INFLUENCE
OF
SALICYLIC ACID AND ITS SALTS ON
THE EXCRETION OF URIC ACID.

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IN a paper which I read before the Society in May, 1887, I drew attention to the relation of a certain form of headache to the excretion of uric acid, and showed that the headache in question coincided with a plus excretion of uric acid, and was possibly due to an excess of uric acid in the blood. And in the 'Journal of Physiology,' vol. viii, p. 211, I have narrated some experiments on the effects of acids and alkalies on the excretion of uric acid, and have mentioned that by giving acids I am now able both to cure the above form of headache and to stop the plus excretion of uric acid which accompanies it.

It may be taken then, as shown in the latter paper, that alkalies, as soda and potash, always, within certain limits, increase the excretion of uric acid, while *acids* as nitro-hydrochloric, citric, acetic, always diminish the

excretion of uric acid; but there is one important exception to this rule in the case of salicylic acid, and as the value of this drug in rheumatism and gout is so great I propose to go at some length into its exceptional action and the results of my experiments with it as viewed in the light of my papers above referred to.

Shortly stated, the action of salicylic acid, or salicylates, is to dissociate the excretion of uric acid from its general relation to acidity, so that an increase of acidity, while there is plenty of salicylate in the blood, is not accompanied by any diminution of uric acid excretion.

The great importance of this fact may be roughly estimated by considering the rôle played by acids in dyspepsia, in gout, and in rheumatism; and if, as I hope to be able to show, salicylates prevent these acids causing retention of uric acid, a large part of their action in these diseases will admit of easy explanation. Thus of gout Sir A. Garrod says ('Gout and Rheumatic Gout,' ed. iii, 245): "When a few glasses of wine, ale, or porter quickly and invariably produce in any individual an inflammatory affection of a joint, such inflammation is of a truly gouty character." The way in which these beverages act in producing the inflammation is now, I think, sufficiently clear. I shall not go further into the ultimate pathology of rheumatism and gout but at once bring forward the results of my experiments with salicylates.

The results of one of my first experiments is given in Fig. 1.

On the first day in this figure acidity of the urine is very high (owing to drugs taken on the preceding days not shown in the figure), and uric acid is, as one would expect, below the urea, *i.e.* there is retention of uric acid due to the high acidity.

It is here assumed, for reasons given in previous papers, that the normal relation of uric acid to urea in this case is 1 to 33, and on this relative value the curves in all the figures are based.

On the second, third, fourth, and fifth days salicylate

FIG. 1.

of soda is taken in amounts varying from 30—45 gr. a day.

It does not appear to have any definite effect on the acidity of the urine, which rises or falls from other causes, but it is at once seen that the uric acid excretion is not influenced by the acidity in the usual way, for on the third day it rises high above the urea, while the acidity is almost the same as on the previous day, and on the fourth day uric acid actually falls below urea, though as acidity has fallen we should have expected a rise. Again, on the fifth day acidity has risen yet uric acid is not kept down by this, but actually rises also ; so that we see that

under salicylate the uric acid excretion fails to keep up its usual inverse ratio to the urinary acidity; indeed, it almost seems as if the reverse effect were produced, so that a fall of acidity corresponds with a fall of uric acid, and a rise of acidity with a rise of uric acid.

For the purpose of contrast with these salicylate of soda curves, I have given in Fig. 2 several days when no

Fig. 2.

drugs were taken, so as to show the ordinary relation of uric acid to acidity. This is no picked instance but the first that comes to hand; indeed, I have very few curves of periods when no drugs were taken, and even during these curves in Fig. 2 meat was being taken from the second onwards for purposes of experiment.

Now, at first sight it might appear as if this figure and

its curves would upset all my previous results as to the intimate relation of the excretion of uric acid to acidity, for while on the second day acidity is rising, uric acid is a long way above urea, and my notes show that there was a very decided headache on that day; but on closer examination I think it will appear that this exception is more apparent than real, and that the uric acid is really influenced by the acidity in the way I have pointed out in previous papers.

