The Treatment of Acute Rheumatism by Salicin, by T.J. Maclagan — The Lancet, 1876

Thomas John Maclagan (1838–1903) was born in Scone (pronounced skoon), the traditional place where Scotland's kings were enthroned[1], north of the town of Perth, in Perthshire, Scotland[2]. His father had been a physician in Jamaica who retired to Scone. Maclagan was educated at a local school in Perth, after which at the age of 15 he studied the "humanities" at Glasgow University. He entered the Edinburgh Medical School 2 years later, and qualified LRCSE in 1859 and MD the following year[3]. His final year dissertation was "On Oxaluria"[2]. He then spent a *Wanderjahr*, visiting the medical schools of Munich, Paris, and Vienna[2]. On his return he took up the post of resident medical officer at the dispensary on the island of Jersey in the Channel Islands. When he resigned this post to become Resident Medical Superintendent at the Dundee Royal Infirmary in 1864, the governors of the Jersey dispensary wrote their appreciation of his ability and capacity for hard work[2].

Maclagan found his work at the Dundee Royal Infirmary mainly to consist of caring for patients with infectious fevers, especially typhus, typhoid, and smallpox. Despite contracting typhoid fever, from which he made a full recovery, and heavy clinical duties, Maclagan managed to publish several papers[4-6]. His paper on "thermometrical observations"[6] recorded studies in the use of the clinical thermometer, and followed a review of Carl Reinhold August Wunderlich's paper on the subject in the *Edinburgh Medical Journal* in 1862[7,8]. Stewart and Fleming[2] claim that Maclagan was the first to make investigations on the use of the clinical thermometer in Scotland. His studies certainly antedate those of Sir Thomas Clifford Allbutt (1836–1925), who is generally recognized as being responsible for the introduction of the use of the clinical thermometer in 1868[9].

Clinical thermometry goes back to the 16th and 17th centuries, with publications on the subject by Santorio Santorio (Sanctorius) (1561–1636)[10] and George Martine (1702–1741)[11], respectively.

During the years 1867 to 1879 Maclagan practiced as a general practitioner in Dundee, but continued to publish papers on the temperature of newly born children[12], fevers[13–15], and renal pathology[16], and a book on the germ theory[17]. He also published a translation of a French book on the pathology of cerebral hemorrhage[18].

It was at the Dundee Royal Infirmary that Maclagan published his papers on the use of salicin, extracted from the bark of the white willow tree, *Salix alba*[19-22]. He was later in 1886 to publish a book on rheumatism and its treatment[23].

Figure 1. The only known photograph of Thomas John Maclagan (1838-1903), taken at his wedding. Courtesy of Drs. W.K. Stewart and L.W. Fleming; reprinted with permission from the Scottish Medical Journal 1987;32:141-6.

In 1879 Maclagan left Dundee to take up private consultant work in fashionable London. Among his many famous patients were his fellow Scots Thomas Carlyle (1795–1881) and the Prime Minister Sir Henry Campbell-Bannerman (1836–1908)[2]. He did not obtain a hospital appointment, and although becoming a member of the London College of Physicians in 1882, he was never promoted to fellowship. He continued to publish on fevers[24-26] and became president of the pharmaceutical section of the British Medical Association in 1884[2]. Maclagan died of gastric cancer in 1903 and was buried in Brookwood Cemetery, Woking, Surrey. He was paid many tributes by his colleagues, including Sir Frederick Treves (1853–1923) of elephant-man fame[2]. Maclagan would probably be better known in

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2002. All rights reserved.

Downloaded on April 9, 2024 from www.jrheum.org

his homeland had he stayed there and continued his academic pursuits, rather than seeking his fortune among the rich sick of London.

It seems that the idea of using salicin in the treatment of acute rheumatic fever first occurred to Maclagan in November 1874, when he had a 48-year-old man under his care with high fever, tachycardia, and acutely painful and swollen joints, of 3 days' duration. Before prescribing the remedy Maclagan first took 5, then 10, and finally 30 g himself, "without experiencing the least inconvenience or discomfort." Thus satisfied with the safety of administration, Maclagan prescribed for the patient 12 g every 3 hours.

The result, he records, "exceeded my most sanguine expectations," with rapid improvement in fever, tachycardia, and arthritis. "Indeed, on the second day of treatment, after 168 gr. of salicin, the patient had a normal temperature and the arthritic pain had 'all but gone'." But the canny Scot that he was, Maclagan, although impressed by the striking improvement with salicin, was aware that a single case "could not be regarded as proof of the beneficial action of Salicin." He was "quite aware that cases of acute rheumatism do sometimes unexpectedly improve without any treatment," and he "had no surety that this was not a case in point."

