SALICIN COMPARED WITH SALICYLATE OF SODA

AS TO EFFECT ON THE
EXCRETION OF URIC ACID, AND VALUE IN THE
TREATMENT OF ACUTE RHEUMATISM;

WITH SOME DEDUCTIONS AS TO THE CAUSATION
OF THE DISEASE.

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It seems to be a pretty general opinion that salicin is not nearly so useful in acute rheumatism as salicylic acid or salicylate of soda.

Dr. T. J. MacLagan has noticed this general impression ('Lancet,' i, 79, p. 875), and sought to explain it by suggesting that the specimens of salicin used were not pure, and more recently ('Lancet,' i, 1890) he has maintained that the dose of salicin in general use is not large enough.

Dr. Brunton ('Pharmacology and Therapeutics,' p. 939) says of salicin, "Its action is less powerful than that of salicylic acid, and its depressing effect on the circulation less marked."

I have myself also noticed apparently great differences in the effects of salicin and salicylic acid both in health

and disease. In consequence of these observations I was led to make comparative experiments to test the effects of these drugs on the excretion of uric acid, and I propose in this paper to bring forward some of my results.

Fig. 1 shows the excretion of uric acid under salicylate of soda taken to the extent of 45 grs. in the twenty-

FIG. 1.

Uric acid excretion by salicylate of soda.

four hours. It is the ordinary curve of excretion obtained with this salt or with salicylic acid, and corre-

sponds very well with the figure on p. 136 of my paper on salicylic acid and its salts in vol. lxxi of the Society's 'Transactions.'

Fig. 2 is on the same scale as Fig. 1, and shows the excretion of uric acid on a day when 100 grs. of salicin were

FIG. 2.

Showing that 45 grs. of the sodium salt has six times the excretive power of 100 grs. of salicin, or weight for weight thirteen times the power.

taken in the twenty-four hours. I have several times before got similar results, showing the greatly inferior excretive power of salicin as compared with a salicylate. And there is this further point of difference as regards the action of the two substances: the urine on day 3 of Fig. 1 gave with perchloride of iron a purple colour so dark that no light would pass through it in a test-tube; while on day 2 of Fig. 2 the reaction was much less marked, and light passed easily through it. It happened fortunately that the amount of urine on these days was the same within 20 c.c., so that there could be no error on the score of dilution; and I have noticed the same thing several times before, viz. that salicin has much less effect on uric acid and gives

a much slighter perchloride reaction in the urine than an equal weight of a salicylate.

Fig. 3 is given to show the comparative effect of a dose of salol, 25 grs. being taken on day 2 and 50 grs. on day 3. From this it seems as if 50 grs. of salol had nearly as much effect as 100 of salicin, but far less effect than 45 of salicylate of soda.

Uric acid excretion by salol.

It may be objected that after the salicylate had swept out all the uric acid as shown in Fig. 1, there might be little left for the salicin to do, and hence the comparatively small effect in Fig. 2; but unfortunately for this objection, Fig. 1 is really consecutive to Fig. 2, day 3 in Fig. 2 being the same as day 1 in Fig. 1. I purposely gave the weaker drug first to avoid this very objection.

These figures show that, speaking roughly, salicylate of soda has about thirteen times the excretive power of salicin, weight for weight; and that salol is intermediate, much weaker than a salicylate, but stronger than salicin.

I now propose to go at some length into the action of these compounds in disease, and see how far this corresponds with their action on the excretion of uric acid.

We see that salicin has been generally found to have less effect in acute rheumatism than a salicylate, and salol the same ; and in the ' Brit. Med. Journ.,' ii, 1887, p. 1438, it is stated that some people consider the carbolic element in salol an actual drawback, and cases are recorded in which when salol has failed to cure acute rheumatism salicylate of soda has been successful. Again, in the ' Lancet,' vol. i, 1888, p. 1073, it is stated that salol acts in rheumatic fever like a small dose of salicylate ; and we see from Fig. 3 that its action on the excretion of uric acid is only one third of that produced by an equal weight of a salicylate.

