

# Why the MRC therapeutic trials committee did not introduce controlled clinical trials

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## Introduction

The failure of the Medical Research Council (MRC) Therapeutic Trials Committee (TTC) to introduce rigorously designed clinical trials of new medicines in the 1930s is now part of the standard account of the development of medical research in the UK.<sup>1,2</sup> Historically, this appears significant because the TTC was active in the period immediately before the clinical trials of patulin<sup>3,4</sup> and streptomycin<sup>5–7</sup> which were also sponsored by the MRC, and did establish the modern principles of clinical trial design.<sup>8,9</sup>

Viewed from this side of the streptomycin trial in particular, the designs for clinical trials endorsed by the TTC seem curiously antiquated, displaying little regard for the scientific framework necessary for fair trials – comparison, control and the conscious avoidance of bias – which had become well-known during the period of its operation.<sup>10</sup>

Some explanation for this seems necessary. The TTC included the most eminent biomedical researchers of the day. It was aware of the problems arising from poor trial design – the serum trial for lobar pneumonia, which the TTC inherited and managed, was problematic precisely because it lacked rigorous trial design.<sup>9,11</sup> Nor was the technique of random allocation particularly controversial – a few randomised trials had taken place under the auspices of the MRC well before World War II, for example, the trial of light therapy undertaken by Dora Colebrook in the late 1920s.<sup>12</sup>

Why then did the TTC not make use of the principles of clinical trial design, which were known to it, which would have increased the validity of its work, and were shortly to become the norm? A full explanation would need to include not just the change in the intellectual understanding of the design of clinical trials but also the organisational, social and political context in which clinical trials were conducted in the years 1920 to 1950. Such an undertaking is beyond the scope of the present work, but aspects

of such an explanation for the UK are available in the literature,<sup>2,11,13,14</sup> and for the USA in the work of Marks<sup>15</sup> and Meldrum.<sup>16</sup> This paper describes the origins and work of the TTC in detail in order to begin to understand its intentions, and the aspirations of its sponsoring body, the MRC, in the context of the clinical research landscape of the 1930s. Additional material and references are included in Toth.<sup>17</sup>

## Part 1: The origins of the Medical Research Council Therapeutic Trials Committee

Initially created ‘by historical accident’<sup>18</sup> as part of the National Insurance Act of 1911, the Medical Research Committee, later Council (MRC), rapidly outgrew its origins and was re-established as a corporate body in 1920 with a distinctive and independent role alongside the newly created Ministry of Health. Early research activities focusing on basic biomedical science and the physiological mechanisms of health and disease were highly successful, enabling the MRC to establish itself as an internationally significant biomedical research organisation by the 1920s.<sup>19,20</sup>

The MRC’s first scheme of research, approved in December 1913, did not include research into therapeutic drugs. This changed with the outbreak of World War I. At issue was the requirement for a British version of Salvarsan, a treatment for syphilis produced exclusively in Germany under patent. With British stocks limited to what was already in the country, the Board of Trade used emergency powers to suspend the patents and trademarks of Salvarsan and Neo-Salvarsan and grant production licenses to Burroughs Wellcome of England and Poulenc Frères of France (with May and Baker to be responsible for distribution in Britain). In granting licenses, the Board of Trade stipulated that a sample of each batch produced should be submitted to the MRC to its biological activity against syphilis bacteria.<sup>21</sup>

The work of assessing biological potency was overseen by Henry Dale, who had recently joined the MRC from the Wellcome Physiological Research Laboratories to head its Department of Biochemistry and Pharmacology, and had significant experience in testing and standardisation through his work on diphtheria anti-toxin.<sup>22</sup> The independence of the MRC was of central importance because of skepticism among the medical profession concerning the commercial interests of pharmaceutical companies. Dale played a vital role in the development of policy on therapeutic drugs. He was well connected to the network of companies that formed the British pharmaceutical sector. He led work on insulin standardisation and played a significant role in shaping the Therapeutic Substances Act 1925, which placed biological standardisation at the centre of the governance of therapeutic drugs.<sup>23</sup> The Act provided for a system of licensing 'to control the regulation of the manufacture, sale and the importation of vaccines, sera and other therapeutic substances...of which the purity or potency cannot be adequately tested by chemical means' (Therapeutic Substances Act 1925, 15 & 16 Geo. 5. Ch. 60). The National Institute for Medical Research (NIMR), the MRC's central laboratory facility based in London was designated in the Regulations as the guardian of biological standards. As a result, the MRC had statutory responsibility for the preparation and distribution of British national standards and for the testing and control of therapeutic substances.

