

# SOME NEW DRUGS IN THE TREATMENT OF RHEUMATIC FEVER

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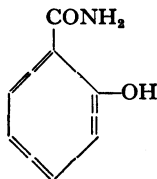
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## Introduction

The usefulness of salicylates in rheumatic fever is unquestioned, though their undesirable side-effects on the gastro-intestinal tract and on the special senses are a drawback in prolonged therapy. Attempts to find allied substances with a greater safety margin have been made and three compounds, salicylamide, sodium gentisate and  $\gamma$ -resorcylic acid, have recently been introduced.

The treatment of rheumatic fever with ACTH and cortisone has been the subject of a number of general reviews<sup>1, 2</sup> and will not be discussed in the present article. The cost and scarcity of these materials have stimulated a search for simpler compounds with a similar physiological action and a cinchoninic acid derivative (HPC) for which an ACTH-like activity is claimed, has been tried clinically in acute rheumatic fever. It has been postulated that salicylates themselves exert their therapeutic effects by stimulation of the pituitary and adrenal glands. This view that salicylates are a sort of chemical ACTH is not borne out by all the available experimental evidence and must be treated with reserve.<sup>3</sup>

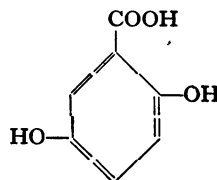
## Salicylamide



The amide of salicylic acid forms a white crystalline powder which is sparingly soluble in water. Its chronic toxicity in animals is less than that of aspirin.<sup>4</sup> Clinical trials of the drug in cases of rheumatoid arthritis, rheumatic fever, fibrositis and osteoarthritis have been carried out. A marked analgesic effect was observed in about half of the 60 patients and a 'moderate' one in about a quarter.<sup>5</sup> Only seven cases of rheumatic fever were treated, but the results were considered promising. The recommended dosage is 2 gm.

every 4 to 8 hours. Symptoms such as dizziness, drowsiness and nausea developed in a small proportion of the subjects, but in no instance were these side-effects serious. The substance differed from salicylic acid in producing a depression of the central nervous system in laboratory animals and a decrease in the prothrombin time in man. The favourable clinical reports have led to the proposal that a large well-controlled trial should be made.<sup>6</sup>

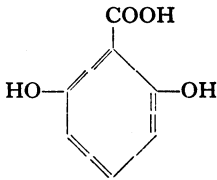
## Gentisic Acid (2:5-dihydroxybenzoic acid)



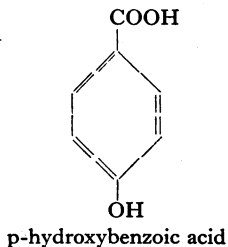
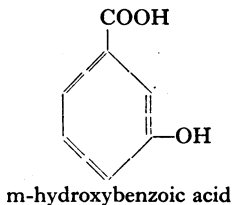
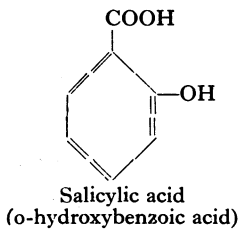
Gentisic acid is a normal metabolite of salicylate in the body, occurring to the extent of 4 to 8 per cent. in urine. The substance was reported to inhibit hyaluronidase activity in much smaller concentrations than salicylate.<sup>7</sup> The enzyme hyaluronidase depolymerises hyaluronic acid which acts as an interfibrillar cement in the tissues, and it has been suggested that there is increased hyaluronidase activity in rheumatic disease.<sup>8</sup> These considerations led to the introduction of the sodium salt of gentisic acid in the treatment of rheumatic fever. Favourable results in five cases were reported by Meyer and Ragan<sup>9</sup> and supporting clinical evidence has been provided by American<sup>10</sup> and French workers.<sup>11, 12</sup> The general opinion was that the substance appeared to be as active as salicylate in controlling the manifestations of rheumatic fever and possessed the great advantage of being virtually non-toxic. A suitable dosage is 2 to 3 gm. at 4-hourly intervals (0.25- and 0.5-gm. tablets are available commercially), and no untoward effects have been noticed with doses up to 20 gm. per day. A number of methods for the determination of plasma gentisate concentrations are available.<sup>13</sup> A point of difference from salicyl-

ates is that no reduction of the plasma alkali reserve occurs in patients receiving gentisate therapy. The absence of toxicity of gentisate is a very valuable property and if its effectiveness in rheumatic fever receives confirmation by large trials, then this drug should be an important oral therapy.

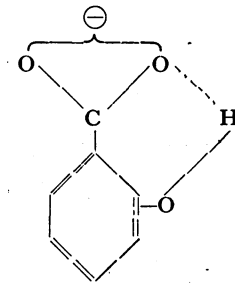
**$\gamma$ -Resorcylic acid (2:6-dihydroxybenzoic acid)**



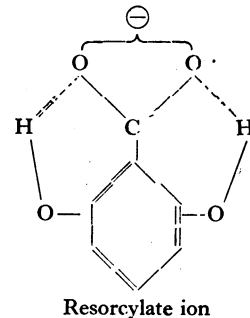
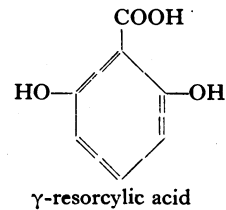
Salicylic acid is the only one of the three isomeric monohydroxybenzoic acids to possess any therapeutic activity in rheumatic fever. An examination of the properties of salicylic acid and its m- and p-isomers was made to determine if any essential difference in chemical structure existed which paralleled the therapeutic activities.