On the day on which this apparent exception occurs meat was taken twice, viz. at 2.0 and 7.30 p.m., and as it is well known that meat increases acidity I take it for granted that the rise in acidity is due to the meat; but it is also well known that the great excretion of uric acid in each twenty-four hours takes place during the alkaline tide after breakfast in the morning and the few following hours. On the day in question, however, the first meal of meat was not taken till 2 p.m., and it would not have any action on acidity for one or two hours more, so that the great uric acid excretion for the day had taken place *before* the acidity rose, and so could not be affected by it. This is the explanation of several apparent exceptions to the rule, and I have often found that taking meat and wine at dinner affected acidity, but had little influence on uric acid, though their action on the uric acid excretion of next day was clear enough. In this case we see that on the third the uric acid is little more than half the distance above the urea it was on the second; on the fourth and fifth it gets still nearer to it, and on the sixth, with a further rise of acidity, it is below it. And while speaking of this matter, I will just draw attention to Fig. 3, showing the acidity, uric acid, and urea curves, as obtained from urine collected in consecutive periods of three hours from 7 a.m. one day to 1 a.m. the next. This shows clearly enough the effect of acidity on the uric acid excretion, but also shows that the greatest uric acid depression does not occur for some three hours or so after the greatest rise of acidity. So that we see that a rising

FIG. 3.

acidity takes several hours to exert an appreciable influence on uric acid excretion; and further that, if the rise in acidity is not caused till late in the day, it cannot influence the uric acid of that day's excretion to any great extent, but will act most on the alkaline tide excretion of the next day.

Now, to return to the effects of the salicylate in counteracting this usual effect of acidity on uric acid. In Fig. 4, which is consecutive to Fig. 2, one day being common to each, it will be seen that the uric acid curve, though above the urea, is clearly dependent on the acidity curve, being always further above the urea when acidity falls, and closer to it when the acidity curve rises; and this holds good up to the tenth. But on the eleventh, the first day of salicylate (taken as salicylic acid so as not in any way to diminish the acidity and so complicate

matters), there is a marked change in the relations, for acidity rises sharply, and in spite of that uric acid rose considerably. If this were due to the factors I have already spoken of as causing apparent exceptions to the rule, one would expect that the high acidity would bring down the uric acid of the next day (the twelfth); but quite the reverse is the case, for the uric acid still further rises to the large excretion of 17·4 grs., which exceeds its general relation to urea by more than 6 grs. So that I am unable to explain this extraordinary curve except as the result of the salicylate taken, and it coincides with the results obtained in previous experiments with it. It is further to be remarked that this excessive excretion of uric acid was not accompanied by any headache, which it would almost certainly have been if it had occurred apart from the action of salicylate.

On the thirteenth acidity falls and uric acid also falls, and this coincides with what we have before seen to occur under the influence of salicylate.

On the fourteenth, however, there is an exception, for acidity rises and uric acid falls and comes much nearer to the urea than it has been for some time; and on the fifteenth it is nearer still to the urea. My belief is that with the rise in acidity from the thirteenth to the fifteenth and sixteenth the uric acid would have been below the urea instead of above it, had it not been for the action of salicylate, and on the sixteenth, two days after the last dose of salicylate, it does actually fall below it.

From these experiments (Figs. 1 and 4) two facts stand out clear and distinct.

(1) That under salicylate, uric acid excretion is not kept down by rise in acidity but rather the reverse; and

(2) That a large excess of uric acid excretion when it occurs under salicylate is not accompanied by headache; and there are several facts which may be placed beside this; thus, it has been shown by Dr. Brunton,¹ that salicylate of soda is a valuable remedy in headache, and

¹ 'Pharmacology, Therapeutics, and Materia Medica,' p. 559.

FIG. 4.

we know, moreover, that salicylate in one form or other relieves the pains of acute rheumatism, and prevents or relieves the pains and discomforts of many phases of gout; and I believe that this headache, for the reasons given in my previous papers on headache and uric acid excretion, is merely a symptom of so-called "quiet gout."¹ I consider therefore that I have good grounds for supposing

¹ See Mr. J. Hutchinson, 'Lancet,' Nov., 1884. p. 903.

that in these instances the salicylate prevented the headache which would otherwise have accompanied such a large excretion of uric acid.