Although it necessarily remained independent of commercial interests, the MRC provided support for the emerging UK pharmaceutical industry where it could, as part of expanded state support for the chemical industry after World War I.<sup>24</sup> Standardisation provided a means for protecting the interests of the nascent British pharmaceutical industry as it tried to come to terms with the efficiency and innovation of the German pharmaceutical industry. Significant increases in the efficiency of the production of insulin were made at the NIMR during the period in which the MRC held the patent.<sup>25</sup> Following the evident success of cooperation between academia and industry in Germany in the production of Salvarsan,<sup>26</sup> funds were made available to support cooperation between a university and industry to study the bactericidal activity of several compounds.<sup>20</sup> The MRC also supported what would now be called translational research, based on a network of clinical research centres associated with the NIMR. Research activities in the 1920s financially supported by the MRC expanded to include cerebrospinal fever, influenza, pneumonia, rheumatic fever, venereal disease, child life problems, growth

disorders, accessory food factors, disorders of the cardiovascular system, biochemistry, chemotherapy, and status lymphaticus.<sup>2</sup>

Owing to the reluctance of the medical profession to engage with commercial interests, pharmaceutical companies faced a particular difficulty in finding doctors willing to undertake clinical trials of novel biologically active substances. The Association of British Chemical Manufacturers (ABCM), formed in 1916, sought guidance from the MRC on how to overcome the problem in 1922,<sup>2</sup> but it was not until 1926 that the MRC committed to a systematic attempt to promote the testing of promising chemicals and to coordinate the work of chemists and biologists. It did this through the creation of a joint exploratory committee of the MRC and the Department for Scientific and Industrial Research, with a view to increase the productivity of British pharmacology. Then, in 1927, the MRC established an internal Chemotherapy Committee to coordinate the activities of academic scientists and commercial organisations.

In forming the Chemotherapy Committee, the MRC intended to 'encourage cooperation between chemists, biologists and pathologists [in universities and the NIMR], and clinicians, in producing new compounds in their experimental trials, and in the observations of their effects on human disease'.<sup>27</sup> It was anticipated that the Committee would not organise trials itself but that a further specific body would be needed to organise the practical arrangements for clinical trials.

The majority of the Chemotherapy Committee's work consisted of arranging grants to chemists and pharmacologists in universities to enable them to employ research assistants. In terms of producing new substances for clinical trial, the approach appears to have had little impact. At the fifth meeting of the Chemotherapy Committee on 13 November 1928, the minutes record:

*9a 'Dr Dale stated that the biological workers were somewhat restless because the chemists were not providing them with nearly as many compounds to test as they had hoped for. Dr Keilin's department had had very little time occupied; and had been turning its energies in other directions. Dr Scott Macfie had tested a few compounds received from Prof. Robinson and elsewhere, and had then spent his activities in testing substances received from outside sources, not through the committee [including] May & Baker and there was some doubt as to whether these results would be available to the committee at all' (MRC Archives held at the National Archive Kew. File FD1 7205 Chemotherapy Committee minutes).*

The focus of the Chemotherapy Committee had been on universities but this changed after its sixth meeting on 18 December 1928. At that meeting, Henry Dale reported that, following an interview with Dr Ewins, who had worked with Dale at both the WPRL and the NIMR and was now chief chemist at May & Baker, '*May & Baker were now ready to give the committee, in confidence, a complete account of their research programme on chemotherapy*' (FD1 7205 Chemotherapy Committee Minute Book. Minutes of 6th meeting, Item (3) 18 December 1928). Given the lack of progress by in-house chemists at NIMR and universities, and the willingness of a leading pharmaceutical company to engage with the Chemotherapy Committee, the time appeared ripe for more sustained engagement between the MRC and the British pharmaceutical industry, thanks to the network of trusted connections built up by Dale, who had successfully moved from university to industry and back again.<sup>25</sup>

The immediate events which led to the creation of the TTC began towards the end of the 1920s, when the MRC entered into discussion with the Association of British Chemical Manufacturers (ABCM) to resolve 'the problem of securing trustworthy clinical trials of products produced by manufacturers'. The MRC Annual Report for 1930–1931 sets out the case for closer cooperation between the MRC and the pharmaceutical industry:

*In these intermediate stages of work [between the discovery of a drug and its introduction to practice] it is often necessary for rapid and economic progress that close cooperation should be established between the original scientific investigators and those whose work lies in finding the adaptations needed for large scale production and use. The general social and political reasons that make it obviously desirable for State-supported work like that of the Council to be brought into the field of co-operative effort with British manufacturing firms are reinforced by the intimate relations of this kind of manufacturing to health and life within the country (MRC Report for 1930–1931).*

On 16 February 1931, a group of senior figures from the MRC met with representatives of seven leading drug manufacturers (Boots Pure Drug Company; British Drug Houses; Graesser Monsanto; Allen and Hanbury's; Burroughs Wellcome; Evans Sons; and May and Baker) and the ABCM. The account of the meeting (MRC Archives File FD1 2498) records that Mr Pratt of the ABCM felt that a committee was urgently needed. Dr Carr believed that doctors in Britain were afraid of publishing clinical trials in case they

should be suspected of pecuniary interest. Francis Fraser, Professor of Medicine at St. Bartholomew's Hospital, disagreed with this view. Thomas Elliott, Professor of Medicine at University College Hospital said that in any case such criticism could not be levelled at official trials conducted under the auspices of a committee of the MRC.

