

# Major Greenwood and clinical trials

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## Introduction

Major Greenwood (1880–1949) was the foremost medical statistician in the UK during the first half of the 20th century.<sup>1</sup> The son of a general medical practitioner, he obtained a medical degree from the London Hospital in 1904 and then studied statistics under Karl Pearson at University College London. Instead of general practice, he opted to pursue a career in medical research, first under the physiologist Leonard Hill at the London Hospital, where, in 1908, he set up the first department of medical statistics and gave the first lecture course in the subject in 1909. He established the second department of medical statistics in 1910 at the Lister Institute and established the second course of lectures there.

After enlisting in the Royal Army Medical Corps in 1915 to undertake sanitary work, he transferred in 1916 to the Ministry of Munitions. While there he investigated, among other things, absenteeism among factory workers and the causes of industrial accidents. In 1919, he was the first statistician appointed to the new Ministry of Health.

In 1924, Greenwood became chair of the Medical Research Council's Statistical Committee, and he was appointed as the first professor of Epidemiology and Vital Statistics at the London School of Hygiene and Tropical Medicine in 1927 (a post he retained until retirement in 1946). Shortly thereafter, he was also appointed as the second director of the Medical Research Council's Statistical Department following the death of John Brownlee, its first director.

Major Greenwood authored more than 200 scientific papers, 24 major reports and nine books (including one that was never published); and his associates included many distinguished scientists, politicians, and members of the medical profession. Further details can be found in the literature.<sup>1–4</sup>

## References to Greenwood's work in clinical trials

Greenwood was a renowned epidemiologist who is not usually associated with randomised clinical trials. At the time of his retirement, randomised clinical trials were still under development and Peter Armitage has no recollection of Greenwood commenting on trials when Greenwood visited the London School of Hygiene and Tropical Medicine during his retirement (personal communication). Indeed, randomised clinical trials were a major component of the work of Austin Bradford Hill,<sup>5</sup> who began his employment in Greenwood's department in 1923 and succeeded him as professor at the London School of Hygiene and Tropical Medicine and director of the Medical Research Council's Statistical Unit. It is of passing interest that Hill introduced much of the nomenclature of clinical trials in opposition to that of Almroth Wright, an influential clinician adversary of Greenwood,<sup>6</sup> although Wright had done controlled clinical trials using alternate allocation to treatment comparison groups in Africans with pneumonia.<sup>7</sup>

Early in his career, Greenwood<sup>8</sup> was involved in plague investigations in India. Although his writing on these investigations appears to be limited to epidemiological aspects, he surely would have been aware of the clinical trial work reported by the Advisory Committee on Plague Investigations in India,<sup>9</sup> which involved alternation in treatment assignment. In general, there can be little doubt that Greenwood was aware of methodological developments in clinical trials but perhaps chose to leave them to the next generation of researchers.

It is therefore somewhat surprising to read in Hogben's<sup>10</sup> obituary of Greenwood of 'Greenwood's pioneer work on large-scale trials to assess the efficacy of prophylactic and therapeutic measures'. The statement is made in the context of Greenwood's<sup>11</sup> contribution to persuading the medical profession to adopt the statistical methods

of Karl Pearson (with no mention of those of Fisher); but Hogben's words require explanation because they are quite precise and he wrote not just as a friend of Greenwood's but also as a professor of medical statistics.

In their book *Statistics in Medical Research: Developments in Clinical Trials*, Gehan and Lemak<sup>12</sup> remark:

Many students today probably think of Fisher as the statistician who first proposed randomisation as a procedure for unbiased assignment of treatments. In fact, Greenwood and Yule (1915) had discussed random allocation earlier in relation to trials of anti-typhoid and anticholera vaccines, but the method had not been used in any of the series they described. 'The inoculated men volunteered, they were not selected at random.' (p. 81)

With respect to this comment, we believe that Greenwood and Yule were probably thinking about random sampling of those *already inoculated*, not random allocation to treatment comparison groups of those *to be inoculated*. If so, they cannot be said to have made clear the importance of random allocation to treatment comparison groups.

In a more general comment, Chick et al.,<sup>13</sup> in their history of the Lister Institute, describe Greenwood's department of statistics as, although ephemeral, 'of great significance'. From 1910, they wrote:

... many of the errors that beset scientists too ready to draw conclusions from inadequate or unreliable data were uncovered by Greenwood. Together with the distinguished statistician George Udny Yule, who was an honorary consultant to the Institute, he [Greenwood] did much to set the standards for assessing the value of prophylaxis or treatment of disease.

Some of the salient issues were presented in Greenwood's<sup>11</sup> article published in *The Lancet*, entitled 'Is the statistical method of any value in medical research?' However, in neither this paper, nor in Greenwood and Yule,<sup>14</sup> is there any reference to experimental design or alternate or random assignment of participants to treatment comparison groups.

Finally, one indication that Greenwood<sup>15</sup> was aware of the requirements of good experimental design is found in his book *Epidemics and Crowd Diseases*, in which he writes as follows (chapter VI, The artificial immunization of man, p. 79):

What are the necessary and sufficient conditions for believing that an immunizing process diminishes the

risk either of taking a disease if exposed to risk or of dying of that disease if it has been contracted, below the average measure of such risk run by persons not artificially immunised.