Maclagan describes the effect of salicin in 8 patients, noting that pain relief was prompt, and paralleled the fall in temperature. In chronic rheumatism, however, salicin was sometimes noted to fail. Stricker[27] also considered the use of salicylic acid in chronic joint rheumatism of doubtful value. In his textbook, *The Principles and Practice of Medicine*, in 1892 Sir William Osler recommended high dose salicylates for rheumatic fever, but did not even mention their use in chronic forms of arthritis[28]. Even as late as 1941, the *Rheumatism Reviews*, written by the leaders of American rheumatology, failed to mention salicylates in the treatment of rheumatoid arthritis[29]. However, aspirin became popular as treatment for rheumatoid arthritis, when therapeutic trials showed no superiority over the "wonder drug" cortisone[30]. High doses of aspirin were shown to have both analgesic and antiinflammatory action in the 1960s[31,32]. Maclagan was therefore not alone in his belief that salicin was of little value in chronic articular inflammatory disease.

Maclagan showed commendable restraint for salicin's effect on the heart — "regarding the cardiac complications of rheumatic fever, I have no experience."

Osler[28] also considered salicylates useless in preventing the cardiac sequelae of acute rheumatic fever. Nevertheless, the belief that salicylates given in sufficient doses to relieve acute manifestations and reduce the erythrocyte sedimentation rate would prevent cardiac complications continued to be debated up until the middle of the 20th century[33,34]. We now know that Maclagan's skepticism was well founded.

Maclagan did not perform dose response studies, commenting, "it is very possible that less might suffice; for I have not tried to find the minimum dose." Maclagan's patients did not appear to suffer from dyspepsia, which he had noted with salicylic acid and which he attributed to chemical impurities in the latter. It was dyspepsia as a result of high doses of salicylate that later prompted the director of research at the Bayer Company, Heinrich Dreser (1860–1929) to direct one of his chemists, Felix Hoffman (1869–1946), to find an alternative. This the latter happily did, finding acetylsalicylic acid in a bottle on the shelves of his laboratory. Acetylsalicylic acid had been synthesized by Charles Frederick von Gerhard (1816–1856), Professor of Chemistry at Strasbourg, in 1853[35].

Maclagan made the observation, and was probably the first to do so, that the more acute the case, the more effective the therapy appeared to be, occurring usually within 24 hours and always within 48 hours. In the 1970s Lee and colleagues[31] were to confirm this observation in patients with rheumatoid arthritis. The only significant determinant in predicating response to an analgesic is the amount of pain the patient has[31]. Thus, the delta of response to an analgesic is determined by the severity of pain when the drug is administered. Patients with severe pain experience marked pain relief, those with moderate pain only moderate relief, and those with mild pain scarcely any relief at all. This fact seems not to be widely appreciated, even by those who organize clinical therapeutic trials!

Maclagan records that he was strongly impressed that "the maladies on whose course they (the Cinchonaceae) exercise the most beneficial action are most prevalent in those countries in which the Cinchonaceae grow most readily; nature seeming to produce the remedy under climatic conditions which give rise to the disease." This belief was know as the Doctrine of Signatures, and the philosophy that led the Reverend Edward Stone of Chipping-Norton in Oxfordshire, England, to make his discovery on the effects of extract of the bark of the willow in 1763[37]. Maclagan, however, makes no reference to the Reverend Stone's paper, which described the effect of willow bark in 50 patients. It is of interest that recently "the wheel has come full-circle" and that salicin has proven better than placebo for low back pain[38]. Stone had, like others in the 18th century, sought an inexpensive substitute for cinchona, containing quinine, as a treatment for fever and muscle and joint pain. As Stewart and Fleming[2] point out, application of the Doctrine of Signatures, that "nature planted remedies" close to the cause of a disease, was incorrect as far as the cinchona tree was concerned, since it grew high in the Andes in Peru, where there were no swamps. Maclagan might have guessed as much had he recalled that the cinchona tree was also referred to as "Peruvian bark"! Maclagan also subscribed to the concept of "miasmotic agents" as a cause of rheumatic disease. In this he was not altogether wrong, since acute rheumatic fever is one of the classic examples of a reactive arthritis, following a beta-

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2002. All rights reserved.

Downloaded on April 9, 2024 from www.jrheum.org

hemolytic streptococcal infection of the throat (but nowhere else), and not being present in the heart, joints, or subcutaneous nodules.

Sir William Osler made no comment in the first edition of his famous textbook of 1892 to either salicin or Maclagan. Both were contemporaries and although there is no record of Osler visiting Dundee or meeting Maclagan he would certainly have read his paper on salicin.

W. WATSON BUCHANAN, MD(Glas), FRCP(Glas, Edin & C),
Emeritus Professor of Medicine,
22 Jerome Park Drive,
Dundas, Ontario Canada L9H 6H2
WALTER F. KEAN, MB, ChB, MD(Glas), FRCP(Edin & C), FACP, FACR,
Clinical Professor of Medicine (Rheumatology),
McMaster University Faculty of Health Sciences,
Hamilton, Ontario, Canada.

Address reprint requests to Dr. Buchanan.