It was agreed that a committee should be formed to receive applications from manufacturers to have therapeutic substances subjected to clinical trial. On 6 March 1931, a memo was circulated within the MRC, and on 13 March the Council ratified the formation of a committee. A number of titles for the committee were suggested, including the Clinical Trials Committee, the Clinical Committee for New Remedies, the Therapeutic Committee and the Therapeutic Trials Committee, the last of which was selected by Henry Dale.

### *The work and membership of the TTC*

The TTC met at the headquarters of the MRC in London 10 times between July 1931 and March 1939. It worked by receiving written applications from companies through the ABCM to have therapeutic substances tested under the auspices of the MRC, using a standard pro-forma. Applications for clinical trial, and the decision of the TTC, are listed in Appendix 1. Most of the 67 applications were accepted; 13 applications (20%) were rejected outright, with some other applications deferred or provisionally accepted. During its existence, two sub-committees were formed, one concerned with the testing of sex hormones, the other with anti-syphilitic remedies.

The initial membership of the TTC consisted largely of MRC staff and clinicians with close connections to the MRC through committee membership or grant award (Table 1). Although, as Williams has shown, the TTC was created largely in response to pressure from the emerging UK pharmaceutical industry<sup>2</sup> this was evidently not a committee intended to include stakeholders, but one in which authority rested firmly with the MRC.

The composition of the TTC did not change significantly over its lifetime. Membership was broadened by the inclusion of the President of the Royal College of Physicians, Lord Dawson; Professor Edward Mellanby, Professor of Medicine in Sheffield joined from 1931. JA Gunn, Professor of Pharmacology at the University of Oxford, and Colonel LW Harrison, head of the venereal diseases department at St Thomas's Hospital, joined the Committee in 1937. The minutes of the MRC meeting of 18 March 1938 record that 'it was agreed to

**Table 1.** Initial membership of the MRC Therapeutic Trials Committee.

TR Elliott	Clinical Research Department, NIMR. Director of the Medical Professorial Unit at University College London. Member of Committee/Council 1920–1926, 1927–1931
EF Buzzard	Regius Professor of Medicine, University of Oxford
HH Dale	Director of NIMR
AWM Ellis	Director of Medical Professorial Unit, London Hospital
FR Fraser	Director of Medical Professorial Unit, St Bartholomew's Hospital
John Parsons	Member of Council, 1928–1932
John Ryle	Clinician. Later Professor of Social Medicine, University of Oxford. Member of Council 1935–1939
JW Thomson-Walker	Hunterian Professor of Surgery, Royal College of Surgeons
Wilfred Trotter	Member of Council 1929–1933
DPD Wilkie	Regius Professor of Surgery, University of Edinburgh. Member of Council 1933–1937. Later Director of MRC Unit for Clinical Research in Surgery
FHK Green	MRC Headquarters staff, Secretary to the Committee

Source: FD1 5319 TTC Minute book.

appoint Dr A Bradford Hill as an additional member of the [Therapeutic Trials] Committee, in view of the fact that some of the trials organised were on a statistical scale' (MRC Archive, Kew FD1 5319 TTC Minute book). Austin Bradford Hill was a member of the MRC Statistical Unit based at the London School of Hygiene and Tropical Medicine and would become head of the Unit in 1945. His invitation to join the TTC may well have been prompted by publication of his *Lancet* series and book *Principles of Medical Statistics*.<sup>28</sup> Hill was to become a leading proponent of randomised controlled trials in the late 1940s.

### *Changing relationships between the TTC and pharmaceutical companies*

The establishment of the TTC was a response to the pressure brought to bear on the MRC to support the emerging British pharmaceutical industry. The subsequent history of the TTC reflects a dynamic relationship between the two parties. At the outset, drug manufacturers needed the TTC because they lacked ready access to clinicians who might provide an endorsement of their products. For its part, the MRC saw an opportunity to engage productively with pharmaceutical manufacturers because the experience of the Chemotherapy Committee was that commercial companies were as active as university and government laboratories in developing new

chemicals that might be valuable therapeutic substances.<sup>17</sup>

Despite their mutual need for each other, each party had reason for caution. The MRC would not want to be seen as working too closely with commercial interests. For their part, the companies might have preferred to work independently of the MRC because in submitting applications they lost control over their chemicals: in making applications to the TTC they had to reveal the structure of their new chemicals (this was a risk because patent law had been amended in 1919 to exclude new chemicals);<sup>29</sup> had to allow selected independent MRC experts to test their products; and were encouraged to delay marketing activity until tests were complete). Finally, they had to agree to the principle that results, favourable or not, might be published in whatever manner and place the TTC saw fit.

In practice, the TTC worked hard where it could to support British pharmaceutical manufacturers. This is particularly evident when British interests were under threat from foreign companies. In 1931, Green tried to speed up the completion of the trial of Harmol, a treatment for angina, because an equivalent formulation was being tested for the German company Merck (correspondence between Green and Gunn, and Green and Evans in December 1931, in FD1 2516). The case of ergotoxine, discussed below, shows a similar concern to provide evidence about the effectiveness a British version of a drug.

