EXPERIMENTAL RESEARCH AS TO THE GENERAL COMPARATIVE ACTION OF THE NATURAL AND ARTIFICIAL SALICYLIC ACIDS, AND THEIR SALTS OF SODIUM.

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IN commencing the following investigations, specimens of the above *British Pharmacopœia* preparations were obtained from Mr. Morson, of London, so that there could be no dubiety as to their genuine character.¹ The following points were noted as to their physical properties.

1. Natural salicylic acid obtained from salicin by oxidation or from the oil of winter green is seen in acicular crystals having a strong resemblance to strychnine.

2. Artificial salicylic acid obtained by the combination of the elements of carboic acid and carbonic acid, and subsequent purification, is a white satiny powder in fine silky crystals resembling quinine.

Both are equally soluble in rectified spirit, 20 minims of the spirit dissolving 5 grains of each acid.

Salicylate of sodium (natural) is seen in crystalline plates of a white satiny appearance. Salicylate of sodium (artificial) is seen in small crystalline plates, with a slight pink colour. Both are equally soluble in water.

We elected to commence our experiments with the readily soluble salt, but we resolved to begin tentatively, and watch what might happen.

Salicylate of Sodium (artificial).—On June 1st, 1889, a rabbit weighing 14 oz., strong and healthy, was subjected to the following experiments:² Before injecting a solution of sodium-salicylate (strength 1 in 3; 2 grains in 6 minims), the temperature in the rectum was taken, and found to be 100.2° F.; after two hypodermic injections of 3 minims, at intervals of five minutes, there was no action, but the temperature fell to 99.8°. Within an interval of fifteen minutes, the 3-minim injection was repeated twice. Immediately after the last injection the rabbit became excited, and executed a backward and circular or rotatory movement, which gave place to a transient paralysis of the flexors of the hind limbs, so that in attempting a forward movement the animal dragged along on its belly. All this was of a transient character, and as the experiment was not continued further the animal made an excellent recovery, without the development of any other symptom.

On June 4th the experiment was resumed on the same animal, which appeared in every way healthy. The temperature in the rectum before any injection was 101.8°. At intervals of five minutes 3 minims of the solution (1 in 3) were injected hypodermically. Immediately after the fourth injection the circular or rotatory and backward movements were observed, and the same degree of paralysis of the hind limbs, namely, a paresis of the flexors of the hind limbs, which was again of a transient character, not lasting over one minute. Five minutes after the cessation of these symptoms the rectal temperature was taken and found to be 103°. Three more injections were given at short intervals without the production of any abnormal symptom. The total quantity of the artificial salicylate given at that time was 7 grains. The experiment was not pushed further, and the rabbit again recovered quickly and completely.

On June 6th the injections were recommenced, 6 minims being given at each injection, or 2 grains. Immediate backward and circular movement, with spasm of the hind limbs and arching of the back, were observed after the second injection. The spasm of the hind limbs was soon replaced by paralysis of the flexors of the hind limbs. The temperature was 101° before the injection. In half an hour another in-

jection was given; but, as the last seemed to act so strongly and so quickly, the dose was reduced to 4½ minims without producing a renewal of the symptoms. After a lapse of ten minutes a 6-minim injection was given again, with the result of producing the same phenomena previously mentioned, but of transient duration. After an interval of ten minutes a 6-minim injection was given. The symptoms became now very pronounced, the back being arched and the gait stiff and performed with difficulty. Very distinct backward and circular movements followed, replaced by paralysis of flexors of hind limbs, involving dragging of the legs on progressive movement. The rectal temperature was now taken, and found to be 100.6°. For some time the animal seemed dazed and prostrate, but it made a complete and good recovery, the experiment not being continued further on this day. The total amount of artificial salicylate injected was 9½ grains.

On June 8th the experiment was continued, the rabbit being in every way healthy, and the rectal temperature 101°. The injection was begun at 12 minims, or 4 grains, and immediately after the introduction of the first dose there were backward movements, followed by paralysis of flexors of hind limbs, transient in duration. Six minutes afterwards the 12-minim injection was repeated, and again decided symptoms came on—rapid backward and circular movement, with paresis and dragging of the hind limbs. Within the next hour two injections of 12 minims were administered, and now the paralysis became more pronounced and the prostration progressively more marked. The temperature was found to be 100.6°. Another injection of 6 minims was given, and soon a new symptom set in. As yet only paralysis of the hind limbs had been observed, but now a very distinct paralytic condition of the fore limbs was evinced. On attempting progressive movement the fore limbs, over which the animal had no control, slipped from under it, so that the breast and lower jaw lay upon the table. This paralysis deepened and became more general till there seemed to be entire loss of control over muscular movement. Just before death the paralysis of the fore limbs seemed to be more pronounced than the paralysis of the hind limbs, which appeared in a sense to be passing off. The whole experiment occupied an hour and a half, and the rabbit had in all 18 grains of the artificial salicylate of sodium.

