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In 1989 Joan Austoker and I set out our goal in *Historical Perspectives of the Role of the MRC* 'to discuss the role of the Medical Research Council in shaping a national system of medical research in Britain'.[1] We noted that the only general history of the Medical Research Council (MRC) at that time was authored by an MRC staff member, A Landsborough Thomson, who had produced two volumes in 1973 and 1975.[2,3] Our book remains the only attempt apart from Landsborough Thomson's to construct a general overview of the work of the MRC, but over the past two decades, there has been considerable interest in the history of the MRC, particularly in relation to the lead-up to its world-famous streptomycin trial for pulmonary tuberculosis, which it reported in 1948.[4] This commentary provides a review of the information that has accumulated since 1989 – which is scattered in monographs, articles and unpublished theses – relating to the pre-history of this important trial.

## Walter Morley Fletcher and 'pure science'

The Medical Research Committee was set up in 1913 under the 1911 National Insurance Act. In 1914, Walter Morley Fletcher (1873–1933) was appointed Secretary of the Committee and from 1920, the Medical Research Council (MRC), a post he held until his death in 1933. Our 1989 history argued that Fletcher played a crucial role in determining the direction of medical research in Britain. Joan Austoker stated in her chapter on Fletcher that 'The development and expansion of the medical sciences in Britain was, to a considerable extent, dominated by a single individual [Fletcher]'.[5] Specifically, Fletcher prioritized basic biomedical science and laboratory-based research over clinical research. In his chapter in our volume, David Cantor also pointed out that Fletcher tended to differentiate 'science' from 'clinical practice' and believed that medical research should not be in the hands of clinicians. Cantor cited Lord Moynihan, President of the Royal College of Surgeons, who lamented that only one of the 12 members of the MRC 'possesses any adequate knowledge of scientific clinical surgery; one only practises medicine, and his very able mind sways rather to the laboratory than to the wards'.[6] In his chapter on clinical medicine, Christopher Booth, too, wrote that Moynihan attacked the MRC 'for its concern with mice rather than men'[7] and that the latter complained that the MRC was 'too aloof from the day-to-day practice of medicine'. Booth acknowledged that under Fletcher the MRC did set up a Clinical Committee in 1932 to oversee and provide grants for research projects carried out at medical schools around the country.[7] The Clinical Committee included the MRC's clinical members (Lord Dawson, President of the Royal College of Physicians, Edward Mellanby and Wilfred Trotter) with Thomas Lewis, who was based at University College Hospital London, as secretary. Trotter and Lewis were also members of the Therapeutic Trials Committee, which had been established the previous year specifically to test therapeutics, and is further discussed below. Nevertheless, Booth pointed to Fletcher's continued distrust of clinicians, claiming 'Fletcher … had little sympathy for fashionable practitioners, who to their financial advantage "hoodwinked" the public with such transient crazes as ultra-violet treatment, opsonic indices and superstitions such as "status lymphaticus"'.[7]

Subsequent researchers have endorsed the view that Fletcher thought medical research should be laboratory-based rather than ward-based. In his

2007 monograph, Martin Edwards wrote that Fletcher 'repeatedly affirmed his conviction that medicine and therapeutics could only progress through fundamental scientific research, frequently performed by non-clinical scientists rather than clinicians'.[8,9] Edwards noted that this trend was reinforced in 1920 when the Medical Research *Committee* was separated from the Ministry of Health, and became the Medical Research *Council*, which was responsible to the Privy Council. The way in which the new Council distinguished itself from the Ministry of Health was through its laboratory-based research, with the National Institute of Medical Research at the centre of its operations. The two bodies reached an agreement in 1924: the Ministry of Health was to be concerned with 'applied research' relating to clinical problems; the MRC would initiate and organize all new research in the basic biomedical sciences. Fletcher argued that 'progress in physiology, biochemistry, and pathology was essential to the development of clinical practice'.[8,9]

## The National Institute of Medical Research

In 1914 the Medical Research Committee had acquired premises for its research on the site of the Mount Vernon Hospital, in Hampstead, London. In 1920, this became the National Institute for Medical Research, which remained there until it moved to Mill Hill in 1950. While there was some discussion initially about establishing hospital beds for research purposes, this was quickly rejected in favour of the alternative of giving financial support to hospital units already in existence. As Booth has pointed out, the MRC supported the research of the Department of Clinical Research and Experimental Medicine at University College Hospital in London, and provided grants to other hospitals for research purposes.[7] The National Institute for Medical Research absorbed about one-third of the MRC budget. Those based at the new research centre included Henry Dale (biochemistry and pharmacology, and director of the new Institute), Almroth Wright (bacteriology), Leonard Hill (applied physiology) and John Brownlee (medical statistics).

