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Introduction

It has been suggested without convincing documentation that people drank a potion of willow bark and chewed willow leaves to ease joint pains in the days of Hippocrates.[1] What has been documented is that, in 1763, the Reverend Edmund Stone, a vicar in Chipping Norton, Oxfordshire, reported that a preparation he had made from dried willow bark was helpful in reducing fevers.[2] Efforts to obtain a reliable extract of willow did not begin until the following century.[1] In 1826, the Italians Brugnatelli and Fontana tried to produce a pure extract, and two years later Joseph Buchner, Professor of Pharmacy at Munich University, succeeded in producing bitter-tasting yellow crystals that he named '*salicin*', after *salix*, the Latin name for willow.[1] The formula of salicin is $C_{13}H_{18}O_7$, and, in 1820, a French chemist, Henri Leroux, refined Buchner's procedure and produced about 25 g of salicin.

Thomas MacLagan's rationale for using salicin

Although the antipyretic properties of extracts of willow had been recognised for hundreds of years, salicin had fallen into disuse in Britain by the middle of the 19th century and had been dropped from the British Pharmacopoeia.[3] It was at this time that a Scottish doctor in Dundee, Thomas John MacLagan,[4] was impressed by the parallels between rheumatic fever and intermittent and remitting fevers, and by the benefits of cinchona bark in the latter.[5] Like the Reverend Edmund Stone a century earlier, MacLagan was a lifelong believer that Nature provides a locally grown remedy for the diseases prevalent in the areas where the plants were growing: '. . .it seems to me that a remedy for rheumatic fever would most hopefully be looked for among those plants and trees whose favourite habitat presented conditions analogous to those under which the rheumatic miasma seemed most to prevail'.[6]

Although there were examples showing that the theory was flawed – for example, cinchona bark was not available in most places where malaria was a problem – MacLagan later said in his defence that: 'It will thus be seen that the employment of salicin in the treatment of acute rheumatism was no haphazard experiment but had a fair foundation in reason and analogy'.[7]

Eight influential case reports

In 1874, MacLagan decided to try salicin in a patient with rheumatic fever who had not responded to the alkalis he had prescribed.[8] To assess the drug's safety, MacLagan himself first took five, then 10, then 30 grains of it. Because he did not experience any 'inconvenience or discomfort', he gave the patient 12 grains every 3 h. Prior to this, the patient's temperature had ranged between 101.8° and 103° F, with a pulse of 120 beats per minute, and swollen and very painful joints. One day after the salicin had been started and 84 grains had been given, MacLagan's patient's pulse rate had fallen to 100 and his temperature to 99.6, and his pain and swelling had been dramatically reduced. Within a further two days, all pain had gone and the swelling was much improved, leading to an uneventful recovery.[9]

Over the next two years, MacLagan investigated salicin, giving it to some patients and not others (albeit not providing any details of how these choices were made). The *Lancet* published his observations on eight patients – four acute, three subacute and one chronic – including graphs showing trends in temperature, pulse and pain.[6,9,10] Commenting on these observations, he wrote:

> The sudden arrest of the painful symptoms, and the coincident rapid fall of pulse and temperature, followed so immediately on the administration of the salicin that it is impossible not to attribute them to its use. Cases of acute rheumatism do sometimes improve in the most unexpected manner, but I

> never saw a case get well so quickly as those of which I have given details above. A succession of such cases cannot but be attributed to the peculiarity of the treatment.[6]

MacLagan summed up his opinion on salicin as follows:

> 1. We have in salicin a valuable remedy in the treatment of acute rheumatism;
> 2. The more acute the case the more marked the benefit produced;
> 3. In acute cases, the beneficial action is generally apparent within 24 h, always within 48 h of its administration in sufficient dose;
> 4. Given thus at the commencement of an attack, it seems sometimes to arrest the course of the malady as effectively as quinine cures an ague or ipecacuanha a dysentery;
> 5. The relief of pain is always one of the earliest effects produced;
> 6. In acute cases, relief of pain and a fall of temperature generally occur simultaneously; and
> 7. In subacute cases, the pain is sometimes decidedly relieved before the temperature begins to fall.[6]

MacLagan described salicin as 'the most effective means yet for the cure of acute articular rheumatism' and that 'it may even show itself to be a specific for the disease'. In subsequent correspondence, MacLagan stressed that record keeping must be rigorous and that regular doses must be given.[10]

Disputes about the relative merits of salicin and salicylic acid

MacLagan's reports stimulated private as well as published correspondence. A letter he received from Frederick Ensor, a surgeon in Port Elizabeth, South Africa, revealed that the benefits of willow in fever were known to Hottentot herders there.[3,11] And MacLagan was not the first to report the benefits of salicylates in rheumatic disorders. In 1838, the Italian Raphaele Piria had produced a more potent acid which he named salicylic acid,[1] and impressive results had been reported for this drug in the German literature before MacLagan's reports were published in the *Lancet*.[12,13]

Until his death, MacLagan was unmoved by suggestions that salicylic acid might be equally effective and less expensive.[7,14,15] He claimed that salicin had superior pharmacological properties, especially when taken orally, because it was more pleasant to swallow, though he himself experienced a burning sensation in the mouth and severe dyspepsia, sufficient for him to take his salicin with an aqueous solution of magnesium. Various theories were suggested for the dyspepsia associated with salicylic acid. Stricker of Berlin puts it down to impurities such as carbolic acid, which were never found in pure salicylic acid. Another suggestion to reduce dyspepsia was for the salicylic acid to be given with bicarbonate of soda. Interestingly, writers spoke of irritation and erosion of the mucous membranes of the oesophagus and stomach, but in no paper on salicin or salicylic acid was there mention of postmortem examinations.[3] Maclagan believed that many illnesses, including rheumatic fever, were caused by germs – minute organisms which could directly attack internal structures, making them swell up. An example concerns the cardiac valves which, he claimed, swelled up so that they rubbed against each other allowing for the production of vegetations on them, a process which could be prevented with large enough doses of salicin.[10] No postmortem proof of this theory was offered.

Much confusion existed about salicin and salicylic acid, whether one was preferable to the other in terms of therapeutic benefit and adverse effect profile. Even Dr William Broadbent, a noted cardiologist, fell foul of MacLagan for mistakenly referring to the two drugs – salicin and salicylic acid – as if they were one and the same thing, a mistake for which he apologised.[3,16]

In conclusion

It is clear that Thomas John MacLagan was a shrewd clinical observer who, in the frenetic life of a junior hospital doctor, recorded all he saw, recognised what was needed, tried and tested medications, then wrote up his findings for publication in articles and books, all within a few years of leaving hospital practice. Furthermore, he was said to have been an astute and caring physician, keen to learn and share discoveries and insights with colleagues, assured but not arrogant, eager to research practice, albeit slow to change his views. Although it is easy to criticise his research (why did he not compare those patients who had not received salicin with those to whom he had given the drug), his results were and remain a convincing demonstration that salicin helps resolve the symptoms and signs of rheumatic fever: the dramatic effects on pulse, temperature and pain are difficult to explain in any other way.

One is left regretting that MacLagan never accepted the evidence that acetyl salicylic acid might be as good as or better than salicin, and compared the two preparations in further research. However, the German pharmaceutical industry, and in particular

Bayer, was within sight of manufacturing *Aspirin*, which was finally launched in July 1899 four years before MacLagan's death.[1]

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