With regard to Dr. MacLagan's objections previously mentioned, the impurity of the salicin in the market might have been a good reason for some failure of action at the time it was introduced and when the supply was small ; but now it is cheap and easily obtainable, and a careful examination of the specimen I made use of showed that it was quite free from impurity.

We have only, therefore, now to deal with Dr. MacLagan's second objection, that the doses given are not large enough, and this I quite admit ; for if, as I have now shown, salicin has only one thirteenth of the effect on uric acid excretion that salicylate of soda has, by giving thirteen times the dose of salicin you may make up for part of its defects. But Dr. MacLagan himself admits that salicin will cause some toxic symptoms such as singing in the ears when given in the large doses he recommends (3ss omn. hor. till 3j has been taken), and in my experience many cases of rheumatic fever can be quickly and certainly cured by salicylate of soda gr. xv 4tis horis without producing even those slight symptoms. Where, then, is the advantage of using salicin ?

Prof. Senator, of Berlin,¹ has suggested that salicin is partly converted into salicylic acid in the organism, and owes its activity to this conversion ; and some such partial conversion might perhaps explain the slight reaction with

¹ ' Lancet,' ii, 1879, p. 79.

perchloride of iron in the urine after salicin as compared with an equal weight of a salicylate.

A most interesting series of cases from the Leeds General Infirmary showing the inferiority of salicin as compared with salicylic acid in acute rheumatism is published in the 'Lancet,' vol. ii, 1876, p. 254.

The late Dr. Hilton Fagge ('Lancet,' ii, 1881, p. 1031) drew up some valuable tables on the comparative treatment of rheumatic fever by mint water, alkalies, and salicyl compounds; these show that with mint water patients got well on the seventh to the eleventh day, with alkalies on the fourth to the ninth day, and with salicylates on the second to the sixth day, and I think the experience of others will now fully bear out his conclusions in favour of the salicylates.

In my paper on salicylic acid in the 'Transactions' of the Society previously referred to (vol. lxxi, p. 137) I have said that the important point in the action of salicylates is that they appear to be able to render the excretion of uric acid independent of acidity, a point in which, so far as I know, they stand alone amongst drugs; and in my thesis for the degree of M.D. ('Brit. Med. Journ,' July 7th, 1888) I have said that their curative action in rheumatism seems to me a strong point in favour of the uric acid causation of this disease. It now seems to me that the fact I have just been pointing out, viz. that salicyl compounds are active in the cure of acute rheumatism exactly in proportion to their power over the excretion of uric acid, is another and by no means a weak argument in the same direction.

I propose now to examine shortly some of the best known and attested facts with regard to the action of drugs and diet in acute rheumatism, and see how far they will bear out the supposition of uric acid causation.

To begin with diet: is there any fact better known and more completely attested than that a lowly nitrogenous or non-nitrogenous diet is of the greatest importance in acute rheumatism? and is there any adequate explana-

tion to be given of its effects, except its influence on the formation and excretion of uric acid?

Among other authors Bouchard ('*Leçons sur les maladies par ralentissement de la nutrition*,' pp. 241-2) narrates in a most interesting passage that children fed much on meat, meat juice, and jelly suffer from gastro-intestinal derangements, constant affections of the skin, and early migraine; and he goes on to say, "*Le rhumatisme avec ses manifestations diverses est précoce et grave.*"

With regard to migraine I have the best of all reasons (viz. personal experience) for endorsing this opinion, and I believe that meat produces rheumatism by producing and accumulating uric acid just as it produces migraine.

Look again at the effects of beer, of excessive muscular exertion or exposure to cold and damp,¹ and do they not all affect uric acid, and affect it in just the same way both in rheumatism and gout?