At the same times and dates as the experiments with the artificial salicylate were being conducted, similar doses of the natural salicylate in a watery solution were given hypodermically to another rabbit. The rectal temperature before the experiment was 101.2°, and after receiving 3 grains at intervals of five minutes it fell to 100.6°. At the end of the first day's experiment the rabbit looked seedy, but was otherwise unaffected, and the recovery was complete.

On June 4th, when the experiment was recommenced, 6 grains in all were given, but without eliciting any result. Again the animal recovered completely.

Two days afterwards—namely, on June 6th—the experiment was repeated, but double the quantity was used. The temperature was 101°. After the second injection of 2 grains, the following symptoms were noted—namely, immediate backward movements, stiffness of limbs, arched back, passing off almost at once. The temperature was now found to be 103°. Three successive doses of 6 minims at short intervals were injected without inducing any further phenomena, except that the temperature became reduced to 100.8°. At the end of the experiment 9½ grains in all of the natural salicylate had been given, and the animal made again a complete recovery.

On the 8th, when the experiment was renewed the dose was increased to 12 minims, or 4 grains, at each injection. The first two injections caused nothing more than a slightly spastic condition of the hind limbs of a transient nature but no paralysis. The third injection was followed by slight paresis of the hind limbs and a slight general tremor, which increased until the fourth injection was given. It then became more pronounced, but ultimately passed entirely off.

The rabbit made a perfect recovery, after having had in all 18 grains of the natural salicylate.

On the 4th of July we resolved to test in a more potent manner what result would be obtained by pushing the injections of the natural salicylate beyond what we observed was a lethal dose of the artificial. We took this time another rabbit. At 10 a.m. we injected 12 minims=4 grains, previously having ascertained that the temperature of the rabbit was 101.8°, and from this injection there was no result. At 10.20 a.m. it was repeated, and the animal screamed, and when placed on the table voided a large quantity

¹ The specimens were manufactured by Dr. F. von Heyden Nachfolger, Nadebuel, near Dresden, Germany.

² In the subsequent experiments the rabbits weighed in each case 14 oz.

of urine. It then walked with arched back and gingerly steps along the table, but there was no sign of paralysis. At 10.40, the injection was repeated, and again we noticed the same spastic gait, and afterwards slight prostration. At 11 a.m. the prostration following on this injection was more marked, and on taking the temperature we found it had fallen to 99°. At 11.20, no definite symptom was produced by this injection, nor after the three that followed at intervals of twenty minutes. In all 32 grains were given. At 1 p.m. it was noted that the animal, though inclined to rest, could walk easily and take food. Its temperature was now 98°. At 2 p.m. the animal had recovered and was hopping about in a natural manner.

Natural salicylic acid, 5 grains, was dissolved in 20 minims of rectified spirit, and injected into a rabbit through a hypodermic syringe. There was no result, and twenty minutes afterwards the injection was repeated, and at the expiry of an hour from the last injection we noted that "it was eating cabbage, and moving about easily. Urine passed gave characteristic reaction with the perchloride of iron."

Artificial salicylic acid, 5 grains, dissolved in 20 minims of rectified spirit was injected into a rabbit on the same day, and twenty minutes afterwards "it was observed to be slightly seedy, but could take food." The injection was repeated, and ten minutes afterwards it was observed to be very weak about the legs, so weak that when the legs were stretched out it could not recover its position. Succeeding rapidly came flexor paralysis of hind and fore limbs, and subsequently supervened violent convulsions, head arched backwards, and snapping of the jaws.

In an hour and twenty minutes from the first injection death occurred after a very severe convulsion.

Salicin.—On July 2nd, 10 A.M., a grey rabbit was anaesthetised, and 18 grains of salicin in solution in warm water were introduced into the stomach. The temperature was 101.8°; at 10.45 A.M. the temperature was 100.8°, and at 11.15 100.4°. There was no evidence that the animal was affected in any other way by the salicin. An hour and a half after it had been administered a large quantity of urine was passed, which gave the characteristic reaction with the perchloride of iron.

On July 4th, to another rabbit 30 grains of salicin were similarly administered at 11 A.M. At 11.30 the temperature was 100.6°, but there was no sign of the animal being in any way injured. Urine passed two hours after the administration of the salicin gave the reaction with iron.

These experiments prove: 1. That salicin in a dose of 30 grains seems to have no injurious influence on the life of a rabbit of above weight, but that it diminishes the temperature about 1°. 2. That salicylic acid obtained naturally by oxidation of salicin, or from the oil of winter green in 10-grain doses, has also no deleterious effect. 3. That salicylate of sodium obtained from the natural salicylic acid, in 32 grains, is not lethal, but that it causes prostration and lowers the temperature.