Under Sir Henry Dale's leadership from 1924, the National Institute for Medical Research became a centre for international biological standardization of therapeutic drugs, under the auspices of the League of Nations. The work of the centre enabled new therapies to be seen to be based on physiological principles. As Benjamin Toth noted in his 1998 PhD thesis, 'The proof of newer therapies did not rely on empirical clinical testing, but on the demonstration that they behaved according to scientific laws and principles, which could be established under a microscope, in a test-tube, or in a laboratory animal. Clinical trials on patients were therefore of secondary importance, as well as being difficult to organise.'[10] Drugs were tested in animals and their effects and dosages calibrated. This began during World War I, when German supplies of salvarsan for syphilis were disrupted owing to war conditions.[11,12] The MRC was responsible for testing the quality of British-manufactured salvarsan and neosalvarsan, as well as other sera and anti-toxins which had been imported before the war. The National Institute for Medical Research went on to play a key role in the biological standardization of insulin from 1922, as discussed by Jonathan Liebenau in our 1989 volume.[13] The Therapeutic Substances Act of 1925 gave the MRC statutory responsibility for the preparation and custody of British national standards for certain therapeutic drugs. Internationally, the task of establishing standards was shared by the State Serum Institute in Copenhagen and the National Institute for Medical Research, and both entered into a formal contract with the League of Nations for this purpose.

The National Institute for Medical Research included a Statistical Unit, set up in 1914 under John Brownlee. As Keith Williams concluded in his 2005 PhD thesis, the MRC 'did invoke the use of statistics to a degree, but mostly for their public health, epidemiology and vaccination studies'.[11] In 1920 the Industrial Health Statistics Committee was established under the MRC's Industrial Fatigue Research Board (set up in 1918). Austin Bradford Hill, Leonard Hill's son, received a grant from this Committee in 1923 to collect information on mortality related to migration from rural to industrial areas. In 1925 the Industrial Health Statistics Committee was renamed the Statistics Committee, and Major Greenwood was appointed chairman. When

Brownlee died in 1927, the MRC amalgamated Brownlee's former Statistical Unit and the Statistics Committee chaired by Greenwood, who was now Professor of Epidemiology and Vital Statistics at the London School of Hygiene and Tropical Medicine. In 1945, Austin Bradford Hill succeeded Greenwood as chair at the London School of Hygiene and as head of the MRC Statistical Unit. Like Williams, Martin Edwards maintained that the Statistical Unit had little to do with clinical trials before the 1940s, pointing out that, 'The designs of the therapeutic trials conducted by MRC prior to the 1940s appear to have been influenced very little by statistical considerations'.[8,9] Bradford Hill himself later reflected that he and Greenwood had worked on correcting and improving reports the MRC planned to publish, implying that they had had little involvement at the planning stage. Edwards further pointed out that 'Greenwood's published output prior to the 1940s reveals more interest in epidemiology and statistical experiments on mouse populations than in any application of statistical methodology on therapeutic innovation'.[8,9]

## The origins of the MRC Therapeutic Trials Committee

In 1926 the MRC and the Department of Scientific and Industrial Research set up an *ad hoc* committee to report on the scope of work required for chemotherapy. In their joint report, they recommended more permanent facilities for conducting clinical trials of proposed new remedies. As a result, the MRC set up the Chemotherapy Committee in 1927, headed by Henry Dale. The Chemotherapy Committee was tasked with organizing the biological study or clinical testing of new drugs prepared at the National Institute for Medical Research. This was intended to promote co-operation between chemists, biologists, pathologists and clinicians in the production of new compounds, and their evaluation in preclinical and clinical research.[14] In 1929, for instance, the Chemotherapy Committee agreed to promote clinical trials of a concentrated pneumococcal serum that had been first described in America. With supplies from America and from Burroughs Wellcome in the UK, these trials were to take place at the Royal Infirmary in Edinburgh, at University College Hospital in London and in Glasgow (and later in Aberdeen).