As to treatment, look at alkalies; do they not represent next to salicylates by far the most successful treatment of rheumatic fever? And what is their action on uric acid? just like salicylates, they cause a *plus* excretion of uric acid both in health and disease,—only in the latter, having first to overcome the acids present, their action is slower and less powerful than that of salicylates. And in accordance with this we see from Dr. Fagge's table that a large number of patients get well on the second day or sooner with salicylates, but not till the fourth day or later with alkalies.

Some interesting points in this connection have been brought out by those who have used acids or substances which raise the acidity in the treatment of acute rheumatism.

In the '*Lancet*,' i, 1874, p. 231, is recorded a case in which Dr. Wilks gave dilute nitro-hydrochloric acid $\mathfrak{m}$ xv, *quartis horis*, with milk, bread, and beef-tea as a diet. I will only note two points in the history of the case: first, that

¹ "Collective Investigation Report," '*Brit. Med. Journ.*,' i, 88, p. 387.

on the ninth day of treatment the patient was observed to be perspiring freely, but the temperature was still as high as 101.2° ; second, that five days later (14th day) the swelling of the joints had gone and the urine was alkaline.

I would also refer to some interesting remarks by Dr. Fuller in the 'Lancet,' ii, 1862, p. 669, where he points out that ammonia does not act as an alkali, and does not relieve rheumatic fever, and that under its use the urine remains acid and the pains bad; but when potash is substituted for it within two days the urine becomes alkaline, and the pains are much relieved.

The action of ammonia in this matter, and the fact that it acts as an acid and not as an alkali, is now well known; and anyone who is interested in the point will find the facts well stated in Dr. Mitchell Bruce's book on 'Materia Medica and Therapeutics,' 4th ed., p. 48.

This no doubt explains the value of a dose of Sp. Amm. Aromat. in the uric acid headache, which has been pointed out by myself and others; that is to say, it acts like an acid, and it raises the acidity of the urine very decidedly, as I have plenty of curves to show.

It will not be supposed that nitro-hydrochloric acid made the urine alkaline (though I do not deny that indirectly by causing dyspepsia it might do so); how then did Dr. Wilks' patient get well even on the fourteenth day?

From Dr. Fagge's table we see that most of the mint water patients got well on the seventh to the eleventh day, and if mint water had no action at all nitro-hydrochloric acid must have had a bad or adverse action.

The explanation is, I think, that rheumatic fever is a self-curing disease, and with favorable circumstances, rest in bed and low diet, tends to recovery.

To illustrate this point a little let us suppose that some one, who is estimating his urinary excreta from day to day, goes to bed and puts himself on milk diet; what will be the result on the excretion? His urea will fall, say from 500 grs. to about 300 grs.; his uric acid, which was pre-

vously slightly below its natural amount in proportion to urea, having a relation of 1 to 35 or 1 to 38, will tend to rise above it, having a relation of 1 to 28 or 1 to 26 (*i. e.* a *plus* excretion of uric acid); and the acidity of the urine, previously equal to say 60 grs. of oxalic acid, will fall to about 40—45 grs. If in addition he puts on plenty of blankets so as to keep the skin moist, there will be a further fall of acidity, and a further tendency on the part of the uric acid to rise and be excreted in excess of the urea: we have here, in fact, a natural *plus* excretion of uric acid under the influence of alkali, *i. e.* of the lowered acidity of the urine and increased alkalinity of the blood and tissue fluids.

And if we get these results in a natural physiological condition, how much more shall we get them in a condition of disease such as acute rheumatism! The patient is in bed, and the limbs so painful that he cannot move a muscle; he has little or no appetite, and what food he does take is imperfectly digested owing to the effect of the fever on the digestive organs; it is little wonder, then, that his urea and acidity run rapidly down and soon become very low indeed, and though the fever no doubt keeps them up for a time, it soon has insufficient supplies to work upon, and begins to lose its power.

This action of the skin in lowering acidity is clearly seen in Dr. Wilks' case mentioned above, where it is noted that the patient perspires freely, and five days later the note says that his urine is alkaline and his pains are gone.

