RHEUMATISM, ITS TREATMENT PAST AND PRESENT;

WITH SPECIAL REFERENCE TO RECENT EXPERIMENTAL
RESEARCH ON SALICYLIC ACIDS AND THEIR SALTS.

BY

MATTHEW CHARTERIS, M.D.,
PROFESSOR OF THERAPEUTICS AND MATERIA MEDICA, UNIVERSITY
OF GLASGOW.

(COMMUNICATED BY DR. MITCHELL BRUCE.)

Received January 22nd—Read February 11th, 1890.

IN the treatment of rheumatism we observe five distinct epochs: (1) the antiphlogistic, (2) the alkaline, (3) the blistering, (4) the expectant, (5) the salicylate.

The antiphlogistic treatment in English medicine was inaugurated by Sydenham, and was bold, comprehensive, and decisive. It dominated practice until Dr. Fuller, of St. George's Hospital, recommended the administration of alkalies in such doses as to maintain **an alkaline** reaction of the urine. The chief rival to **this treatment** was that of Dr. Herbert Davies, who advocated the application of blisters to all the inflamed joints. Then came as the reaction to these methods the "expectant treatment" of Lebert, which was further supported by Sir William Gull and Dr. Sutton in 1866.

For the next ten years the therapeutics of rheumatism was in a state of chaos, which was terminated by the rise of the salicylate treatment, the history of which is peculiarly interesting.

In 1874 Kolbe obtained a crystalline acid (salicylic) by the combination of the elements of carbolic acid with those of carbonic acid. Attention was directed to this compound by its subsequent employment for antiseptic dressing. Later on the internal administration of this acid, and especially of its salt, sodium salicylate, speedily evinced their antipyretic properties.

When given in large doses they reduced the temperature in enteric fever, phthisis, erysipelas, and other affections of a febrile character. Much was expected from their use as antipyretics, but impartial observers showed that the reduction of the temperature was not attended by any modification of the local morbid process, nor by any lessening of the mortality. There was one noteworthy exception to this unfavorable statement, for it was found that when they were administered internally in acute rheumatism the temperature was speedily reduced, and the pain and swelling of the joints disappeared.

In Great Britain, about the same time, and pursuing an independent line of reasoning, Dr. Maclagan tried salicin in the same disease, and with equally satisfactory results in regard to the fever and the affection of the joints.

The connection of the action of the two remedies was shown by Senator to consist in salicin being split up in the living organism by ferments, first into saligenin and subsequently into salicylic acid.

Gradually yet steadily since 1876 the salicylate treatment of rheumatism has grown into professional favour in all lands. Dr. Fagge's words on this point are striking and suggestive: "When I made trial of these drugs I was for a little while sceptical as to their value. The patients rapidly recovered, but I could not forget that I had sometimes seen the administration of other medicines followed

by results which appeared very striking. But when case after case recovered with scarcely a failure I became satisfied that I had a most potent remedy in my hands, and all further experience has strengthened me in this conviction. The immense majority of practitioners and physicians now, I think, entertain a similar opinion."

Now we come to a crucial point. Granted that salicin is changed by the ferment into salicylic acid, is its action superior to or different in any way from that obtained from artificially prepared salicylic acid and its salt of sodium? All experience shows that in a case of acute rheumatism without complications either method will reduce the temperature and relieve the pain within forty-eight hours. Apart from nausea, which is sometimes occasioned by both preparations, there has been a steadily growing conviction that artificial salicylate of sodium—the salt generally given—is depressing, and further that in certain cases there is cerebral excitement culminating in delirium, the patient, it may be, shouting and struggling to get out of bed.

Any hospital physician trying salicin and artificial salicylate of sodium on two rheumatic cases in the same ward, at the same stage of the fever, and in proportionate doses, will find in a given time the patient treated by the salicylate to be weak, exhausted, and perhaps delirious, while the patient to whom salicin has been administered will only suffer, if at all, from slight deafness. True, if the salicylate treatment is discontinued, the patient becomes rational in a few hours, but what would happen if one were to insist on the continued administration of the drug on the human subject I do not know, although after the experimental investigation on animals to which I shall now allude I cannot fail to guess.

The research on the natural and the artificial salicylates on animals was begun in June last, and the results were published in the 'British Medical Journal' of November 30th, 1889. The experiments showed—

1. That salicin in a dose of thirty grains seems to have

no injurious influence on the health of a rabbit, but that it causes a reduction of the temperature about 1° .

2. That salicylic acid obtained from natural sources has no deleterious effect in 10-grain doses.

3. That salicylate of sodium from the natural salicylic acid is not lethal in 32-grain doses, but causes some prostration and lowering of the temperature.