The solution to this apparently simple problem is beset with difficulties of two kinds, material and formal. In real life the material differences are almost insuperable, as we shall see; for the moment I postpone them, and suppose that the groups we have to compare are alike in all respects save two: they are alike in age constitution, sex constitution, race, social class, in all environmental circumstances; they differ only in respect of having been or not having been immunized, and, in the character we desire to measure, viz. their group reaction in the face of the disease. On these assumptions our difficulties are only formal or analytical, viz. how the alleged advantage is to be measured.

## Greenwood's involvement in clinical trials

The apparent misunderstandings of Greenwood's role in clinical trials motivate an examination of his involvement in these studies. This occurred in two separate areas of medical research – nutrition and the common cold.

### Nutrition trials

Greenwood studied several aspects of human nutrition in his career, beginning in 1918 with a report on the diet of munitions workers, which was published in the *Medical Research Council Special Report Series*. During the years 1920–1930, there was increasing research interest in malnutrition,<sup>16–19</sup> but there was also increasing tension between the Medical Research Council and the Ministry of Health over its study (in Glossop, Ipswich, London and elsewhere), which also involved committees set up by consultative bodies, such as the Economic Advisory Council. Eventually, in 1931, the Ministry responded by setting up its own Advisory Committee on Nutrition. This was chaired by Greenwood<sup>20</sup> (it was known as 'The Greenwood Committee') and included Frederick Gowland Hopkins, Edward Cathcart and Edward Mellanby (who used alternate allocation to assess the effects of vitamin supplementation in preventing puerperal sepsis). Unfortunately, the committee was not a fruitful venture for Greenwood, who came into conflict with the British Medical Association and eventually resigned in July 1934 (for further details, see Greenwood<sup>2</sup> and Oddy<sup>21</sup>).

It seems very likely that Greenwood would have been familiar with controlled nutritional experiments

conducted during the 1920s and 1930s,<sup>18,19,22</sup> and certainly the nutritional experiments in schools conducted by the Ministry of Health in the early to mid-1940s investigating the effects of multivitamin and specific dietary supplements.

The four published papers from these trials<sup>23–26</sup> do not name Greenwood. The first mentions the three towns above, but is brief and states that ‘a full report of the test has been prepared, but it is too lengthy for publication’, and acknowledges that many people assisted in the feeding tests and analysis, ‘but lack of space forbids individual acknowledgment’. The second paper reports dietary information from two later surveys (1943 and 1944) conducted in two north of England industrial towns by the Wartime Social Survey on behalf of the Ministry of Health. The third paper provides a review of the literature on the effects of vitamin supplements and provides further results from the two later surveys, with analysis by SH Qualye (Controller, Statistical Branch, Customs and Excise). The fourth paper assesses the vitamin C content of home-cooked vegetables gathered from three surveys.

Although Greenwood is not mentioned in these published papers, the records show that he was apparently involved in the analysis of the studies.<sup>27</sup> These trials were multicentre, double-blind, placebo-controlled, stratified by school class, and treatments were ‘randomly assigned by alternation’, with odd-numbered children in the experimental group and even-numbered in the control (it is not known how the children were numbered individually). At one point, it was suggested that children in each group be divided to receive an additional pint of milk or not (creating a factorial trial), but this was not implemented.

Greenwood would also have known about the multicentre trial of vitamin and mineral supplements conducted by Hilda Fowke in five orphanages in the north of England, the report of which states simply that the girls ‘were divided at random into two approximately equal groups’.<sup>28</sup> Greenwood<sup>29</sup> and Fowke both attended the 18th scientific meeting of the Nutrition Society held at the London School of Hygiene and Tropical Medicine in February 1944, at which Greenwood presented a paper on the statistical validity of methods used in budgetary and dietary surveys and Fowke was the first discussant of his paper. However, neither of them made any mention of alternation or random allocation.

### Trial of patulin for the common cold

The origins of Hogben’s statement may lie in Greenwood’s other area of involvement in clinical

trials – assessment of the antibiotic patulin for treating common colds. Some small trials done in the armed forces using alternate allocation<sup>30–32</sup> suggested that the drug was worth rigorous investigation, and the government asked the Medical Research Council to conduct a trial to address the uncertainty about its worth. The Medical Research Council patulin trial was the first properly controlled multicentre clinical trial done under the aegis of the Medical Research Council.<sup>33,34</sup> It dealt with the danger of allocation bias by rotation to one of four comparison groups (two receiving patulin and two placebo); measurement bias by using a placebo; and statistical imprecision and generalisability by its multicentre design, involving as it did recruitment from government departments, several industries and schools. The Medical Research Council’s recognition of the importance of the trial was signalled by its appointment of Harold Himsworth (who was later to become the Council’s first secretary) as the chair of its steering committee.