This Chemotherapy Committee does not appear to have been particularly effectual, however. Two years later, following consultation with the Association of British Chemical Manufacturers, the MRC decided to establish more formal machinery for clinical trials; this was the Therapeutic Trials Committee. The impetus for its establishment appears to have come partly from the pharmaceutical industry itself, which had approached the MRC several times in the decade prior to the Committee's establishment, particularly through Francis Carr, who developed synthetic drugs at Burroughs Wellcome, Boots and British Drug Houses.[11] The industry was keen to secure an authoritative system of clinical testing and 'approval' of new drugs, including synthetics. The Therapeutic Trials Committee also seems to have resulted from nationalistic concerns, namely the desire to test British-made drugs, particularly in the wake of the economic crisis in the early 1930s.[11,12] Finally, the new Committee must be seen in the light of the growing public demand for the regulation of drugs, which had led to the passage of the Therapeutic Substances Act in 1925. *The Times* reported in 1931 that the MRC had announced a new Therapeutic Trials Committee, 'to advise and assist them in arranging for properly controlled trials of new products that seem likely on experimental grounds to have value in the treatment of diseases'.[11]

The new Committee looked impressive. The chairman was Professor Thomas Renton Elliott, of University College Hospital, whose department at the hospital had long been supported by the MRC.[7] Henry Dale, director of the National Institute for Medical Research, represented the Chemotherapy Committee and provided a link between the MRC and the pharmaceutical industry, having worked at Burroughs Wellcome and on the standardization of salvarsan and other drugs. Also appointed to the new committee was Sir Thomas Lewis, an eminent cardiologist at University College Hospital who had enjoyed a long association with the MRC. Lewis was first appointed to its staff in 1916 and became secretary to the MRC's Clinical Committee in 1932.[7] Other members included Professor Francis Fraser (later Sir Francis) of the Clinical Laboratories at St Bartholomew's Hospital, London, Professor

Arthur Ellis of the London Hospital, Dr John Ryle (later Sir John), Regius Professor of Physic at Cambridge and subsequently Professor of Social Medicine at Oxford, Sir John Thomson-Walker, senior urologist at Kings College Hospital and surgeon at St Peters Hospital, London, Sir Edward Farquhar Buzzard, a neurologist and successor to William Osler as Regius Professor of Medicine at Oxford, Professor David Wilkie (later Sir David), a general surgeon and urologist in Edinburgh, Sir John Parsons CBE, a senior ophthalmologist, and Wilfred Trotter, a distinguished thyroid surgeon at University College Hospital (and also a member of the MRC's 1932 Clinical Committee). Edward Mellanby, who was to become secretary of the MRC in 1933, also joined the Therapeutic Trials Committee, as did Thomas Watts Eden, one of the foremost gynaecologists in London who had helped to found the British College of Obstetricians and Gynaecologists in 1929, and was President of the Royal Society in 1930.[11] The *British Medical Journal* declared that the new Therapeutic Trials Committee was a strong one, 'including individuals of the highest reputes, and both medicine and pharmacy ought to benefit by its existence'.[11]

## The Therapeutic Trials Committee and the trial of serum treatment of pneumonia

The Therapeutic Trials Committee inherited from the Chemotherapy Committee a study of the use of serum for lobar pneumonia which had been initiated in 1931.[15] Discussion about the design of this study had existed since at least 1929, when Francis Green, who was appointed secretary of the new Committee, had written to Professor Murray Lyon in Edinburgh, who had proposed that serum be given 'to every alternate case'.[8,9] There had already been a remarkable series of alternate allocation trials of serum for pneumonia during the previous two decades in the United States.[16] Furthermore, another such trial was done during the winter of 1931–1932 at St Bartholomew's Hospital and a number of London County Council hospitals.[17] However, the Committee paid little attention to these methodologically important precedents in overseeing its own trial.