On the other hand, it was demonstrated that—

1. Artificial salicylic acid in a 10-grain dose caused paralysis of the flexors and death.

2. Artificial salicylate of sodium in 18-grain doses causes not merely paralysis of the hind limbs, but paralysis of the fore-limbs and entire loss of control over muscular movements; and death supervenes in a short time from exhaustion, in some cases being preceded by convulsions.

Further, it was shown that salicylic acid and the salicylates of sodium in ordinary use contained an impurity—probably creasotic acid—five grains of which when injected into a full-grown rabbit caused slow respiration and intense prostration, followed by death.

The article referred to concluded with the remark that “in a further communication we shall state the physiological action of the acid from which the impurity has been removed.” I must state frankly here what happened. We obtained from the chemical laboratory of the University of Glasgow an acid from which all impurities had been apparently removed. It had a melting-point of 156° C., and was in fine acicular crystals, corresponding to those described in the British Pharmacopœia. But when we injected five grains of it thrice at intervals of fifteen minutes into a rabbit weighing $2\frac{1}{2}$ lbs. the animal died.

We further tried a sample of the salicylic acid of Schuchardt, of Berlin, guaranteed pure, and the same lethal action was the result of the same doses in a rabbit of similar weight.

The conclusion seemed irresistible that artificial salicylic acid could not be purified so as to stand the physiological

test, and Dr. MacLennan and myself moodily reflected that our efforts of four months had been in vain, and that we had detected an impurity, but could not entirely remove it.

Our attention was shortly afterwards directed to an article published by Mr. John Williams in the 'Pharmaceutical Journal' of June, 1878. In this article Mr. Williams stated that he had detected a foreign acid in samples of artificial salicylic acid, which was much more soluble in water than calcium salicylate. On this fact he based a method of separating it, which consisted in saturating a boiling solution of salicylic acid with calcium carbonate, and causing the salicylate of calcium to crystallize out as completely as possible. Upon acidulating the mother liquor the foreign acid was obtained.

"Regarding the medicinal properties of this acid," Mr. Williams writes, "I can say nothing as yet. It may be, like parabenzoic acid, inert, and would then be only a diluent of salicylic acid, or it may be active as an antiseptic, or it may be mischievous;" and he concludes by stating that "until this foreign acid could be removed, neither salicylic acid nor its salts should be used in medicine."

So far as I am aware Mr. Williams did not follow up his investigations, but he had distinctly proved that salicylic acid could be so purified, and that its appearance then was similar to that of the acid obtained from natural sources. This was the key-note of our further research.

We resolved to go upon the lines laid down by Mr. Williams. We set free the salicylic acid by the action of hydrochloric acid on the calcium salicylate, and we simplified his process by slowly crystallizing the acid from hot solutions three or four times repeated. We were thus able without the aid of alcohol, as Mr. Williams recommended, to produce purified acid resembling the natural acid in its appearance, and in no way differing from it by the test of the melting-point, which is 156° C.

Specimens of these purified crystals, and also of those of salicylic acid from natural sources, I now show to

this meeting, as verifying the statements which have been made.

On three different occasions, December 19th and 20th, 1889, and on January 19th, 1890, we tested the physiological action of these purified specimens. The result was most satisfactory. We gave three injections of five grains each to rabbits weighing $2\frac{1}{2}$ lbs., and we found "there was no paralysis, and no depression, but that on the contrary the animals were neither up nor down, but able to run about with ease after the last injection."

For the purpose of estimating the loss by purification, and the time involved in the process, we weighed out one ounce (480 grains) of the salicylate of sodium, and we found that out of the corresponding 414 grains of salicylic acid, 140 grains were first obtained, but by working up the mother liquor nearly the whole of the apparent loss of 274 grains was recovered. Time, ten days.

We weighed out half an ounce of Schuchardt's salicylic acid, and out of the 240 grains 183 grains were obtained, showing a loss of 57 grains by purification. Time, two days.

These facts show that the process of purification, even on a small scale, is not tedious or difficult, and in all probability it could be done easily and thoroughly on a large scale with less loss of time, and at only a slightly increased cost, as compared with the present method.

It may now be asked, "Can no pure specimens of artificial salicylic acid be purchased?" So far we had found none able to stand the physiological test, except those which had been purified at our laboratory. But on January 1st, 1890, unsolicited, a Berlin firm communicated with me through their agents in London. This letter bears incisively on many practical points. They stated that the great bulk of the artificially prepared salicylates used in pharmacy in this country came from their principals; that they guarantee the superior qualities to be free from cresotonic acid, which they believed in reality to be the lethal property discovered in the specimens under our

observation ; that their factory passed no acid which did not show a melting-point of 156° C. ; that the products of ordinary purity should not be dispensed in pharmacy ; and that for every ten pounds of the salicylate of sodium only one pound of it was asked for as manufactured from the purest crystals."