In 1932, Green reported to the TTC that he had persuaded JF Wilkinson, a haematologist working in Manchester who was financially supported by the MRC, not to publish results showing the comparatively poor activity of British preparations of hog stomach in the treatment of pernicious anaemia (MRC Archives FD1 2499; confidential supplementary item dated 12 January 1932 circulated before the second meeting of the TTC). In 1935, Mellanby turned down a request for scientific cooperation between the MRC and the American Council on Pharmacy and Chemistry because of sensitivity towards British commercial interests.

The supportive approach towards British manufacturers is also seen in the TTC's approach to publishing results. Although the policy of the TTC stressed freedom to publish, it did not always publish the results of a trial when they were disappointing. Between 1931 and 1936, the trials of amylmetacresol, halarsol, nonylharmol hydrochloride and four other substances were not published because of poor results. However, trial results were rarely definite, and the companies may have regarded any publication as useful to their marketing. The TTC meeting of 11 February 1937 discussed the possibility of 'a special form of publication for those reports of any anti-syphilitic remedy which might be found to be satisfactory, but which did not represent any real advance', suggesting that members thought the TTC had set the threshold for publication too stringently.

Pharmaceutical companies became more commercially successful during the 1930s. Despite the economic depression, May and Baker's sales grew steadily, due in the main to sales of specialty drugs on behalf of its (by now) parent company Rhone-Poulenc. Glaxo's income from pharmaceuticals doubled between 1935–1936 and 1938–1939.<sup>17</sup> With growing economic success, drug companies became more assertive in their relations with the TTC. Initially, the TTC worked only with the ABCM. However, individual companies quickly bypassed the ABCM and dealt with the TTC directly. The application structure set up by Green began to break down after the first few meetings, making it difficult to determine whether or not substances had been formally considered. By 1938, companies were beginning to dictate terms to the TTC. In a submission to the TTC, Ciba proposed to make desoxycorticosterone acetate available to the committee but stated they could not be bound by the usual undertaking not to also issue it to researchers who were independent of the MRC.

Increasing success gave the companies greater freedom to test new medicines outside the framework provided by the TTC. M&B 693, or Dagenan, a

chemotherapeutic substance for streptococcal bacteria first synthesised at the Wandsworth research laboratory of May and Baker, was an immediate worldwide success. Lionel Whitby, Assistant Pathologist at the Bland Sutton Institute of Pathology, Middlesex Hospital, tested Dagenan with direct funding from May and Baker. However, at its last meeting, the TTC discussed a preliminary report on Dagenan, despite the fact that it had not received an application from May and Baker, nor had Whitby's research had any connection with the MRC.

## Part 2: Methodological aspects of the work of the MRC Therapeutic Trials Committee

The single most important observation about the clinical trial methodologies promoted by the TTC is that the Committee did not organise one rigorous comparative clinical trial, despite *prima facie* evidence of the problems of not doing so provided by the trial of serum treatment for lobar pneumonia, for which the TTC assumed responsibility in 1931.<sup>9,11,17,30</sup>

By standards soon to be regarded as the norm,<sup>9</sup> the TTC made little attempt to frame research questions, did not require patients to be allocated in an unbiased way to comparison groups and took little interest in clinical outcomes. By the second half of the 1930s, these issues had been discussed in Bradford Hill's *Lancet* articles and his book,<sup>28</sup> and had been used to evaluate the effectiveness of therapies, even by researchers who had reported to the TTC. For example, several well-designed and analysed trials of sulphonamides were done by Snodgrass and Anderson at the Ruchill Hospital in Glasgow during the late 1930s.<sup>31–35</sup> The first of these (Snodgrass and Anderson<sup>33</sup>) was reported by them as having been 'undertaken at the request of the Therapeutic Trials Committee of the Medical Research Council'. It employed alternate controls and included analyses using chi-square values and standard errors. However, none of the subsequent reports of the controlled trials done at Ruchill Hospital made mention of the TTC. One other clinical researcher made brief mention of the TTC: a paper by Banks<sup>36</sup> reported that sulphanilamide had been supplied by Evans (the manufacturer) 'through the Therapeutic Trials Committee of the Medical Research Council'.

The MRC would begin to adopt rigorous clinical trial methodologies in the 1940s, in the trials of patulin<sup>4</sup> and streptomycin.<sup>7</sup> But none of the factors shortly to be recognised as vital to producing meaningful evaluations of therapies were required by the TTC during the course of its existence.

Studies approved by the TTC followed three concepts of trial design. The first was conceptualised as an extension of a laboratory study, in which the patient was the *in vivo* substrate for physiological tests. The second was a case series, in which patients were selected because they were deemed likely to benefit from the drug or were relevant in relation to the likely effect of the drug. The third was some sort of comparative test, only required by the TTC when a British drug was being compared to a variant produced by a foreign pharmaceutical company. The three approaches were sometimes used exclusively, but more often in combination, as the following examples illustrate.