REFERENCES

1. Keay J, Keay J, editors. Collins encyclopedia of Scotland. London: Harper-Collins; 1994:847.
2. Stewart WK, Fleming LW. Perthshire pioneer of anti-inflammatory agents. Scot Med J 1987;32:141-6.
3. Obituary: Thomas John Maclagan. BMJ 1903;1:766 and Lancet 1903;1:1000.
4. Maclagan TJ. Typhus statistics of the Dundee Royal Infirmary. Edin Med J 1867-68;XIII:140-57.
5. Maclagan TJ. On enteric fever in Dundee and neighbourhood. Edin Med J 1867-68;XIII:297-318.
6. Maclagan TJ. Thermometrical observations. Edin Med J 1867-68;XIII:601-25.
7. Periscope. On the state of the temperature in abdominal typhus. (Review of Wunderlich, C.A. Prag vieter Prak Halk.) Edin Med J 1862-63;VIII:465-6.
8. Wunderlich CRA. Das Verhalten der Egeinwärme in Krankheiten. Leipzig: O. Wigand; 1868.
9. Allbutt TC Sir. Medical thermometry. Brit and Foreign med-chir Rev 1870;45:429-41.
10. Santorio S. Commentaria in primam fen prini libri canonis Avicennae. Venetüs, apud M. A. Brogiollum, 1625.
11. Martine G. Essays medical and philosophical. London: A. Miller; 1740.
12. Maclagan TJ. Observations on the temperature of newly-born children. Trans Roy Soc, Edinburgh 1869;XXV:435-40.
13. Maclagan TJ. On the nature of intestinal lesion of enteric fever. Edin Med J 1870;XVI:865-98.
14. Maclagan TJ. On the phenomena of idiopathic fever. Edin Med J 1873-74;XIX:648-50.
15. Maclagan TJ. Is typhoid fever contagious? Nineteenth Century (Lond), 1879:809-18.
16. Maclagan TJ. The pathology of the contracting granular kidney. Brit and Foreign med-chir Rev 1875;LVI:188-201.
17. Maclagan TJ. The germ theory applied to the explanation of the phenomena of disease — the specific fevers. London: Macmillan; 1876.
18. Maclagan TJ. A study of some points in the pathology of cerebral hemorrhage. Translated from the French of Ch. Bouchard, with notes. Edinburgh: Maclachlan Stewart; 1872.
19. Maclagan TJ. The treatment of acute rheumatism by salicin. Lancet 1876;I:342-3.
20. Maclagan TJ. Treatment of acute rheumatism by salicin [letter]. Lancet 1876;I:58.
21. Maclagan TJ. The willow as a remedy for acute rheumatism by salicin. Lancet 1876;I:910.
22. Maclagan TJ. The treatment of acute rheumatism by salicin. Lancet 1876;2:601-4.
23. Maclagan TJ. Rheumatism: its nature, its pathology, and its successful treatment. London: Pickering; 1881, New York: Wood; 1886, London: Black; 1896.
24. Maclagan TJ. Fever — a clinical study. London: Churchill; 1888.
25. Maclagan TJ. An outbreak of cerebro-spinal fever. Edin Med J 1886-87;XXXII:141-50, 237-42, 307-14, 391-8, 496-506.
26. Maclagan TJ. The pathogenesis of cholera. Lancet 1893;1:1305-9.
27. Stricker S. Ueber die Resulate der Behandlung der Polyarthritis rheumatica mit Salicylsäure. Berl Klin Wschr 1876;13:99-103.
28. Osler W Sir. The principals and practice of medicine. New York: D. Appleton and Co.; 1892. Reprinted by the Classics of Medicine Library, Birmingham, AL; 1978.
29. Hench PS, Bauer W, Boland E, et al. Rheumatism and arthritis: review of American and English literature for 1940. 8th Rheumatism Review. Ann Intern Med 1941;15:1001-108.
30. Goodwin JS, Goodwin JM. Failure to recognize efficacious treatments: a history of salicylate therapy in rheumatoid arthritis. Perspect Biol Med 1981;25:78-92.
31. Fremont-Smith K, Bayles TB. Do salicylates have a clinically significant anti-inflammatory action in rheumatoid arthritis? Arthritis Rheum 1964;7:309-16.
32. Boardman PL, Hart FD. Clinical measurement of anti-inflammatory effects of salicylates in rheumatoid arthritis. BMJ 1967;4:264-8.
33. Coburn AF. Salicylate therapy in rheumatic fever. A rational approach. Bull Johns Hopkins Hospital 1943;73:435-64.
34. Reid J. Does sodium salicylate cure rheumatic fever? Q J Med NS 1948;17:139-51.
35. Krantz JC Jr. Felix Hoffman and aspirin. In: Historical medical classics involving new drugs. Baltimore: Williams and Wilkins; 1974:37-41.
36. Lee P, Webb J, Anderson J, Buchanan WW. Method for assessing therapeutic potential of anti-inflammatory anti-rheumatic drugs in rheumatoid arthritis. BMJ 1973;2:685-8.
37. Stone E Rev. An account of the success of the bark of the willow in the cure of agues. Philosophical Transactions 1763;53:195-200.
38. Chrubasik S, Eisenberg E, Balan E, et al. Treatment of low back pain exacerbations with willow bark extract: a randomized double-blind study. Am J Med 2000;109:9-14.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2002. All rights reserved.

Downloaded on April 9, 2024 from www.jrheum.org