On the other hand, it is conclusively demonstrated that: 1. Salicylic acid, artificial, in a 10-grain dose, causes, first, paralysis of flexors; secondly, death by violent convulsions. 2. Salicylate of sodium, artificial, in 18-grain doses, is lethal; in 4-grain doses it causes paralysis of the hind limbs; in 8-grain circular and rotatory movement, with paresis and dragging of the hind limbs; further in 12-grain doses it causes pronounced paralysis of the hind limbs, and marked progressive prostration and that 18 grains cause not merely paralysis of the hind limbs, but a paralytic condition of the fore limbs, and entire loss of control of muscle movements, and death supervenes in a short time.

The deductions from these experiments indicate that artificial salicylic acid and its salt of sodium are dangerous and, in large doses, fatal to animals. While salicin, natural salicylic acid, and its salts of sodium are not. Now, on what does this difference depend? Doubtless on some impurity in the artificial acid, and corroborative evidence, though not yet completed, is afforded by the following letter which we have received from G. G. Henderson, M.A., B.Sc., of the Chemical Laboratory of the University of Glasgow:—

"I find, on examination, that the sample of artificial salicylic acid you left with me is not pure, but contains a small quantity of another acid, which I have no doubt is the cause of the appearances observed after the use of artificial salicylic acid. I attribute the presence of this impurity to the fact that the phenol used in preparing salicylic acid synthetically is not pure, but always contains other substances (cresol, etc.), of some one of which the acid found in salicylic acid is probably a derivative. I had not enough of

the impurity to make a further examination of it, but it is certainly not salicylic acid. I should add that no trace of this substance is to be found in natural salicylic acid."

After a very careful analysis, Mr. Henderson isolated the impurity referred to. It was in the form of a buff-coloured powder, and it was found to be more soluble than salicylic acid; 1 grain of it was injected into 20 minims of rectified spirit, and injected into a rabbit weighing 6 lbs., but without any visible effect. After the expiry of half an hour, 2 grains similarly dissolved were injected, and in ten minutes, and without any rotatory movements, the breathing became very rapid, the arteries of the ear were alternately dilated and contracted, and the animal lay prostrate, with its fore and hind legs stretched out. Again, in half an hour, the same quantity—2 grains—was injected, and the prostration became more intense, the respirations lower, and a fine tremor was detected in the muscles of the face. In the course of two hours there was a slow improvement, but never a complete or even partial recovery, and ultimately the rabbit died, after thirty-six hours, being unable during that time to eat anything.

The action of this impurity seems to be of the nature of a slow but certain poison, and the lethal dose is relatively much less than that of salicylic acid. The rabbits in the previous experiments weighed only 14 ounces, and in this case 6 lbs., so that the lethal dose would correspond to about 1 grain for a 1 lb. rabbit.

The obvious conclusions from these experiments are that artificial salicylic acid contains an impurity or impurities, and until this or these can be extracted by the aid of chemistry the internal administration of it or its salt of sodium should be discontinued. Large and repeated doses of the sodium salt are necessary in the treatment of acute rheumatism, and hence we may account for the restlessness, the confusion, and the delirium sometimes attendant on its use, which have been testified by clinical experience. It is more than probable, too, that the retarded convalescence occurring in some cases of acute rheumatism after the salicylate treatment is due to the great and protracted prostration which the impurity or impurities give rise to. It is to be remembered in connection with these symptoms that prescriptions of the salicylate of sodium are invariably made up, unless otherwise indicated, from the artificial and not the natural salt.

In a further communication we will state the physiological action of the acid from which the impurity has been removed, and also the effect of pure salicylic acid made artificially.

THE INFLUENCE OF OPIUM AND MORPHINE ON URIC ACID CONSIDERED WITH REFERENCE TO THEIR ACTION IN HEALTH AND DISEASE.

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As the action of morphine in uræmia and in uræmic and puerperal convulsions has recently been attracting some notice,¹ and as its effect on arterial tension has been previously pointed out by others, I propose in this paper to give the results of my investigations on its influence on the excretion of uric acid.

These results show, I believe, that it causes retention of uric acid, and that the result of this is a fall of arterial tension, the effect being exactly the same whether the retention is produced by opium, by acids, or other substances, so that my results with it completely confirm the previous observations of others.²

I shall further bring evidence to show that the effect of morphine on mental depression and other mental states and conditions, as already well known, is the result of its action on uric acid and arterial tension, or is at least the exact parallel of the action of other drugs which affect the excretion of uric acid and arterial tension in the same way, and that it is thus possible to produce what is practically the same result by several drugs. And I shall also point out that the effect of opium and morphine on uric acid and arterial tension may explain the good effects

¹ JOURNAL, i, 1889, 588 and 943; also Debate at Medical Society, April 8th, 1889; see JOURNAL, i, 1889, 837.

² Loc. cit.; JOURNAL, February, 1889.