The MRC study had commenced in four centres around the country – London, Edinburgh, Aberdeen and Glasgow (though the Glasgow element remained independent of the MRC). The Committee called a meeting to 'draw up a standardised scheme of investigation'. In his history of therapeutic trials, Edwards analysed how the Committee envisaged controlling the trial and concluded that it 'rendered the serum trial "controlled" by regulating the activities of individual clinicians, co-ordinating their activities and unifying the means of public presentation of their results'.[8,9]

The Committee did specify that future researchers should use adequate controls in trials and that they should alternate patients to treatment and control groups wherever possible.[18] But, as Edwards showed, the investigators at each centre used different criteria for deciding which patients to recruit to the study and for allocating patients to control or treatment groups. Moreover, they adopted different treatment regimens and different measures of treatment outcome.[8,9] Edwards maintained that the results of the Edinburgh study were worthless: 'patients had not been allocated to receive serum, or to function as controls, alternately. Instead, patients with a poorer prognosis – those aged over sixty, and those moribund on admission to hospital – had frequently been allocated to the control group for fear of wasting precious serum on them. The control and treatment groups were therefore not comparable, and the results impossible to interpret.'[8,9]

Toth argued that when the Therapeutic Trials Committee sent instructions to the groups experimenting with serum for lobar pneumonia, the aim was primarily to assert some form of central control over researchers, to make the trials appear more scientific and reliable.[10] Edwards came to a similar conclusion, noting that, upon inheriting the study and its attendant embarrassments, the Committee tried to bring idiosyncratic or maverick investigators into line, and hence contain them within the rhetoric of its own 'properly controlled clinical tests'.[8,9] But the Committee's attempts to enforce some sort of uniformity apparently failed.

## What did the MRC Therapeutic Trials Committee achieve?

The Therapeutic Trials Committee met only 10 times between 1931 and 1939. During that time it


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considered 67 applications for clinical trials, of which it supported 51.[10,11] In his 500-page, two-volume history of the MRC, Landsborough Thomson devoted a mere five pages to 'Clinical evaluation of remedies',[3] yet declared that the Therapeutic Trials Committee had 'set a standard for the methods of trial'.[3] Similarly, Joan Austoker and I wrote of this Committee: 'The success of its ventures had made the clinical trial of new products respectable in the eyes of the pharmaceutical industry'.[14] More recent researchers are not so convinced, and a more detailed study of the operations of the Committee and the clinical trials it oversaw supports their assessment.

The process followed by the Committee was that it sent drugs to doctors for simultaneous 'trials' at different centres around the country, where, as Desirée Cox-Maksimov noted in her 1997 PhD thesis, 'each physician tested the therapy in his own idiosyncratic way'.[18] Cox-Maksimov cited the views of one of the Committee's members, John Ryle, 'who explained that whether the experiment was controlled or not depended on the physician who could compare cases and judge therapeutic efficacy … by control he meant that they should conduct a close study of the case. It was not cases that made a controlled experiment, but the care and scrutiny with which those cases were examined.'[18]

In his PhD on the history of clinical trials in British medicine, Benjamin Toth provided the following assessment of the Therapeutic Trials Committee:

> *During its existence* [the Therapeutic Trials Committee] *did not organise one rigorous comparative clinical trial, despite* prima facie *evidence of the problems of not doing so. None of the factors that were later to be recognised as vital to producing meaningful evaluations of therapies were advocated by the TTC. By standards soon to be regarded as the norm, there was little attempt to frame research questions, little attempt to select patients, no random allocation, little systematic recording of results, and almost no attempt to measure results. In the case of multi-centre studies, it was usual for Green* [the Committee's secretary] *to ask the clinicians to work to a standard schedule, but there was no enforcement of a schedule.*[10]

Toth attempted to explain why this was the case. He believed that the MRC saw the laboratory as the more important site for experimentation, with clinical trials of secondary importance. He thought the Committee members conceptualized the clinical trial primarily as a test on a series of cases, selected because they were likely to benefit from the drug. Furthermore, Toth thought that an overriding goal of the Committee was to compare British drugs with foreign products.

