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Thomas Graham Balfour's clinical trial of belladonna given to prevent scarlet fever appears to have been his only published example of clinical research, his main achievements being his key role in the compilation and analysis of naval and military statistics (Balfour 1845; 1872; 1880), work which was subsequently reflected in his presidency of the Royal Statistical Society (Balfour 1889).

Balfour was recognised as exceptional during his involvement in assembling and analysing the military statistics that had accumulated since the Waterloo campaign. A letter to the War Office just after Balfour's 27th birthday by 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 (scarlatina). A searching review of the evidence bearing on this question was published by J Warburton Begbie the year after Balfour's controlled trial, and helps to set the study in context (Begbie 1855).

Half a century earlier, Samuel Hahnemann, the founder of homeopathic medicine, had published a pamphlet recommending homeopathic belladonna as a prophylactic against scarlet fever. Hahnemann's designation of this "divine remedy as a preservative" led others to adopt it, and not only homeopaths. For example, Cristoph Hufeland (1762-1836), who has been described as the greatest German clinician of the late 18th century (Habrich 1991) and founded a respected and still extant medical journal in Göttingen, reported in an article published in *The Lancet* in 1829 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."

The evidence for these and similar inferences was examined and challenged by Begbie, who refers to "the interesting experiments of Dr. Balfour", which had been recorded, between quotation marks, in the 3rd edition of a book of lectures on the diseases of infancy and childhood published the previous year by Charles West, founder of the Great Ormond Street Hospital for Children (West 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 the application of eligibility criteria, control of allocation bias, the problem of Type 2 statistical errors (that is, false negatives), and the dangers of reliance on uncontrolled case series as a basis for causal inferences about the effects of treatment.

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 when, in his Croonian Lectures on 'The numerical method, and its application to the science and art of medicine' (Guy 1860), he used 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 controlled trial is one of three controlled evaluations of the effects of belladonna in scarlet fever considered in Begbie's 1855 review of the evidence. In an evaluation that appears to have been contemporary with Balfour's, Dr Andrew Wood reported his experience in Heriot's Hospital 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)

In an earlier evaluation reported by Bayle (1830), Dusterberg is reported as follows:

"Pour mieux faire ressortir l'effet de la belladonne et en écarter celui du hazard, j'ai choisi dans chaque famille un enfant, lequel fut excepté de cet mode de traitement. Or, tous les enfants auxquels l'usage du préservatif était demeuré interdit, furent attaqués de la contagion." (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". Quarter of a century later, 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)

Begbie concludes:

"It is our opinion that experience has altogether failed to recommend the employment of belladonna, and that we should now be prepared to abandon the practice, as not only insufficient but absurd." (Begbie 1855, p 101)

Begbie's mid 19th century opinion did not prevent continued use of and research into belladonna as a means of preventing scarlet fever well into the 20th century (Dean 2001).

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