### The laboratory approach

Tests on the pure extracts of foxglove, digoxin and *digitalinum verum* were agreed at the first TTC meeting on 8 July 1931, to be carried out by EJ Wayne of the Department of Clinical Research, University College Hospital. Selected outpatients with auricular (atrial) fibrillation were admitted to hospital. The patient was rested in bed and ventricular contraction rates were measured using an electrocardiograph. A low dose of drug was then given intravenously in dilute alcohol solution, with regular measurement of the ventricular rate. Dosage was successively increased over several days. Control patients were given intravenous dilute alcohol only. In three patients, the effects of the active drug were compared with that of an American standardised preparation of the cardiac glycoside ouabain. In a further 13 cases, digoxin was given by mouth, and in four cases *digitalinum verum* was given by mouth. In these patients, the successive dose of digoxin was varied to stabilise the ventricular rate at between 60 and 70 beats per minute. Further tests were carried out to establish whether or not the drugs could be given by subcutaneous injection. The results showed that the glycosides slowed the ventricular rate, while the alcohol control did not. Digoxin, but not *digitalinum verum*, was effective when given orally. Digoxin reduced the excess filling of the veins in the neck in 8/10 patients with mild congestive heart failure.<sup>37</sup>

Wayne's glycoside study is characteristic of what can be termed the laboratory approach to drug testing. Reduced to its essentials, the method involved observation of the pharmacological activity of a drug in human experiments. This was an approach rooted in the MRCs orientation towards basic clinical science, allied here to the possibility of standardising dosage, determining the best means of administration, and comparing a British product to an American one.

### The case series approach

The most common method used to test drugs approved for testing by the TTC would now be called the case series approach. As the modern name suggests, the substance is given to a selected series of patients. Clinical impressions and other measurements are noted during the 'trial', and these are subsequently considered with a view to assessing the effects of the drug.

The first example below shows the case series approach in its purest form. In the second example, the experimenter added two statistical features: a control group to measure the rate of calcification of the wrist without calciferol; second, to reduce observer error, requiring one person to make all the observations. This method for reducing error is in direct opposition to the modern approach, which would reduce error by introducing several observers.

*First example: Harmol hydrochloride.* Harmol hydrochloride, a coronary artery dilator, was derived from an alkaloid in the seeds of *Peganum harmala* (Wild Rue). Boots Pure Drug Ltd. submitted it for testing to the first meeting of the TTC. The drug was supplied to doctors at the professorial units at The London Hospital and Guy's Hospital, and to Crighton Bramwell, Assistant Physician at the Manchester Royal Infirmary. By the second meeting of the TTC, a full report had been submitted. It showed that Harmol hydrochloride was effective in providing short-term relief from angina, but was an irritant when given subcutaneously and had produced renal colic in several patients. At the third meeting it was reported that Harmol hydrochloride had little value. In the interim, Boots had offered for test the lactate salt of Harmol, which they claimed to be more soluble. The committee agreed to accept the application from Boots to have the lactate salt tested, and expressed the hope that the original researchers would test this substance also.

The results with both were discussed at the fourth meeting. It was agreed that Harmol hydrochloride was ineffective. Evans and Campbell considered the lactate salt useless, but Bramwell considered it to be useful in 'early' cases of coronary disease. Seeking to publish the results, the committee deferred the decision, proposing a small conference, to be attended by Professor Gunn, who had worked with Boots in submitting the original application. The results were eventually published in a short report in the *Lancet* in July 1933.<sup>38</sup>

*Second example: Calciferol.* The second case series concerns the administration of calciferol as a treatment for rickets, which was carried out on behalf of the TTC by JC Spence, Assistant Physician at the

Royal Victoria Infirmary, Newcastle. The purpose of the study was to assess the therapeutic value of calciferol (pure vitamin D), as opposed to cod-liver oil and the International Standardised version of Vitamin D. The purpose was not therefore to confirm the antirachitic effect of vitamin D, but to test the value of its purified version against other versions in use.

Forty-four children with uncomplicated rickets were chosen for the study, which began in February 1932. Of these, 19 were rejected because they had received gifts of food or because their fathers had obtained employment. Of the remaining 25, three were chosen to act as standards for the optimum rate of cure. 'These were put under good hygienic conditions and given an adequate anti-rachitic diet containing milk, meat, liver, eggs, butter and vegetables, with one ounce of cod-liver oil daily in two cases, and four tablets of calciferol daily in the other'.<sup>39</sup> The remaining group of 22 was studied in various ways. The majority lived at home and received 3 cm<sup>3</sup> of an oily solution of calciferol. Eight patients went without treatment, partly to control for the known healing effects of sunlight. Two pairs of twins were observed, one of each pair acting as control. One boy, part of a family of five living in one room, confined to bed because he was unable to stand, was closely studied for 12 weeks. Serial radiographs of the wrist were used to measure the extent of calcification, with the radiographs of the optimally treated children being used as a standard. Results showed that calciferol 'had an active curative effect on the rickets, and that it produced healing at an optimum rate, acting as quickly and effectively as the usual therapeutic doses of cod liver oil or irradiated ergosterol'.<sup>39</sup>

The calciferol study extended the laboratory approach into the community. The boy confined to bed was regarded as a windfall because it allowed the researchers to closely monitor his conditions. The use of control patients gave the researchers some ability to account for the factors associated with the results, such as sunlight. The use of radiographs allowed a precise measurement of healing, in a manner analogous to a laboratory study.

