

Chalmers I, Toth B. 19th century controlled trials to test whether belladonna prevents scarlet fever

Commentary on: Balfour TG. Quoted in West C (1854). Lectures on the Diseases of Infancy and Childhood. London, Longman, Brown, Green and Longmans, p 600.

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Author contact details: Iain Chalmers, James Lind Library, Summertown Pavilion, Middle Way, Oxford OX2 7LG, UK. E-mail: ichalmers@jameslindlibrary.org

Ever since its introduction by Samuel Hahnemann at the end of the 18th century, there has been debate about the effects of homeopathic medicine. In 1848, prompted by support for homeopathic treatments by some individuals in the orthodox medical establishment, John Forbes published a searching review of relevant evidence in the journal that he had founded - *British and Foreign Medico-Chirurgical Review* (Forbes 1846). It is a superb analysis of the criteria that should be taken into account in assessing the effects both of homeopathic and of orthodox treatments. A brief quotation from his 22-page article illustrates Forbes' style:

"Many years ago, when in charge of a large body of men in the public service, we had occasion to treat an epidemic diarrhea, of considerable violence but not dangerous. Finding our patients recover as fast under one as another of several methods of treatment adopted, we thought there would be no unpardonable *lèse-majesté* either to our royal master of London or our divine master of Delos, in carrying our trials one step further. Accordingly, we put half of our remaining patients on a course of orthodox physic, and half on homoeopathic doses of flour (*farin*.30) in the shape of bread pills; and it puzzled us sadly to say which was the most successful treatment." (Forbes 1846, p 249)

The medical establishment did not forgive John Forbes for calling into question the efficacy of orthodox treatments as well as homeopathy (Agnew 2008).

One of the claims made by Samuel Hahnemann (1801) was that homeopathic belladonna protected people from developing scarlet fever (scarlatina). Hahnemann's designation of this "divine remedy as a preservative" led others to adopt it, and not only homeopaths. For example, in an article published in *The Lancet* in 1829, Cristoph Hufeland (1762-1836), who has been described as the greatest German clinician of the late 18th century (Habrigh 1991) and who founded a respected and still extant medical journal in Göttingen, reported that:

"I. The proper use of belladonna has, in most cases, prevented infection, even in those instances where, by the continual intercourse with patients labouring under scarlet fever, the predisposition towards it was greatly increased.

"II. Numerous observations have shown that, by the general use of belladonna, epidemics of scarlet fever have actually been arrested.

"III. In those few instances where the use of belladonna was insufficient to prevent infection, the disease has been invariably slight.

"IV. There are exceptions to the above three points, but their number is extremely small."

These issues were considered in a review in John Forbes' journal in 1855 by J Warburton Begbie (1855). Among other things, Begbie's review refers to three controlled trials. The earliest of these, conducted by Dusterberg, was reported by Bayle (1830) as follows:

"To better distinguish the effects of belladonna from those of chance, I selected one infant in each family from whom this form of treatment was withheld. All the children from whom the prophylaxis was withheld were attacked by the infection (cited in Begbie 1855, p 85).

Dusterberg's experience using belladonna during three consecutive epidemics of scarlet fever led him to conclude that it was "as effective as vaccination". Begbie comments on this notion as follows:

"The truth is, in regard to scarlet fever, as well as many other infectious diseases, that an amount of capriciousness so evidently attends their progress, indeed, if we might so speak, regulates their progress, as to make it a very difficult matter to decide if, at any time, or in any degree, their occurrence is at all affected or moderated by external circumstances; and if this be true, as undoubtedly it is, how far more difficult must it be to decide if the exhibition of any prophylactic means does good.

"Vaccination in its effects made itself at once recognised, and the contrast between the ravages of small-pox at the commencement of this century, and the almost entire immunity from that disease in an epidemic form, which now prevails, are facts so plainly recognisable, and so appreciable, as in the instance of that disease entirely to remove the difficulty referred to. It is altogether otherwise with scarlatina; notwithstanding the introduction of belladonna, and its extensive employment, both in this country and abroad, as a prophylactic against scarlet fever, we are not aware that the mortality in either has been reduced; a circumstance which itself militates very strongly both against the prophylactic and the remedial efficacy of belladonna." (Begbie 1855, pp 98-99)

The other two experiments to which Begbie refers were both done a couple of decades later. In one of these, Dr Andrew Wood reported his experience in Heriot's Hospital, in Edinburgh, as follows:

"The plan I proposed to myself was this - viz.: whenever scarlatina appeared in any particular ward, and not till then, I immediately made inquiry, and having ascertained the boys who had previously had the fever, these I left out of the question. I then divided the remainder into two nearly equal sections: to one I gave one-eighth of a grain of belladonna, twice a day: to the other, no belladonna was given. This experiment was continued for several weeks, and the reason why it was then discontinued was simply this - that a fatal case occurred in the person of a boy (J.B.) who had been taking the belladonna for nearly four weeks. Taking alarm, I resolved to discontinue the experiment." (cited in Begbie 1855, p 93)

Begbie refers to the third controlled trial as "the interesting experiments of Dr. Balfour". Who was Dr Balfour, and what were his "interesting experiments"?

