accordingly put her on the ordinary mist. hydrarg. perchlor. c. pot. iod. three times a day, and the rest of the figure shows its effect on the blood and urine.

On March 13th there were 39 ounces of urine, containing 304 grains of urea and 10.8 grains of uric acid—relation 1 to 28. Note the increase of water and urea and the decrease of uric acid in illustration of the law above mentioned.

On March 16th there were 42 ounces of urine, containing 232 grains of urea and 9.1 grains of uric acid—relation 1 to 25.

On March 23rd there were 45 ounces of urine, containing 332 grains of urea and 9.7 grains of uric acid—relation 1 to 34, or normal.

And with this clearance of the blood and urine of uric acid the blood decimal went up by leaps and bounds, and having risen in eleven days on iron only 0.03, it rose 0.06 in three days on iodide of mercury, and 0.15 in thirteen days, reaching 0.53 on March 23rd, a height which more than three months on iron had quite failed to raise it to; and we now know why this was so, for the one drug cleared the blood of uric acid and the other failed to effect this result. I know, however, from experience in other cases that even the iodide of mercury may fail to clear the blood and urine of uric acid, and then, like iron in the above case, it also fails to produce any continuous improvement in the blood decimal.

The marked rise in urinary water, which coincided in this case as it always does with the equally marked fall in uric acid, soon removed the excess of water from the tissues, and her face assumed a natural appearance, her appetite and digestion improved, and she considered herself cured.

In this case I have very little doubt that but for the dyspepsia the iron would have been able to clear out the uric acid at first,⁶ and then she would have been cured in six or eight weeks instead of remaining almost unaffected at the end of three months. Now it is well known that Murchison and others have pointed out that in some cases iron will not cure anæmia till the liver has been got into proper order, and the drug he used to get the liver into order was mercury. We can now see that this mercury did good, not by any special action on the liver, as was supposed, but because it cleared the blood of uric acid, and so altered at once the circulation and nutrition of the whole body; and any other drug that clears the blood and urine of uric acid produces the same fall in excretion of uric acid and rise in excretion of urea, but some have more power, and will succeed in clearing the blood of uric acid when others have failed.

On the other hand, we now know that you have only to introduce into the body and blood an excess of uric acid to quickly undo all the good that iron, mercury, salicylates, or anything else has done, which still further emphasises the fact that they do good merely by clearing the blood of uric acid; and if you give uric acid along with iron the blood decimal falls, or at least fails to rise any further, so long as the uric acid is continued, which parallels what we see in Nature, that when there is a great excess of uric acid in the urine and blood, iron may be administered for months without effect.⁷

In concluding this part of the subject I will merely point out that it is open to anyone to repeat my results, and I hope you will all repeat them.

You may not have time to estimate uric acid from day to day, but, if you can collect the urine, you may safely take a steady increase in its quantity as a proof of a steady decrease of uric acid, and, even if you cannot examine the blood, a marked improvement, such as that shown in Fig. 2, very soon becomes obvious to the naked eye.

I may, perhaps, be allowed to remind you in this connection that uric acid is contained in all meat food, and also in the *Pharmacopœia*, for caffeine is chemically trimethyl-xanthin, and I have shown⁸ that xanthin and hypoxanthin may, as regards introduction into the human body, be considered equivalent to uric acid.

Defective metabolism, the result of defective circulation,

is probably as near as we can get at present to the action of uric acid in producing these blood changes, and its action is probably precisely similar in several other important diseases, but for details I must again refer to my book.

And now as to the causation of chlorosis. It will, no doubt, be readily admitted that we meet with it chiefly in women between the ages of 16 and 25. How do girls and women of these ages differ from boys and men of the same ages? As you know well, a girl at about the 13th year develops with enormous rapidity, and her weight may increase by as much 11 lbs. in this one year, as she dashes at a bound from childhood into womanhood.