Salicylic acid is a much stronger acid than the other isomers and this has been attributed to the close proximity of the o-hydroxyl and carboxyl groups, the hydrogen of the OH group being shared with the carboxyl group to form an additional ring. The structure of the salicylate ion may be written as follows, the negative charge being equally shared by the two carboxyl oxygens.



If the formation of this type of ring structure, which is known as a chelate ring, is responsible for the therapeutic activity of salicylates it was reasoned that the formation of a second chelate ring in the molecule might enhance the activity;  $\gamma$ -resorcylic acid can form a double chelate ring and a trial of its action in rheumatic fever was therefore carried out.<sup>14</sup>

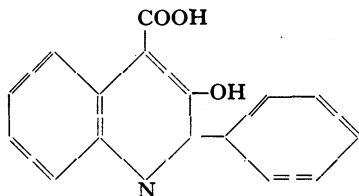


Sodium  $\gamma$ -resorcylic acid in doses of one-tenth the usual therapeutic dose of salicylate had about the same action in rheumatic fever, but the undesirable side-effects seemed to be equally potentiated, though the lethal dose of  $\gamma$ -resorcylic acid in animals was less than that of salicylate. The authors admit that, because no proportional reduction in the side-effects have been produced by the introduction of the extra hydroxyl group, the substance may have little or no advantage over salicylate in practice.

If salicylic acid is taken as the parent compound then the marked increase in therapeutic activity due to the introduction of a second chelate ring, as in  $\gamma$ -resorcylic acid, is of great theoretical importance. In gentisic acid the extra hydroxyl group is situated in position 5 so that a second chelate ring is not possible and its effect seems to be a

reduction of the toxicity without affecting the therapeutic activity.

### H.P.C. (3-hydroxy-2-phenyl cinchoninic acid)



During the investigation of a series of cinchoninic acid derivatives as antidiuretics it was found that certain of these compounds caused a stimulation of the adrenal cortex.<sup>15</sup> It was suggested that one of these substances, HPC, which showed a minimal toxicity in animal experiments,<sup>16</sup> was worthy of clinical trial in cases likely to benefit from a drug with ACTH-like properties. Ten patients with acute rheumatic fever were given the drug for periods up to 21 days, a dose of 10 or 20 mg. per kg. body weight was given daily or on alternate days. A rapid disappearance of the joint pains and fever occurred and relapses followed withdrawal of the drug. Toxic effects were few and consisted of nausea, vomiting and abdominal cramps.<sup>17</sup> Four cases of rheumatic fever were treated with similar doses of the drug by Rennie, Milne and Sommerville<sup>18</sup> who concluded that the substance was at least as good as sodium salicylate and less toxic. Relapses occurred in two patients after withdrawal of the drug, the symptoms being relieved in one case by aspirin and in the other by a further course of HPC. The characteristic salicylic acid structure, carboxyl and phenolic hydroxyl groups in ortho positions, is present in HPC and the formation of a chelate ring is therefore possible.

### General remarks

The obscurity of the mechanisms concerned in

the activity of rheumatic disease necessitates a somewhat empirical approach to the problem of developing new methods of treatment. A different reason was responsible for the introduction of each of the four substances discussed. Salicylamide is a relatively simple derivative of salicylic acid, investigated in the hope that it would be more active and less toxic, gentisate was considered promising because of its anti-hyaluronidase activity,  $\gamma$ -resorcylic acid was developed in an attempt to correlate the physico-chemical properties of salicylic acid with its therapeutic action and HPC was discovered during a search for simpler compounds with an ACTH-like action. Some of the original hypotheses which led to the trial of these substances may well prove to be untenable, but will have been of value if they produce a useful drug. Maclagan introduced salicin, the glycoside from the willow, in the treatment of acute rheumatism in 1876<sup>19</sup> on the basis that nature produces the remedy under climatic conditions similar to those which give rise to the disease. This conclusion he derived from the fact that trees of the Cinchonaceae grew readily in areas where intermittent fever was prevalent.

The theory that the chelate ring in salicylic acid is important for therapeutic activity is most attractive. The available information is limited, but the presence of this structure in salicylic acid, gentisic acid and HPC and the enhanced activity due to two such rings in  $\gamma$ -resorcylic acid is very suggestive. The reduction of toxic effects when a hydroxyl group at position 5 is introduced into the molecule of salicylic acid, as in gentisic acid, offers promising possibilities, and the activity and toxic actions of a compound in which such a hydroxyl group had been introduced into the molecule of  $\gamma$ -resorcylic acid would be interesting.

The four compounds which have been discussed are certainly developments in the treatment of acute rheumatic fever and large controlled clinical trials are now necessary for their assessment.

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