The letter concluded by proposing to send me specimens of their salicylic preparations for my examination and report.

The proposal contained in this letter I accepted, and specimens were received of—

1. Acidum salicylicum extrafein in krystallnadeln.
2. Salicylic acid chemically pure.
3. Sodii salicylas cryst.

On January 11th we subjected these two acids to the experimental test.

1. Acidum salicylicum extraf. 5 gr. were dissolved in 20 minims of rectified spirits and injected into a rabbit at 11.30 a.m.

At 11.45 a.m. the animal passed urine which gave the characteristic reaction with the tincture of the perchloride of iron. It was noted then that the animal looked somewhat dazed and was very quiet.

At 11.55 a.m. the injection was repeated, and at 12.10 p.m. it looked very dazed. No paralysis.

At 12.25 p.m., injection of 5 gr. repeated. The animal assumed a prone position, with the legs stretched out ; in five minutes there supervened absolute general paralysis, and at 1.30 p.m. the breathing became extremely shallow and slow, with slight twitchings about the mouth, but no convulsions. Half an hour afterwards it died in a collapsed condition. Ten days later we repeated this experiment with the same acid of the Berlin firm on the rabbit which had stood the test of our purified acid, and we found that this time it was not fatal, but that it caused marked prostration and slight paralysis, which lasted for two hours. The recovery, though slow, was complete.

2. The chemically pure salicylic acid was injected in the

same doses and at the same intervals as in the previous experiment. After the third injection the rabbit became somewhat prostrate and lay with its legs stretched out, but on being roused it was able to move about, though with some difficulty. Its recovery in this case also was complete but slow.

We were rather surprised that these results followed on the use of acids which so closely resembled in appearance the ordinary artificial variety. We made in consequence a few experiments with them in solutions of different strengths, and we found that *their small crystalline form* depended on the rapidity of their crystallization. When this was slow, the crystals became large and well defined, thus showing they had evidently lost the traces of impurity which they had contained. But in the form in which we received them, though guaranteed pure, they were not innocuous. In one instance death was the result, and in the other two abnormal symptoms appeared, which, however, in time passed away. In the artificial variety, which we had purified so as to resemble the natural, these symptoms were entirely absent.

From these experiments we were forced to the conclusion that a high melting-point is not the only or even the best test of purity. Something more is required, and this is that the artificial crystals should be identical with those of the natural variety. Similarity of crystallization seems to be absolutely essential to secure a uniform and harmless physiological action. Pharmaceutical chemists may not have the means or the time for applying the melting-point test, but they can all observe easily the difference between well-defined crystals like those of strychnine and others which present an appearance like quinine. For internal use in medicine they should demand the large crystalline form of the artificial acid, and from this alone should the salicylate of sodium be prepared.¹

¹ Since reading this paper the firm in question, Messrs. Schering, have submitted to me samples of purified salicylic acid in the form of white acicular prisms, and I was able to satisfy myself that their physiological action was

We trust that the editors of the 'British Pharmacopœia,' in the new Addendum which they are now preparing, will see their way to act on the suggestions we now venture to give.

1. Under "Characters and Tests of Acidum Salicylicum" we would substitute for "white acicular crystals," "the natural acid, in large crystals resembling those of strychnine, but slightly yellowish in colour. The crystals of the artificial acid are similar in form but smaller and whiter. Both acids should have a melting-point of 156° C."

2. Under "Sodii Salicylas : Characters and Tests," instead of "small colourless or nearly colourless crystalline scales," we should say "in large pearly plates."

3. Other varieties of artificial salicylic acid should be termed Poisons, solely intended for external use.

It is rather apart from the object of this paper to say anything about salicylic acid except so far as it is used in pharmacy, but I wish to draw attention to the fact that, owing to its slight taste and powerful antiseptic properties, it is employed for preserving beer, wine, milk, lime and lemon juice, gum, and other fluids. The French seem to have detected its noxious qualities, and have forbidden its use for preserving articles of food ; and the Germans lately have acted in a similar manner, and have made it unlawful to use it in the preparation of beer. True, our propensity for drinking beer is not so marked as that of the Germans, yet our brewers should understand that if the acid must be pure when used in medicine, it should be equally pure when placed in this common and pleasant beverage of everyday use.

similar to that of the acid obtained from natural salicylates, and therefore of such purity as to be equally eligible for medical use. I have myself found this purified salicylate of sodium very efficacious in the treatment of acute rheumatism.—'Lancet,' May 31st, 1890.

(For report of the discussion on this paper, see 'Proceedings of the Royal Medical and Chirurgical Society,' Third Series, vol. ii, p. 62.)