I have no doubt that the alkalinity of the urine was due to the causes I have attempted to outline above, and that when Nature took the matter in hand she acted so thoroughly that a small dose of acid had very little effect; and I know from experience that when a patient is run down by exhausting disease it is not easy to raise the acidity of the urine very much by giving acids.

While speaking of skin activity and its effect on the acidity of the urine I should like to quote what Sir A. Garrod has said on this subject, as I believe it to be a point

the importance of which has not as yet been thoroughly realised. Thus, in his work on 'Gout and Rheumatic Gout,' 3rd ed., p. 258, he says, "Suppressed perspiration is immediately followed by an increase of urinary acidity;" and I can not only amply confirm this assertion, but can show also that the converse is true, and that increased perspiration lowers the acidity of the urine.

Let us look for a moment at what is said by some recognised authorities on the question of the skin excretion, especially the perspiration; thus Besnier ('Dictionnaire des Sciences Médicales,' p. 496) says, "Dans le rhumatisme articulaire aigu comme dans toutes les affections sudorales la sueur examinée au moment de sa production sur une surface de la peau convenablement débarrassée par le lavage des enduits sébacés et des produits de décomposition de l'épithélium et des corps gras, la sueur est à peu près neutre dans le plus grand nombre de cas, aussitôt qu'il s'est établi une véritable diaphorèse, plus nettement acide quand elle est peu abondante ou qu'elle commence à couler, exceptionnellement alcaline."

Sir A. Garrod (Reynolds' 'System,' vol. i, p. 896) says, "The perspiration is generally considered to be intensely acid in acute rheumatism; in several cases I have found it less acid than in healthy subjects; but it must be remembered that the amount of perspiration is excessive."

Prof. M. Foster ('Physiology,' 5th ed., part ii, p. 695) says, "When sweat is scanty the reaction is generally acid, but when abundant it is alkaline, and when a portion of the skin is well washed the sweat which is collected immediately afterwards is usually alkaline."

With regard to the above quotations my friend Dr. A. E. Garrod tells me that he has himself seen several cases of acute rheumatism where even in the early stages of the disease the perspiration collected after the surface of the skin has undergone careful cleansing has been neutral or even alkaline, so that he is quite prepared to endorse Besnier's observations just quoted.

With regard to this point I would remark, firstly, that

the perspiration must be moderately copious if it is to be collected at all in this way—a fact, it will be observed, very properly pointed out by Sir A. Garrod in the above quotation from Reynolds' 'System ;' and secondly, that it does not follow that a very large amount of acid is not got rid of by the skin in the twenty-four hours because the excretion is neutral or even alkaline for a short time, and when very copious. The urine is often alkaline for a few hours in the morning, but yet the acid excreted in the whole day may be considerable ; and again, when the urine is very copious the acidity may appear very low till we come to multiply the acidity by the quantity excreted.

But the fact of most consequence, and which to my mind absolutely deprives the above line of argument of all force as regards the effect of the skin excretion on the reaction of the blood and tissue fluids, is the one above mentioned as pointed out by Sir A. Garrod, viz. that suppression of perspiration is immediately followed by a rise of urinary acidity ; and the further fact which I can vouch for, and which it is easy to demonstrate, that increased skin action and perspiration are followed by a fall in urinary acidity. I take it, therefore, that in spite of the above observations on the reactions of the perspiration a very considerable amount of acid is got rid of in the excretions of the skin both in health and disease, and that this is often enough to depress very considerably the acidity of the urine, and raise to a corresponding extent the alkalinity of the blood and tissue fluids.

It seems, then, that all the methods of treating acute rheumatism that are of any value have one effect in common, the causation of a *plus* excretion or elimination of uric acid.

And further, that as regards salicin and compounds of salicylic acid, their utility in the disease is directly proportional to their power of eliminating uric acid.