### Comparative trials

The form of test used to determine the effectiveness of ergotoxine shows the approach to comparative trials favoured by the TTC – physiological research in a ward – and the complexities and negotiation associated with achieving that approach.

Ergotoxine ethanesulphonate, submitted by Burroughs Wellcome to the TTC in April 1931, was

considered to be the active ingredient of ergot, long used medically to intensify the contractions of a sluggish labour, and to stem haemorrhage after delivery by promoting the contraction of the uterus.<sup>40</sup> In accepting ergotoxine, the TTC was keen to compare its efficacy to that of ergotamine, which the Swiss–German drug company Sandoz had isolated from ergot in 1921 and was advertising (falsely) as the standard form of ergot approved by the Royal Pharmaceutical Society of Great Britain and the MRC.<sup>41</sup> Green wrote to Dr Aleck Bourne, a leading obstetrician at Queen Charlotte's Hospital, London, asking him if he would be willing to test ergotoxine because of his special experience with ergot derivatives. In referring to Bourne's earlier work, Green appeared to Bourne to be implying that he was looking for a physiological experiment to be carried out on women in labour. On this basis Bourne refused the request. He offered Green some hope, however, suggesting the possibility of clinical impressions rather than exact results:

*It will be possible however, for us to use the drug after delivery of the child for cases of post partum haemorrhage, but as you can understand, the results obtained by injecting it as an ordinary clinical treatment can give no exact records but only clinical impressions. Unless it is employed for a very large number of cases of haemorrhage the impressions obtained by sisters, house surgeons and those in attendance cannot be very satisfactory evidence. However, if you will send me a supply of ergotoxine ethanesulphonate, I will have it used and careful records kept (MRC Archives Kew FD1 2517).*

Green replied:

*I note that you propose using the drugs in cases of post partum haemorrhage. The committee were anxious that its therapeutic effect should be tested against that of ergotamine in order to decide finally whether these two alkaloids, being similar pharmacologically, have a parallel clinical action. I take it that cases of post partum haemorrhage treated with ergotamine could conveniently be used for comparison with those treated with ergotoxine, and would make effective controls for the experiment?*

In accepting ergotoxine for trial the TTC was seeking to provide a British company with a scientific testimonial to allow it to compete with foreign purifications of ergot such as Sandoz's ergotamine tartrate. The controls proposed by Green would achieve this. Vials of ergotoxine were supplied to Bourne in September. In November, Green wrote to

Bourne to enquire about his results, and received the following reply:

*I had a report yesterday, from those who have been using this drug at Queen Charlotte's Hospital, that it appears to produce the same clinical results as other preparations of ergotoxine. It must be clear to you that these remarks cannot have any scientific value whatever, as the observations have been chiefly made by the labour ward sisters and the house surgeons. No system of controls is possible, and in most cases the drug has been used in a routine way without, I fear, an intelligent appreciation that an investigation was being made. I explained, however, at the onset that I could not give you anything more than clinical impressions.*

The reply prompted Green to immediately contact Sir Henry Dale, fearing the disappointment of Burroughs Wellcome if this was all the TTC could provide. On Dale's advice he contacted Elliott at UCH, who in turn contacted his colleague Professor FJ Browne, Director of the Obstetric Unit funded by the Rockefeller Foundation. Elliott wrote:

*I regard the work as worth doing, in order to show that the British product of Burroughs Wellcome is as good as the foreign Sandoz. All that is needed is careful analysis... presumably in alternate cases, that are capable of ordinary clinical measurement. Would Moir care to undertake this? I fear there is no promise of an honorarium, but the work would bring your unit into closer association with the MRC.*

Browne arranged for his assistant Dr John Chassar Moir to carry out tests.<sup>42,43</sup> In accepting the task, Chassar Moir asserted that a clinical trial comparing ergotoxine with ergotamine would be impossible because

*in the puerperium, for example, the rate of involution varies in accordance with so many conditions, e.g. anaemia, state of health of the patient, history, degree of post partum haemorrhage, presence and degree of sepsis and so on, that it would be impossible, I think, to say to what extent any drug influences it.*

Given the confusing effects of patient characteristics and the difficulties of measuring involution, it was judged that the only reliable measure of the efficacy of ergot derivatives was a physiological one:

*Then again involution is very difficult to measure... the only useful test, to our minds, would be to put a bag inside the uterus, connect it with a manometer, inject*

*the drug and note the effect on uterine infection (corrected by Elliott to 'contraction').*

Chassar Moir carried out the experiment and published the results in the *BMJ* in 1932.<sup>44</sup> Even in this comparative trial, the emphasis was on physiological measurement. A bag was inserted into the uterus of each woman in the study during labour. To the bag was attached a tube which was connected to a recording apparatus. The bag was left in place several days after birth to make recordings. There was no indication that the women in the trial needed uterine stimulation, and no record of the clinical, as opposed to physiological, outcome of giving the drug.

