

# Journal of the Royal Society of Medicine

<http://jrs.sagepub.com/>

---

## **A puzzling omission in a great medical textbook edited by a pioneer of controlled trials**

Duncan Neuhauser, Mireya Diaz and I Chalmers

*J R Soc Med* 2008 101: 381

DOI: 10.1258/jrsm.2008.081009

The online version of this article can be found at:

<http://jrs.sagepub.com/content/101/7/381>

---

Published by:



<http://www.sagepublications.com>

On behalf of:



[The Royal Society of Medicine](http://www.rsm.ac.uk)

**Additional services and information for *Journal of the Royal Society of Medicine* can be found at:**

**Email Alerts:** <http://jrs.sagepub.com/cgi/alerts>

**Subscriptions:** <http://jrs.sagepub.com/subscriptions>

**Reprints:** <http://www.sagepub.com/journalsReprints.nav>

**Permissions:** <http://www.sagepub.com/journalsPermissions.nav>

>> [Version of Record](#) - Jul 1, 2008

[What is This?](#)



# A puzzling omission in a great medical textbook edited by a pioneer of controlled trials

Duncan Neuhauser<sup>1</sup> • Mireya Diaz<sup>1</sup> • I Chalmers<sup>2</sup>

<sup>1</sup> Department of Epidemiology and Biostatistics, Case School of Medicine, Case Western Reserve University, 10900 Euclid Avenue, Cleveland, OH 44106, USA

<sup>2</sup> James Lind Library, Summertown Pavilion, Middle Way, Oxford OX2 7LG, UK

Correspondence to: Duncan Neuhauser. E-mail: dvn@case.edu

## DECLARATIONS

### Competing interests

None declared

### Funding

None

### Ethical approval

Not applicable

### Guarantor

DN

### Contributorship

All authors contributed equally

## Acknowledgements

Additional material for this article is available from the James Lind Library website ([www.jameslindlibrary.org](http://www.jameslindlibrary.org)), where it was originally published

At the time of his death in 1965, Russell LaFayette Cecil could plausibly be called ‘the best known American physician in the world’ due to his editorship of his *Textbook of Medicine*.<sup>1</sup> Cecil’s contribution to the history of controlled trials began after he joined the US Army on 16 June 1917. He had been asked by the Surgeon General to study pneumonia, and carried out two very large trials to assess the value of vaccination. The first of these studies was conducted at Camp Union, New York.<sup>2</sup> After ‘preliminary experiments’ had been carried out on mice and a few patients to calculate appropriate dosages, 12,519 soldiers were vaccinated – ‘about 40 percent of the mean strength of the command’ (p 30). Vaccination was not compulsory and 19,481 soldiers were not vaccinated. The ‘vaccinated men were in stable organizations where the personnel underwent little change,’ by contrast with the unvaccinated men, who were coming and going from the camp (p 34). There were only seven cases of streptococcal pneumonia among the 12,519 vaccinated soldiers, compared with 106 cases among the 19,481 unvaccinated soldiers. In commenting on this difference, Cecil’s report notes that the two groups had been similar in respect of the frequency of pneumonia prior to the study, but that ‘the period of observation ha(d) been short’ (p 39).

On 1 September 1918, Cecil was sent to Camp Wheeler, Georgia, to institute ‘voluntary vaccination among the troops’<sup>3</sup> (p 459), and 75% of about 9000 men in the camp were vaccinated before mid-October. Between then and the beginning of November, another 6000 men arrived at the camp. The situation was complicated by the influenza epidemic:

*‘The incoming men were examined by a medical officer as they got out of the train. Any men who were sick were sent at once to the Base Hospital. All the others were marched directly to the vaccinating pavilion, and received at once their pneumococcus vaccine. In this way most of the recruits were*

*vaccinated against pneumonia within 24 hours of arriving at the camp. All those who objected to taking the vaccine were passed by’* (p 463).