May we then go further, and say that acute rheumatism is due to uric acid ? I for one should be inclined to say

that the joint pains of this disease are undoubtedly due to uric acid ; but there remains still the question, what drives the uric acid into the joints ?

To this I would reply, high and rising acidity of the urine and concomitant decreased alkalinity of blood and tissue fluids, acting on uric acid in this disease just as it does in gout. But why then is rheumatic fever so different in many ways from gout ?

I do not know that I can completely answer this question, but I have a very strong impression that it may be due to a difference in the amount of uric acid present, and to a difference in the activity of metabolism of young subjects in whom rheumatic fever occurs, as compared with that of older subjects in whom gout is met with. The chief difference is a greater activity in the metabolic processes of the young, for while an adult forms and excretes some three or four grains of urea per pound of body-weight, a child of three or four years may excrete as much as nine or ten grains per pound, as I can show from my own investigations ; and with this larger formation of urea in a child there is a greater formation of uric acid, and, what is perhaps more important, a greater formation of acids. It thus appears evident that a child might soon have much more uric acid in its blood than an adult could easily get, and any little febrile disturbance might raise the acidity very greatly and precipitate the uric acid into the joints.

Of course it is quite possible that an essential factor in acute rheumatism is the formation of an acid in large quantities by some fermentation process, or, as has been suggested, by a bacterium ('Brit. Med. Journ.,' i, 1887, p. 1381). I cannot express any opinion on these points, but I do believe very strongly that the essential feature of acute rheumatism is the retention of uric acid in the joints and tissues of the body by a high and rising acidity, and that this, and this only, will enable us to explain completely the results obtained with drugs and diet in the treatment of this disease.

Sir A. Garrod has recorded the fact¹ that he has repeatedly examined the blood in acute rheumatism, and has never been able to find any uric acid there ; he says, " The absence of uric acid or urate of soda is important, as it at once shows an essential difference between gout and rheumatism." But this is exactly what I should expect, for it is not likely that the uric acid can be in two places at once ; and if, as I am supposing, a high and rising acidity has driven it all into the joints, it is not likely that any will be found in the blood. And some of Sir A. Garrod's own observations lend, I think, strong support to this explanation, for he has pointed out (' Gout and Rheumatic Gout,' pp. 187 and 274) that there is no uric acid in the fluid of a blister, or in blood drawn directly over the inflamed joint in gout ; and he proceeds to argue from these facts that inflammation destroys uric acid.

It has, however, been shown that fever² lowers the alkalinity of the blood and raises the acidity of the urine. This would, as I have shown (' Journal of Physiology,' vol. viii), cause a diminished excretion of uric acid in the urine, and, as I have argued, diminish also the amount of it in the blood ; and there can be very little doubt that a local inflammation will have the same effect, viz. to diminish the alkalinity of the blood and tissue fluids, and drive the uric acid they contain out of solution. So that while I think that Sir A. Garrod's facts are perfectly correct, I believe that the result he notices is due to a precipitation of uric acid, and not to a destruction of it.

This explanation affords us also an insight into the causation of one of the differences between gout and rheumatism ; for I believe I am correct in saying that the temperature in acute rheumatism is generally considerably higher than in gout, and therefore the effect on the alkalinity of the blood and the precipitation of urates from solution will be more complete in the former than in the latter disease.

¹ Reynolds' ' System of Medicine,' vol. i, p. 897.

² Dr. Peiper, ' Virchow's Arch.,' June, 1889, p. 337.

There has been recently published ('Brit. Med. Journ.,' i, 1890, p. 472) a paper by Dr. B. N. Dalton on the "Ætiology of Rheumatic Fever," in which he urges that this disease may be "caused by breathing air contaminated by the emanations from sewers and drains," and gives many interesting facts and cases in support of his argument.