Now, this very rapid growth and development entails a corresponding rapidity of tissue change and metabolism, with a very large formation of uric acid and urea per pound of body weight—this being always much greater in the child than in the adult. But high urea formation is always accompanied by high acidity,⁹ that is to say, the urine will be highly acid and the blood lowly alkaline. The blood alkalinity being low, it will be but a bad solvent of uric acid, and hence a considerable proportion of the large amount of urate formed in these years of active metabolism will not be held in solution in the blood and excreted, but will be retained and deposited in various parts of the body, giving local signs of which we shall speak presently.

Unfortunately, later on a girl's metabolism falls very greatly, and by the end of the 18th year her increase in weight is almost nil; with this there is a great fall in the formation

of urea and acids, and the blood becomes more alkaline; as a result of this it becomes also a better solvent of uric acid, and it now takes up and passes into the urine so much uric acid—probably several hundred grains—as was stored in the tissues during the preceding period of active metabolism, from 12 to 14. Hence, from 16 to 19, or later, she will have an excess of uric acid passing through her blood, and will suffer from its effects on the blood decimal—namely, chlorosis.

To illustrate this point a little further, I give in Fig. 3 a curve showing the annual increase in weight of boys and girls.¹⁰ From this we see that the greatest development in girls is in the 13th year, and in boys not till the 16th; and though the boys' curve falls very greatly in the 17th and 18th years, they are still increasing about 5 lbs. a year when the curve ends.

Now I think that girls in their more early development will probably form more uric acid and urea per pound than boys in their later development, and when later on the girls' increase is almost *nil*, the uric acid previously retained will pass through the blood both in greater quantity and more suddenly than it does in boys, whose increase is for several years later very considerable and their acidity not so low. I have therefore added to the curves a line representing the probable effects of the girls' increase in weight on the excretion of urea and acids, and a broken line below showing the effect on the excretion of uric acid, and from these we see at a glance that the chlorosis and anæmia of 18 are the result of the passage of an excess of uric acid through the blood, which again is the result of a previous storage of this substance from 12 to 15. Add to this that just at the time when a girl's increase of weight is coming down, and her urea and acidity falling, menstruation is established; and that even if this does not upset digestion and appetite, it often obliges girls to keep quiet for several days, so that its result is to still further reduce urea and acidity, and still more markedly flood the blood with uric acid, thus completely accounting for the increase of her chlorosis, and the functional troubles so often met with at menstrual periods.

Then, again, if we look at this figure, we shall see that we have got not only a complete explanation of the causation of chlorosis, but that we have also unexpectedly come upon an equally complete explanation of the girl's great tendency to rheumatism, as compared with her brothers; for I have for years been pointing out¹¹ that what we call gout or rheumatism is really the irritation of certain joint structures by uric acid or urates retained in those structures; and that they are retained in those structures by the same causes that prevent their excretion, and bring about their retention in the body in general, namely, a rise of acidity, or the presence in the blood of any substance whose urate is insoluble.

Now the retention in this instance is produced by a rise of acidity, and the joints are one of the places in which the urate is retained; it is little wonder, then, that girls are specially liable at this period of their lives to acute rheumatism, and Dr. Cheadle says¹² that girls of 10 to 15 years old are twice as liable to rheumatic fever as boys of the same age; these years including, I remark, the period of their most active metabolism.

Probably boys are liable to rheumatic fever from a similar cause at 16 years of age, but their active metabolism coming when they are older, they probably form less uric acid per pound than girls; and, further, they probably retain much less uric acid at this time owing to their more active habits of life.

For it follows from the first principles of urate excretion, for which I must again refer to my book, that, other things being equal, those in any given period of life retain most uric acid in their body who take least exercise, and those retain least uric acid in their body who take most exercise, which explains Cullen's well-known observation that gout seldom attacks those employed in constant bodily labour.

Now no one, I suppose, will deny that boys take much more exercise than girls all through school life, and especially as compared with girls at and after the commencement of menstruation. We see, then, that boys differ from girls in that their active metabolism comes later, when their formation of uric acid per pound is probably smaller, and that, owing to

their greater bodily activity, they probably retain a smaller amount of the uric acid they form; while, lastly, their activity and nutrition are better continued and maintained, and are not subjected to the depressing effects of menstruation, so that any urates they have retained pass more gradually through their blood; hence they escape the chlorosis and anæmia from which their sisters suffer.