Cecil was creative in conducting his vaccine trials in circumstances largely outside his control, including one of history’s greatest wars and pandemics. But he recognized the deficiencies in his study:

*‘For the purposes of control, it would have been more desirable to have vaccinated only half of the camp... As this method, however, was not feasible and in consideration of the serious influenza epidemic it was decided to vaccinate as large a percentage of the camp as possible’* (p 464).

Cecil’s experience with large controlled vaccine trials in the army was to serve him well after he became a visiting physician at Bellevue Hospital, New York, in 1921. He took advantage of the great size of this hospital to carry controlled trials of the treatment of pneumonia. A report of the first of these, to test the value of Huntoon’s serum-free solution of pneumococcus antibody, was published in 1922.<sup>4</sup> Patients were allocated to comparison groups by rotation:

*‘In order to determine the therapeutic value of pneumococcus, the twelve wards of Bellevue Hospital were divided into two groups. In six wards, all cases of lobar pneumonia were treated with the antibody solution. The other six were used as control wards. In these wards, patients with pneumonia received no antibody, but in other respects were treated in exactly the same way as the patients receiving antibody. It was first determined that no selection of any kind was practiced by the admitting office in assigning patients to the various wards. In Bellevue Hospital, new patients are distributed by rotation, without regard to the character or severity of the disease. The control seemed, therefore, to be a fair one from every point of view’* (p 344).

A further controlled trial of Felton's serum was reported in 1928:<sup>5</sup>

*'... all the patients with lobar pneumonia included in this series received a number as soon as the diagnosis of lobar pneumonia was made. Patients with even numbers received serum, those with odd numbers did not receive any. This method of classifying patients left their selection for treatment entirely to chance. This method produced comparative groups that are surprisingly similar in all essential respects. In the first place the number of cases of the treated and untreated types is approximately the same'* (p 2039).

There were 441 treated cases and 444 untreated cases (p 2040). These two groups were compared by day of admission, age complications, and alcoholism and found to be 'remarkably similar.' The overall mortality was 30% in the treated cases and 39.2% in the untreated cases.

In 1930, Cecil and Plummer reported their evaluation of Felton's serum for treating pneumonia:<sup>6</sup>

*'In our investigations with Felton's serum the alternate case method was used; that is, every patient diagnosed as having lobar pneumonia was given a number; the patients with even numbers received the serum – those with odd numbers served as controls'* (p 1551).

Between 1924 and 1929, 239 patients had been treated with serum and 234 served as controls. There were 48 and 73 deaths, respectively, in the two groups. In comparing these results with the experience of other investigators, Cecil and Plummer refer specifically to the research reported by Park, Bullowa and Rosenbluth,<sup>7</sup> who, they note, 'also employed the alternate case method of treatment' (p 1552). Indeed, in a report of this research by Bullowa,<sup>8</sup> one of the subsections of the paper is subtitled 'Alternation'.

From his studies of vaccines during the First World War through his three trials of treatments for pneumonia in the 1920s we can see Cecil's developing understanding and use of controlled studies. In addition to the reports already cited, Cecil's methodological awareness is clear in the extensive review of treatment for lobar pneumonia which he delivered as the 12th Mellon Lecture at the Society for Biological Research of the University of Pittsburgh.<sup>9</sup> In the published version of the lecture, Cecil refers not only to the methods he had used to avoid allocation bias in his clinical trials, but also makes clear that he is aware of the need to study sufficiently large numbers of

patients. Thus, commenting on a subgroup analysis, he writes: 'Unfortunately, the number of patients treated was not sufficiently large to furnish reliable statistical evidence' (p 316).

Even though sulfanilamide would soon become the treatment of choice for pneumonia in the 1930s,<sup>10,11</sup> Cecil's peers recognized the quality of his research on treatments for pneumonia in patients at Bellevue Hospital during the 1920s.<sup>12</sup> But Cecil's pioneering contributions to the evolution of controlled clinical trials is not the principal reason that, by the time of his death in 1965, he had probably become the most widely known American physician in the world. Cecil's celebrity rather reflected his editorship of a *Textbook of Medicine*,<sup>13</sup> which he edited through ten editions between 1927 and 1959. Later, other editors took up the work. The 22nd edition was published in 2004.