Similarly, Martin Edwards argued that:

> *Examination of the trials published by the TTC until its winding-up at the start of the Second World War rather belies any suggestion that a unified methodology was in place. A minority of studies employed untreated or placebo-treated comparison subjects, sometimes referred to as 'controls'. Subjects in these studies were allocated to receive active or inactive therapy either by alternation or at the discretion of the investigator, who frequently allotted most of his patients to receive the new drug, reserving just a few as 'controls'. Many more trials were simply as reports, describing the effects of drug therapy on any number of patients from one, to a handful, or as series of a hundred or more. Most authors simply described these case reports in some narrative detail; others presented additional animal experiments or employed detailed quantification and tabulation of findings such as blood pressure, blood chemistry, weight, temperature, signs and symptoms.*[8,9]

Edwards went on to explain that many of the investigators cherished their autonomy and disliked being dictated to. As the Therapeutic Trials Committee had no clinical facilities of its own, it relied on the goodwill of individual investigators to test products. He maintained that, as a result, the Committee failed to introduce any methodological innovation during its existence, in spite of the claim by the MRC that the Committee was efficient, and uniquely British. This, Edwards argued, was a rhetorical device to help establish the authority of the MRC in the arena of therapeutic evaluation. Thus, he concluded, 'the MRC's attempts to present the output of the TTC as representative of a unified therapeutic trial methodology were essentially rhetorical'.[8,9]

Keith Williams, likewise, found little evidence of planning for the trials done under the auspices of the Therapeutic Trials Committee. Rather, he concluded, 'the TTC arranged for as many

patients to be treated as could be mustered'.[11] He also concluded that, 'Apart from vaccine and toxoid studies, the TTC studies were generally small and often inconclusive, except where even a small study showed some safety problems'.[11]

The Committee fulfilled its nationalistic goal, prioritizing British drugs over foreign drugs for evaluation, until it undertook research into prontosil, the first of the new sulphonamides, which had been developed at the Bayer Laboratories in Germany. In 1936, research supported by the Committee and carried out by Leonard Colebrook at Queen Charlotte's Hospital used historical controls to demonstrate a dramatic effect of sulphonamides on puerperal sepsis,[19–22] and a later study showed beneficial effects on meningococcal meningitis.[23] Less dramatic effects of these new drugs were investigated under the aegis of the Committee in four alternate allocation trials done by Snodgrass and Anderson at Ruchill Hospital in Glasgow.[24–27] However, the reports of a number of other studies which had used alternate allocation during the life of the Committee make no mention of MRC support (see, for example, Ellison,[28] Sutherland,[29] Moir,[30] Peters and Cullum,[31] Theobald,[32] Evans and Gaisford,[33] Johnstone,[34] Peters,[35] Benn,[36] and Price[37]), although one did.[38]

## The initiation of well-designed, multicentre controlled trials under the aegis of the MRC

Despite my and Joan Austoker's claim in 1989 that the MRC's Therapeutic Trials Committee frequently sought expert opinion from the Statistical Committee, and in particular from Greenwood and Bradford Hill,[14] subsequent researchers have found little evidence of such interaction. It is true that Bradford Hill had been invited by the Therapeutic Trials Committee to comment on a draft report of the 1934 trial of serum for the treatment of lobar pneumonia,[15] and probably contributed the part of the text of the paper discussing methods.[39] In a critical unpublished internal memorandum before the report of the trial was published Bradford Hill argued that greater effort should be taken 'that the division of cases really did ensure a random selection'.[12] Unfortunately that memo, viewed by Joan Austoker at the MRC archives in the 1980s, has been lost. However, Edwards reports that Green deemed Bradford Hill's memo so damning that it was 'to be kept, not only from public scrutiny, but even from the investigators themselves'.[8,9] Iain Chalmers has concluded, 'The limitations of this study – with its relatively small numbers and mixture of ways of generating control groups – are likely to have been very important in leading Bradford Hill to go on to design large trials using concealed allocation schedules'.[39]

In 1937, Austin Bradford Hill accepted an invitation from the editor of *The Lancet* to write a series of articles on principles of medical statistics, including the principles of clinical trial design. The articles were a great success, and were published as a book later that year.[40] In the book Bradford Hill stated that alternate allocation was 'often satisfactory', but Chalmers suspects that he did not really believe that it provided adequate assurance against allocation bias. Chalmers noted that 'in spite of his insistence that alternate allocation must be strictly applied, from the first edition of his book onwards, Bradford Hill did not comment on the fact that the trials of 159 and 163 patients in the serum and control groups [in the 1934 trial] are clearly incompatible with strict alternate allocation'.[39]