Once again the allocation of treatment or placebo was by rotation (alternation), which was explained by an important statement in the published report:

The ease with which the effects of a therapeutic agent on a particular illness can be determined is primarily dependent upon the precision with which that condition can be defined. Such definition of the common cold presents considerable difficulties. [The second of these difficulties was that] “the duration of colds is not constant but varies, not only between different epidemics but also between different patients in the same epidemic, making the assessment of treatment difficult.” [The solution was to] “include a satisfactory series of control cases. This can only be done by ensuring that alternate cases at each centre are given a spurious treatment, which, to the recipient, is indistinguishable from the genuine treatment.”<sup>35</sup>

As Greenwood was a member of the Medical Research Council Patulin Clinical Trials Committee<sup>36</sup> and was named in the published Report<sup>35</sup> (Hill was not), he was presumably responsible for some of these important features of the study. In addition, he was the author of a statistical note appended to an earlier trial of patulin.<sup>37</sup> However, while discussing the requirement of comparable groups differing only by treatment allocation, this note is concerned primarily with the nature of a test of significance.

### Alternation and random allocation

Allocation of treatments in a clinical trial by alternation is not now recommended as a means to eliminate

bias in the creation of comparison groups. Armitage<sup>38</sup> (pp. 182–183) wrote that it is likely to be seriously misleading only if the ordering presents some unrecognised systematic cyclical variation, but also that if the basis for the allocation schedule becomes known, those responsible for allocating participants to comparison groups may be influenced by this knowledge and thereby introduce bias. Armitage advocated that such systematic allocation is ‘best avoided in favour of strictly random methods’.

Similarly, Piantadosi<sup>39</sup> wrote: ‘Although non-random but unbiased treatment assignment schemes (e.g. alternating assignments) can serve the purpose of eliminating bias, they are subject to discovery by investigators and . . . could permit a systematic difference in the treatment groups (bias) . . .’ He concluded that random schemes ‘are more convincing ways of eliminating biased assignments’ (pp. 203–204).

In common with others at the time, however, Greenwood considered that alternation was sufficient. As far as we have been able to discover, Greenwood never mentioned random allocation in print. Like others at the time, including Hill,<sup>40</sup> alternation was reported as if it was random allocation. This is illustrated by our quotation from the Ministry of Health<sup>27</sup> trial, which refers to participants being ‘randomly assigned by alternation’.

The key methodological advance was made not because of a move from alternation to random allocation, but by concealing successfully whichever allocation schedule was used from those involved in decisions about treatment allocation.<sup>40</sup> Prevention of foreknowledge of upcoming allocations became the key to unbiased allocation. Successful concealment of the allocation schedule in the Medical Research Council’s iconic trial of streptomycin for tuberculous pneumonia<sup>41</sup> was its key methodological contribution.<sup>5,40,42</sup>

### Concluding reflections on Greenwood’s involvement in clinical trials

In the light of the limited evidence of Greenwood’s involvement in clinical trials, why did his friend Lancelot Hogben, in his obituary of Greenwood, refer to ‘Greenwood’s pioneer work on large-scale trials to assess the efficacy of prophylactic and therapeutic measures’?<sup>10</sup>

In assessing Hogben’s comment, it is helpful to consider Hogben’s own view of trials. Although these dated from several years after Greenwood’s death, Hogben<sup>43–46</sup> wrote four papers on prophylactic and therapeutic trials. While these papers refer to Greenwood and Yule,<sup>14</sup> Greenwood’s<sup>15</sup> book ‘*Epidemics and Crowd Diseases*’ and Hill’s paper

which clearly sets out the basic principles of clinical trial design, including randomisation of treatments,<sup>47</sup> Hogben does not mention random allocation, and it seems that he was more concerned with the underlying rationale of theoretical statistics.<sup>48</sup> Quoting Hogben’s colleague Raymond Wrighton, Wells<sup>48</sup> suggests that

Hogben’s final view regarding theoretical statistics was that the statistical methods introduced by RA Fisher and his followers in the 1930s were lacking in mathematical validity, and that later developments (the Neyman-Pearson theory; Wald’s decision theory) had succeeded neither in providing a satisfactory rationale nor in offering an acceptable alternative. He felt that a generation of biologists had been seriously misled into a false view of the nature of experimental enquiry and that, as far as medicine was concerned, mathematical innovations had not materially changed matters since Claude Bernard fulminated against the use of averages.<sup>49</sup> Probability considerations, he believed, rightly enter biology when, as in genetics, they can be seen to relate to events objectively determinable as random, but not when invoked as a cloak for ignorance of underlying causal relationships.

Hogben’s characterisation of Greenwood can be judged correct in the sense that Greenwood was involved in a few large-scale trials to assess the efficacy of prophylactic and therapeutic measures. However, Greenwood’s involvement does not appear to have been central in these studies and he did not make the leap to random allocation of treatment. That leap is more rightly associated with his friend and colleague for around 25 years, Austin Bradford Hill,<sup>47,50</sup> a medical statistician but not a ‘medical man’, a term used by Greenwood to describe himself. For more detailed accounts of the progression from alternation to random allocation and the roles of Fisher, Greenwood and Hill, see Armitage<sup>51</sup> and Chalmers.<sup>40,42</sup>

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