Prevention follows from this reasoning in the most simple manner, namely (1) diminish the girls' retention of urates at 13 by not introducing in food a single grain that is unnecessary, and not giving more animal food than is required for healthy nutrition; and, further, by increasing the bodily activity, prevent part of the rise of acidity and its results. In this way you may save her not only from chlorosis but also from rheumatism; (2) later on, at 16 or 17, let her continue her bodily activity, and prevent her becoming a semi-invalid when menstruation is established; in this way any urate she has stored will pass slowly through her blood (as in the case of her brother), and severe chlorosis will be prevented.

With regard to (1) I would direct special attention to the thoughtless way in which urates are often introduced into the body in soups, beef-tea, and meat extracts, which are useless for nutrition and yet contain large quantities of it, and these should in girls of 13 be avoided like poison.¹³ The same applies to coffee and vegetable alkaloids in general. As regards the developed disease there is only one indication, namely, to clear the blood of uric acid; and if iron, mercury, or other metals can do this they will cure; if they fail to do it they will not cure.

In this latter case the best course is probably to cut off at once all unnecessary urates in the food, and give a good course of salicylates to clear out the accumulations already in the body, and on this treatment the blood decimal may improve more in a few weeks than it did on iron or arsenic in as many months, and if you examine the urine you will soon see the reason of this.

Of the relation of anæmia to acute rheumatism I need not, I think, say any more,¹⁴ and the same reasoning applies to dyspepsia and its allies—melancholia and headache.¹⁵ In Bright's disease the excess of urates in the blood is well known, while hot climates will obviously lower the acidity and facilitate the passage of urates through the blood. Then, again, malarial and other fevers cause a fluctuation in urate excretion exactly similar to that traced out above in the case of girls, first a retention and then a plus excretion as its result, and this fluctuation accounts for very many of their symptoms¹⁶ as well as for the anæmia which so often follows them.

NOTES AND REFERENCES.

- ¹ BRITISH MEDICAL JOURNAL, September, 1893, and *Uric Acid*, 2nd Edition. Churchill, London. 1894. ² The blood decimal is the resultant obtained by dividing the percentage of hemoglobin by the percentage of cells. ³ See *Journal of Physiology*, vol. 15, p. 167. ⁴ *Uric Acid*, 2nd Edition pp. 34, 93, 378. ⁵ See BRITISH MEDICAL JOURNAL vol. 1, 1890, p. 1241, and *Medico-Chirurgical Transactions*, vol. 76. ⁶ See *Medico-Chirurgical Transactions*, prev. ref. ⁷ *Uric Acid* 2nd Edition, p. 233. ⁸ *Uric Acid*, 2nd Edition, p. 68. ⁹ *Uric Acid*, 2nd Edition, p. 25. ¹⁰ Copied from a paper by Dr. W. Stephenson, *Lancet*, September 1888. ¹¹ *Practitioner*, February, March, and April, 1891, and BRITISH MEDICAL JOURNAL, July 1888. ¹² *Lancet*, vol. 1, 1889. ¹³ See *Uric Acid*, 2nd Edition, p. 355. ¹⁴ See also *Uric Acid*, 2nd Edition. ¹⁵ *Loc. cit.* ¹⁶ *Uric Acid*, 2nd Edition pp. 106-277.

IRREGULAR AND PROLONGED SUCKLING.—Dr. Danford Thomas, at an inquest held recently, called attention to one source of deaths of infants by suffocation. He said that he had held 300 inquests on children found suffocated in bed, and added that he had no doubt that many, in fact the majority, of these cases, were due to the mothers falling asleep after suckling with the children in their arms. There is no doubt that this practice of letting an infant remain at the breast all night is most pernicious. It not only involves the danger of overlying, but is a fruitful source of over-suckling and dyspepsia. As the coroner said, an infant should be suckled and then put in its cot to sleep. Simple as this precaution, and obvious as it seems to the educated intelligence, it is very commonly neglected by mothers of the working classes. It will be found in practice that attention to this detail will solve many difficulties which are untouched by drugs.