Into the other matter, the reversal by salicylate of the usual action of acidity on the excretion of uric acid, I propose to go at some length, because though a complete explanation is not at present possible, there are several chemical facts which it is well worth while to place by the side of those I have now brought forward. Thus Professor Latham, in his 'Lectures on Rheumatism, Gout, and Diabetes'¹ says salicylic acid combines with glycocine and passes out in the urine as salicyluric acid, and if we may suppose that salicylic acid has the power of splitting up uric acid and combining with its glycocine so as to form salicyluric acid (just as benzoic acid does to form hippuric acid) it would not be very difficult to explain the reactions I have obtained. For what is known of the chemistry of salicyluric acid would lead us to suppose that it is more soluble than uric acid both in the tissue fluids and in slightly acid solutions, and these peculiarities would be sufficient to explain the altered relation of uric acid excretion to acidity under salicylates. I may here say that having arrived at this point with salicylate it was suggested to me by Dr. Lauder Brunton to try whether benzoates would have the same effects, and I at once performed similar experiments with these salts, and found that benzoate of ammonium, which increases acidity, diminishes uric acid excretion, while benzoate of sodium, which diminishes or does not affect acidity, allowed of an increase of uric acid excretion. The benzoates therefore appear to act merely through their effect on acidity, and not as the salicylates do; and this different effect is, I suppose, due to the fact that salicyluric acid is more soluble than hippuric.

With regard to this point, I have thought that it might be useful to give short extracts of what is said of the

¹ 'Brit. Med. Journ.,' 1886, p. 629, *et seq.*, and 'Lancet,' Jan., 1885, p. 1119, *et seq.*

solubilities of these acids in 'Watts's Dictionary of Chemistry.'

Thus "Uric Acid," vol. v, p. 955: "It is nearly insoluble in water, one part of it requiring 15,000 parts of cold and 1800 parts of boiling water to dissolve it; in alcohol and ether it is quite insoluble."

"Hippuric Acid," vol. iii, p. 157: "It is sparingly soluble in cold water, one part of the crystals requiring 600 parts of water at 0°. Boiling water and alcohol dissolve it readily, ether scarcely at all. Hippuric acid likewise dissolves, but very sparingly, in water containing hydrochloric acid. Hippuric acid dissolves in strong hydrochloric acid at the boiling heat, and on continuing the ebullition it is resolved into benzoic acid and glycocine."

"Salicyluric Acid," vol. v, p. 172: "It dissolves easily in boiling water and in alcohol, less easily in cold water and in ether. Heated for a short time with hydrochloric acid it dissolves and crystallizes out again unaltered, but if the boiling be continued for two to three hours the acid is resolved into salicylic acid and glycocine."

I am sorry that the statements about salicyluric acid are not more definite, but I think we may infer that both hippuric and salicyluric acids are far more soluble in water than uric acid, and are also more soluble in water containing hydrochloric acid. This latter point is not definitely stated with regard to salicyluric acid, but I think as it is more soluble in other ways than hippuric acid, and, like it, is soluble in strong hydrochloric acid, that it is probably at least as soluble as hippuric acid in weak hydrochloric acid, and that salicyluric acid is more soluble both in water and in ether, and probably in weak acids, than is hippuric acid.

If we may suppose that on giving salicylate the uric acid in the blood and tissue fluids is converted into salicyluric acid, we should have to deal with a substance which as compared with uric acid is far more soluble in those fluids, and also more soluble in slightly acid fluids;

and if alteration of solubility is the explanation of the action which I have shown that acids and alkalies have on the excretion of uric acid, we have here also a simple explanation of the result I have obtained with salicylates, viz. that a rise in acidity no longer entails a fall in uric acid excretion.

And I believe that here also, just as in the case of alkalies, the salicylic acid acts on the uric acid which is supposed to be stored in the liver and spleen, and, increasing its solubility, rushes it at once into the blood and out by the kidneys. But the rush into the blood under salicylate is not accompanied by any headache, and it differs in this respect from the rush under alkalies, so that we have some grounds for the supposition that the uric acid exists in the blood in a different chemical combination (salicyluric acid) when it is washed out by salicylic acid, to what it does when washed out by alkalies. Fig. 5 will serve to illustrate several of these points. In Day I, acidity is high (probably higher than the previous day, though that was not estimated), but uric acid is far above urea because salicylic acid has been taken; on Days II, and III, uric acid is below urea, meaning I suppose, that it (uric acid) is accumulating in the liver and spleen; on Day IV, salicylic acid is again taken, and in spite of rising acidity there is again a great rush of uric acid.