From its inception, Cecil's textbook contained clear statements about efficacy in the sections on treatment. Given that the book was written during the era when Cecil was pioneering the design and analysis of statistically powerful, controlled clinical trials, one might expect that he would ensure that readers of his book would be offered some guidelines about how evidence about the effects of treatments should be assessed. During the first ten editions under Cecil's active editorship, however, there were no explicit statements about what constituted good evidence of treatment effects, let alone a general chapter on research methods to evaluate the effects of treatments.

Paul Beeson and Walsh McDermott took over as editors of the book for the 11th edition in 1963. In the 14th edition, published in 1975, there was an introductory article by Alvan Feinstein on 'Science, clinical medicine and the spectrum of disease' which mentions 'control group'. (In an article on 'Man and his environment' in that edition, Howard Hiatt states that 'cost benefit studies are necessary'.) The 18th edition, published in 1988, edited by James Wyngaarden and Lloyd Smith, has a contribution by Stephen Pauker on 'Clinical decision making'. The first article on basic biostatistics – by Catarina Kiefe – appears in the 20th edition, published in 1996, and mentions 'treatment and control groups drawn from the same population' (p 84). Only with the arrival of the new millennium and the 21st edition, with Lee Goldman as editor, do we find a paragraph headed 'Randomized controlled trials', in a contribution by Albert Wu entitled 'Principles of outcome assessment'. This is the first clear acknowledgement of the importance of randomized trials in

assessing the effects of treatments in Cecil's celebrated *Textbook of Medicine*. It arrived more than three quarters of a century after Cecil's pioneering contribution to the history of controlled clinical trials, and only after 20 previous editions of the book that still carries his name.

### References

- 1 Neuhauser D, Diaz M. Russell LaFayette Cecil (1881–1965). *The James Lind Library* 2007; [www.jameslindlibrary.org](http://www.jameslindlibrary.org)
- 2 Cecil RL, Austin JH. Results of prophylactic inoculation against pneumococcus in 12,519 men. *J Exper Med* 1918;**28**:19–41
- 3 Cecil RL, Vaughan HF. Results of prophylactic vaccination against pneumonia at Camp Wheeler. *J Exper Med* 1919;**29**:457–83
- 4 Cecil RL, Larsen NP. Clinical and bacteriologic study of one thousand cases of lobar pneumonia. *JAMA* 1922;**79**:343–9
- 5 Cecil RL, Sutliff WD. The treatment of lobar pneumonia with concentrated anti-pneumococcus serum. *JAMA* 1928;**91**:2036–40
- 6 Cecil RL, Plummer N. Pneumococcus Type 1 pneumonia: a study of eleven hundred and sixty-one cases, with especial reference to specific therapy. *JAMA* 1931;**95**:1547–53
- 7 Park WH, Bullowa JGM, Rosenbluth NM. The treatment of lobar pneumonia with refined specific antibacterial serum. *JAMA* 1928;**91**:1503–8
- 8 Bullowa JGM. The use of antipneumococcc refined serum in lobar pneumonia. *JAMA* 1928;**90**:1354–8
- 9 Cecil RL. Specific treatment of lobar pneumonia. *Arch Intern Med* 1928;**41**:295–335
- 10 Podolsky SH. *Pneumonia before antibiotics*. Baltimore: Johns Hopkins University Press; 2006
- 11 Loudon I. The use of historical controls and concurrent controls to assess the effects of sulphonamides, 1936–1945. *The James Lind Library* 2002; [www.jameslindlibrary.org](http://www.jameslindlibrary.org)
- 12 Reisman D. *History of the interurban clinical club 1905–1907*. Chicago: John C Winston Co; 1937. p. 100–3
- 13 Cecil RL. *Textbook of Medicine*. Philadelphia: WB Saunders; 1927. Editions from 1951–1979 were co-edited with Robert F Loeb, whose name was dropped with the 16th edition. The 22nd edition was published in 2004