Bradford Hill was eventually appointed to the Therapeutic Trials Committee the year after the publication of his book, and he attended his first and only meeting in 1939. But he does not appear to have been involved in the first strictly controlled multicentre clinical trial done by the MRC. This was organized by Philip D'Arcy Hart, the medical director of the MRC Tuberculosis Research Unit,[41] who was asked in 1943 to evaluate 'patulin', a proposed treatment for the common cold. D'Arcy Hart devised a system of 'strict rotation', allocating volunteers suffering from a cold into two groups receiving patulin and another two given a placebo, arguing that this method ensured 'an effectively random allocation of the subjects'. In the event, the trial failed to detect any benefit of patulin,[42] and Hart considered that this was why the study has tended to be overlooked in histories of the development of controlled trials. For example, Landsborough Thomson did not even mention the trial, nor did Austoker and I in our 1989 history. Chalmers and Clarke concluded, by contrast, that the '1944 patulin trial deserves wider

recognition as the first well controlled multi-centre clinical trial to have been conducted under the aegis of the MRC'.[43,44]

Bradford Hill only became involved in MRC controlled trials after World War II, first, in an evaluation of different whooping cough vaccines,[45,46] and then, with D'Arcy Hart and Marc Daniels, in an assessment of the effects of the antituberculous drug, streptomycin, which had been developed in the United States. Indeed, the successful organization of the patulin trial appears to have been one of the reasons that the American producers of streptomycin invited the MRC to evaluate it.[43] The MRC Streptomycin Committee was established in 1947 to oversee a 'rigorously planned investigation with concurrent controls', and the results of this study were published in the British Medical Journal in 1948.[4,47]

The details of the allocation schedule for the streptomycin trial were unknown to any of the investigators: they were contained in a set of sealed envelopes, each bearing on the outside only the name of the hospital and a number. Bradford Hill and D'Arcy Hart were both aware of the importance of this precaution to prevent practitioner allocation bias. Chalmers argued, and Bradford Hill himself confirmed, that the decision to use random allocation based on random number tables (not for the first time – see Chalmers[48]) had nothing to do with the statistical models expounded by Ronald Fisher, for example, in his 1935 book *Design of Experiments*. Rather, it was as a precaution against allocation bias. Chalmers points out that 'Nowhere does Bradford Hill allude to randomisation as a way of ensuring the validity of tests of statistical significance. His concern continued to be the control of bias, hence his detailed references to ways of concealing allocation schedules from those involved in recruiting patients for clinical trials.'[49] 'The streptomycin trial deserves a place in the history of clinical trials because of this and other exceptionally clear statements about precautions to minimise allocation bias.'[49,50] Other historians have also questioned whether the MRC introduced random allocation as a result of an adoption of mathematical models. Toth, for instance, saw randomization as a continuation of the MRC's attempts to present itself as scientifically valid, to ensure its own centrality in clinical research, and as a means of controlling distribution of streptomycin in Britain.[10]

## Conclusions

From the start, the MRC prioritized research in 'pure' sciences and in the laboratory over clinical research, probably as a result of the preferences of its very powerful secretary, Walter Morley Fletcher. It became internationally renowned for its work on the biological standardization of therapeutic drugs, carried out at its research centre, the National Institute of Medical Research. Although the MRC funded clinical research, for instance, at the Department of Clinical Research and Experimental Medicine at University College Hospital London – and set up a Chemotherapy Committee (1927), a Therapeutic Trials Committee (1931) and a Clinical Committee (1932) – it did not view this research as central to its operations, and failed to introduce rigorous methodology into clinical research prior to World War II.

Although the MRC had its own Statistical Unit and Committee, statisticians played little part, if any, in designing clinical MRC clinical research prior to the mid-1940s. However, the poor performance of the research overseen by the Therapeutic Trials Committee in the 1930s, and specifically the 1934 trial of serum treatment for pneumonia, which medical statistician Bradford Hill was asked to comment on, probably played an important role in Hill's subsequent decision to introduce concealment of an allocation based on random numbers in the 1948 streptomycin trial. By 1950, clinical research had begun to accrue the same scientific status as research in the laboratory.

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