And there is a further point with regard to this figure; for on Day IV it appears that with the rush of uric acid there were some slight threatenings of headache in the morning. What does this mean? It will be seen on looking at the drugs taken on this day that I here made an abortive attempt to lessen the excretion of the uric acid under salicylate by taking alkali, and what happened was this, that during the alkaline tide part of the day (the morning) there was a rush of uric acid under the influence of alkali, and during the acid tide part of the day there was a rush of uric acid under salicylate. During the rush of uric acid under alkali the uric acid was present as uric acid in the blood, and caused slight headache; during the rush

FIG. 5.

under salicylate it was present in the blood as salicyluric acid and caused no headache. There was no headache on Day I under salicylate and acids, because the whole uric acid rush on this day took place after combination with salicylate, and the same applies to the days in Fig. 4, on which there was a large excretion of uric acid. Salicyluric acid is said to be present in the urine of persons taking salicylates; but uric acid is also present, as I have seen its crystals deposited from such urine on several

occasions; and it may be asked why is not the whole of the uric acid converted into salicyluric acid? The explanation is, I think, to be found in the two sources from which the uric acid excretion comes (see paper in 'Journal of Physiology'). I think that the uric acid which comes direct from the kidney without passing into the blood is not acted on by the salicylic acid and remains as uric acid in the urine, but that uric acid which has its source in the accumulation in the liver and spleen is acted on by the salicylic acid and converted into salicyluric acid. Once in the urine, both the uric and salicyluric acids are estimated as uric acid by Haycraft's process.¹

As soon as I am able to obtain salicyluric acid in a state of chemical purity, I shall endeavour to test the question of its reaction with Haycraft's uric acid process, and also the questions connected with its solubility.

The facts, however, apart from these chemical explanations, have such an important bearing upon my previous work as well as on the action of salicylates in disease, that I do not wish to delay their publication for the indefinite period of time that may be necessary to obtain a final settlement of these chemical questions.

Some part of the explanation put forward must no doubt be regarded in the light of a working hypothesis to be replaced by a better whenever it may be necessary; but the one fact that salicylates can render the excretion of uric acid independent of acidity appears to me to afford an explanation of the action of these drugs in disease, the importance of which it would be difficult to exaggerate.

Additional note on salicyluric acid, March 19th, 1888.

I have said above that I thought it possible that the salicyluric acid, which is supposed to be formed by the combination of uric acid or of glycocine with salicylic acid, might on passing into the urine be estimated as uric acid by Haycraft's process.

¹ See additional note at end of paper.

As I was unable to obtain any salicyluric acid I endeavoured to test the question of its reaction with Haycraft's process by treating urine passed while taking salicylates, and I reached a point at which my residue ought, according to what is known of the chemistry of the process, to contain salicylic acid, salicyluric acid, and perhaps some traces of uric acid.

I then got some of this residue in solution and obtained a reaction with Haycraft's process, showing that about one sixteenth part of the residue consisted of uric acid.

Looking then to the fact that uric acid is quite insoluble in alcohol, while salicyluric acid is freely soluble in it, I treated the above residue with alcohol; and the alcoholic extract, which probably contained salicylic and salicyluric acid, gave no reaction whatever with Haycraft's process.

If these results are in any way to be depended on, salicyluric acid does not give any reaction with Haycraft's process, and when it is present in the urine cannot be estimated as uric acid; and the fact that salicyluric acid and its salts are generally more soluble than uric acid and its salts is in favour of this view; for if salicylurate of silver is soluble in ammonia it could not be estimated by Haycraft's process.

I am therefore obliged to suppose, in explanation of the results obtained with salicylates, that if the uric acid stored in the liver and spleen is converted into salicyluric acid in the blood, it is mostly reconverted into uric acid and salicylic acid as it passes the kidney, and only appears in the urine as salicyluric acid to a small extent.

I give these results for what they are worth because I see no immediate prospect of obtaining any pure salicyluric acid, and I have not been able to get any chemist to undertake its preparation.

(For report of the discussion on this paper, see 'Proceedings of the Royal Medical and Chirurgical Society,' New Series, vol. ii, p. 326.)