### The controversy over Novostab

Controversy about Novostab, a treatment for syphilis, illustrates the mixture of scientific, organisational and political issues associated with British clinical trials in the 1930s. In 1938, the Birmingham venereologist EW Assinder published a comparative trial of three treatments for syphilis.<sup>45</sup> The substances involved were Novostab, a neo-arsphenamine compound produced by Boots Pure Drug Company, Mapharside from the American manufacturer Parke Davis and Company, and a German preparation of neosalvarsan. The results showed that neosalvarsan was the most effective treatment, as measured by its ability to clear spirochetes from the exudate of syphilitic sores.

Why did this small trial, published in a provincial journal, attract the attention of the Ministry of Health and the MRC? First, because of the way its findings were presented. Assinder concluded that 'I am sorry to say that the best manufacturers are German... there is no doubt, I think, that No. 3 should be used as routine'. Such a conclusion was unhelpful to UK commercial interests, and even unpatriotic in 1938, and was responsible for bringing an otherwise insignificant publication to the attention of the Ministry of Health. In addition, the way in which Assinder conducted the trial challenged the MRC's authority over drug testing. The MRC was responsible, through the provisions of the 1925 Therapeutic Substances Act, for the regulation of arsenic based anti-syphilitic drugs. The MRC's approach was to compare the potency of new arsenicals with standardised preparations of Salvarsan and Neosalvarsan using the trypanosome test in mice. In contrast, Assinder was undertaking a simple test on the blood of patients attending his VD clinic. If Assinder's results were correct, they also challenged the validity of the MRC's research on animals rather



than humans, and laboratory rather than clinical settings to test the effectiveness of drugs.

In March 1939, the Ministry of Health began to enquire at the MRC about Assinder's paper, an action that prompted Francis Green, the secretary to the TTC, to write to Sir Henry Dale, seeking his advice on how to respond to the Ministry. It turned out that Dale was aware of Assinder's research and had begun his own enquiries. Dale's response was to have batches of Novostab retested, first by Boots in December 1938, and then at NIMR in January 1939. The Boots report showed that Novostab had a slightly lower potency than Neo-salvarsan; the NIMR test showed it had a slightly greater potency. The results of the repeat test provided some reassurance. However, as Dale recognised, they did nothing to refute the charge that the results of laboratory tests on mice did not predict the efficacy of drugs in humans.

Dale took no further action until the Ministry of Health raised the matter with the MRC in March 1939. There was some reluctance on the part of the MRC to test Novostab in humans, but on 16 May 1939 a sub-committee of the TTC was asked to undertake a clinical trial of Novostab N77 in humans. The outbreak of World War II may have interrupted the trial, which does not seem to have been published and there are no records on file at the National Archive. In any case, the treatment for syphilis was transformed by the large-scale production of penicillin in the early 1940s.

### Part 3: Reflections on the fate of the TTC

Although never formally disbanded, meetings of the TTC lapsed at the start of World War II and it did not meet again as a committee. The committee secretary, Francis Green, continued the work of the TTC without convening meetings, seeking advice from individual members as necessary. Replying to an enquiry about the functioning of the TTC from the research superintendent of Monsanto in April 1947, Green wrote 'the Council's TTC has not been reconstituted as a committee since the end of the war, but the mechanism is still in action' (FD1 2513. Letter from Green to Barrett 28 April 1947). Monsanto then submitted a benzene derivative for trial as a scabies treatment and other companies submitted occasional requests for trials, but Green and his advisers were reluctant to reactivate the TTC. Its moment had passed.

By the early 1940s, the leading British pharmaceutical companies felt enough confidence in their ability to manage research and persuade doctors of the benefits of new drugs that they formed their own

cooperative research organisation, the Therapeutic Research Corporation (TRC). The TRC was intended to foster cooperation among British manufacturers in order to accelerate the research and production of pharmaceuticals during the war years and in particular, the production of penicillin.<sup>46</sup> While the TRC was formed to address specific issues in the context of World War II, its establishment also reflects the growing confidence of pharmaceutical companies. Along with the 1941 Pharmacy and Medicines Act, the TRC marks the emergence of the modern pharmaceutical industry in Great Britain, characterised by consolidation into a smaller number of large firms, an increasingly close relationship between clinicians and pharmaceutical companies, and significant growth in reputation and income. For the MRC, an increasing budget, the growth of the pharmaceutical industry and the emergence of the NHS, enabled it to develop new areas of interest in clinical science, mediated by the Clinical Research Board.<sup>47</sup> First with the patulin trial,<sup>3,4</sup> then with the streptomycin trial<sup>7</sup> the best way to test therapeutic efficacy was set out clearly. The streptomycin trial in particular has been hailed as a permanent contribution to science.<sup>8</sup> However, these two trials were also examples of a new way for the MRC to manage its relationship with the pharmaceutical companies.<sup>3,14</sup>

### *Industry, science and clinical trials in the 1930s – the science of experimental medicine*

The work of TTC has little visibility today except as the failed precursor to the famous streptomycin trial reported in 1948,<sup>7</sup> but it supported the British pharmaceutical industry. The clinical studies organised by the TTC are interesting in at least two ways.