Thomas Graham Balfour's controlled trial

Thomas Graham Balfour (1813-1891) was an army doctor whose talents were recognised during his analyses of the military statistics which had accumulated since the Waterloo Campaign. Just after Balfour's 27th birthday, a letter to the War Office from his superior officer, Major Alexander Tulloch, reads:

"I am happy to have this opportunity of expressing to the Secretary at War my sense of the value of this officer's services, not only in regard to this investigation but in the preparation of the voluminous documents from which the Statistical Reports have been framed, & in which he has constantly afforded me his assistance without any other remuneration than the regimental pay of his rank." (Tulloch 1840).

Seven years later, (then Colonel) Tulloch wrote to the Minister at War seeking funding for Balfour to conduct further analyses of statistics on incapacity and mortality among army pensioners:

"...I am not aware of any other of his standing in the Service who combines the requisite degree of Medical and Statistical knowledge...Medical Men are, generally, the last persons in the world to be trusted in matters of figures, and I had too much experience of the difficulty of dealing with them when I commenced this undertaking, ever to trust to indiscriminate assistance again from that profession." (Tulloch 1847)

The following year (1848), Balfour was appointed surgeon at the Royal Military Asylum for soldiers' orphans at Chelsea, and it was here that he conducted his controlled trial to assess whether belladonna prevented scarlet fever. His account of the trial is recorded (between quotation marks) by Charles West, founder of the Great Ormond Street Hospital for Children, in the 3rd edition of a book of lectures on the diseases of infancy and childhood (Balfour 1854).

Balfour's account of his trial must rate as one of the most succinct and careful accounts of a clinical experiment ever written:

"There were 151 boys of whom I had tolerably satisfactory evidence that they had not had scarlatina; I divided them in two sections, taking them alternately from the list, to prevent the imputation of selection. To the first section (76) I gave belladonna; to the second (75) I gave none; the result was that two in each section were attacked by the disease. The numbers are too small to justify deductions as to the prophylactic power of belladonna, but the observation is good, because it shows how apt we are to be misled by imperfect observation. Had I given the remedy to all the boys, I should probably have attributed to it the cessation of the epidemic".

In these four sentences, Balfour addresses (i) the application of eligibility criteria; (ii) the rationale for and measures taken to control allocation bias; (iii) the problem of Type 2 statistical errors (that is, false negatives); and (iv) the dangers of reliance on uncontrolled case series as a basis for causal inferences about the effects of interventions.

Balfour's caution in referring to the numbers of cases being "too small to justify deductions as to the prophylactic power of belladonna" is especially noteworthy. Indeed, the celebrated medical statistician William Guy was rather less cautious. In his Croonian Lectures on 'The numerical method, and its application to the science and art of medicine' (Guy 1860), Guy challenges homeopathy, and uses Balfour's experiment to illustrate that "Average values derived from small numbers of facts are sufficient to refute rash assertions...based on wild and fanciful hypotheses."

"I think you will agree with me", he wrote, "that a perfectly gratuitous assertion, advanced in support of a very fanciful hypothesis, has met at Dr. Balfour's hands with much more respectful treatment than it deserves, and that the facts adduced are amply sufficient under the circumstances of the case." (Guy 1860)

Balfour's clinical trial of belladonna given to prevent scarlet fever appears to have been his only published example of clinical research (Andy Grieve, personal communication, July 2009). His main achievements resulted from his compilation and analyses of naval and military statistics, some of them done in collaboration with Florence Nightingale (Balfour 1845; 1872; 1880). Balfour went on to be elected President of the Royal Statistical Society for 1889 and 1890.

Evidence and practice

In summarising his review of Balfour's and other evidence, Warburton Begbie concluded that "experience has altogether failed to recommend the employment of belladonna, and [we] should now be prepared to abandon the practice, as not only insufficient but absurd" (Begbie 1855, p 101). Despite this, use of and research into belladonna as a means of preventing scarlet fever continued well into the 20th century (Dean 2001).

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