From my point of view such a mode of causation is extremely probable, for if the sewer emanations give rise to fever (as there is no difficulty in believing that they may do), they will, as we have seen, raise the acidity of the urine, and diminish the alkalinity of the blood and tissue fluids; and under certain conditions of metabolism which are often present in young subjects they may cause the precipitation of a large amount of uric acid in the fluids and tissues of the joints, thus producing what is known as rheumatic fever.

The way in which the uric acid is precipitated on the fluids and tissues of joints I have pointed out in previous papers (see 'Brit. Med. Journ.,' ii, 1888, p. 12).

I have also pointed out that Sir A. Garrod has shown that the tissues and fluids of the joints are less alkaline than the tissues and fluids of the body generally; in this respect they resemble the spleen, in which uric acid is constantly found, so that the precipitation in the spleen and in the joints stands on the same ground, and is supported by the same facts and argument.

In a paper in Wood's 'Medical and Surgical Monographs,' New York, February, 1890, I have suggested that some fevers may act on uric acid in exactly the same way, and thus produce rheumatic fever; and also that tonsillitis and even some local inflammations, as an alveolar abscess, of which a case is narrated, may by raising the temperature, and so the acidity, produce the same result.

Though I speak here mostly of the effects of fever I do not wish to lose sight of the fact that several other causes may raise the acidity, as, for instance, suppression of perspiration, as pointed out by Sir A. Garrod; and a severe

chill is a commonly accredited cause of rheumatic fever. Another is the ingestion of acids and acid-forming foods ; and in this way I believe it is possible to produce "rheumatic" (uric acid) pains in almost anyone. Indeed, I have often produced such pains in patients, the subjects of high arterial tension, when giving them acids, opium, and other drugs to reduce their tension.

Again, acids may be formed in the stomach to a very considerable extent, as pointed out by Bouchard, and I am sure from my own experiences that gastro-intestinal troubles have a most important connection with some cases of rheumatism.

Moreover, as previously mentioned, it has been suggested that some fermentation processes, with or without the agency of a bacterium, may produce considerable quantities of acid.

The excretion of uric acid in rheumatic fever is enormous, and only to mention one case I found upwards of 26 grs. in the urine of a man with this disease on the first day of taking salicylate of soda, having a relation to urea of 1 : 17, the normal relation being 1 : 33. There was here double the ordinary quantity of uric acid per grain of urea ; and if the additional 13 grs. of uric acid were all in the joints, it would, I think, account for most of the trouble they gave. For I can cause very distinct symptoms in my own joints by precipitating only 2 or 3 grs. into them.

Again, when salicylate is left off after a rheumatic attack there is often very marked high arterial tension to be observed for some days, thus pointing, I believe (see paper on "Uric Acid and Arterial Tension," 'Brit. Med. Journ.,' i, 1889, p. 288), to excess of uric acid combined with alkali in the blood ; and if at this time fever, dyspepsia, or excess of nitrogenous food causes a sharp rise in acidity, a relapse is the common and easily explained result.

It would lead me too far to go minutely into the action of all these causes here, but in conclusion I will merely suggest—

1. That the essential feature of rheumatic fever (viz. the joint symptoms) is the result of a precipitation or concentration of all, or nearly all, the uric acid in the body, in the tissues and fluids of the joints.

2. That this concentration is due, as in gout, to high and rising acidity or greatly reduced alkalinity of the tissue fluids, of which the high acidity of the urine may be taken as an index, or the reaction of the blood may be taken as more direct evidence.

3. That the completeness of this precipitation accounts for the absence of uric acid from the blood in rheumatic fever, as noticed by Sir A. Garrod.

4. That such a process of causation enables us to explain completely the action both of drugs and diet in rheumatic fever ; and, lastly—

5. That, as it has been the object of this paper to point out, the compounds of salicin and salicylic acid have a curative power in rheumatic fever which is precisely proportional to their powers of eliminating uric acid, and that they cure the disease by effecting such elimination.

(For report of the discussion on this paper, see 'Proceedings of the Royal Medical and Chirurgical Society,' Third Series, vol. ii, p. 105.)