First, they shed light on the changing relationship between the Medical Research Council and the emerging British pharmaceutical industry. Liebenau,<sup>48</sup> in his account of the MRC and the pharmaceutical industry, does not mention the TTC, yet it was specifically established by the MRC to respond to industry demands for British government support.<sup>2</sup> On the basis of a case study of the MRCs involvement in the supply of insulin to the UK, Liebenau<sup>48</sup> argues 'that Insulin in particular set the model for the relationship between the MRC and the pharmaceutical industry'. Examination of the TTC shows that the relationship between MRC and industry was more complex and more engaged than the model provided by insulin; in particular, patents and licensing played no role in the relationship between the TTC and the pharmaceutical industry during the 1930s.

Standardisation and the testing of batches for physiological activity, rather than patient management, were fundamental to the MRC's approach to therapeutic substances. The 1925 Therapeutic Substances Act gave it a distinctive position of authority – a kind of proving house – in relation to the wider medical profession and the state. As Edwards<sup>11</sup> has described, it also allowed the MRC to promote the view that medicine and therapeutics could only progress through fundamental (basic) scientific research, frequently performed by non-clinical scientists rather than clinicians.<sup>11</sup> In these circumstances, the patent on insulin, which the MRC accepted reluctantly, was not the template for its engagement with the emerging pharmaceutical industry but a tactical response. And while standards testing provided 'moral control' (Henry Dale quoted in Quirke<sup>49</sup>) in a complex area of science, politics and commerce, an account of the TTC shows the extent to which the MRC also supported the science-based marketing of British medicines.

Second, the therapeutic trials organised by the TTC illustrate some aspects of the complex relationship between clinical science and clinical practice in the first half of the 20th century. In a series of influential works, the historian Christopher Lawrence discussed the challenge brought by scientific medicine to the organisation of hospitals and the primacy of 'an epistemology of individual experience' upon which the authority of the elite of the medical profession rested.<sup>50,51</sup> Essentially, Lawrence argued that 'to admit that clinical medicine could be made a science would be to dismantle a discipline and the patronage system on which it thrived'.<sup>50</sup> As Stephen Sturdy has emphasised, Lawrence was not suggesting the relationship between bench and bedside need be antagonistic<sup>52,53</sup>; the question might be re-framed as 'what type of science is possible at the bedside?'.<sup>51</sup> This question occupied the MRC during the interwar years. How best to integrate experimental physiology and pathology with clinical practice – to create what Thomas Lewis called clinical science?<sup>54</sup>

A study of the TTC shows some of the response of the MRC to the difficulties it encountered as it tried to bridge bench and bedside in support of the British pharmaceutical industry. For the TTC, if there was to be scientific testament about drugs for doctors, the science was going to be that of experimental physiology as far as this was possible in a clinical setting. TTC-sponsored case series were a kind of bedside clinical science, which blended experimental physiology, clinical practice and hospital administration.<sup>55</sup> Access to patients was achieved through the network of hospital professorial units and clinicians connected to the MRC. Because the focus was physiology,

sizeable patient cohorts were unnecessary, though perhaps desirable as an acknowledgement of the empiricism of clinical practice.

As a result of the orientation towards experimental physiology, the methods for testing drugs employed by researchers on behalf of the TTC in the 1930s were different to those advocated by the MRC for clinical trials a few years later. But to characterise the TTC as having failed is to miss its role in the economy of knowledge about the effectiveness of drugs in the 1930s: central to this was the idea that therapeutic efficacy should be grounded in the exactitude of experimental physiology rather than the statistical approximations of population (group) outcomes.

### *Towards a population (group-based) approach to clinical trials*

As a result of its orientation towards experimental physiology and standardisation, there was little requirement for statistical expertise within the TTC:

1. Studies were essentially of the physiological activity of the drug as assessed in humans. Patient outcomes were of interest, but were generally secondary to measures of physiological effect.
2. As far as possible, studies took place at single centres, and relied on the scientific expertise at these centres to construct sound methods. In these circumstances, the shortcomings of the results of the serum treatment for lobar pneumonia, which the TTC had to deal with early in its existence, did not point towards the need to introduce rigorous trial methodology, even if it did highlight the difficulties of controlling research workers. In TTC studies, the way to counter inter-observer variation was not to manage observers but to reduce their number.
3. Control patients might be used, but their purpose was to measure the extent of physiological change in varying conditions rather than ensure a fair trial. Variability in patient response was recognised in experimental physiology but did not play a positive role. In comparison, variability in patient response, modelled as a population distribution, plays a positive role in the construction of statistical tests.

Other MRC programmes did concern themselves with populations, but they were somewhat peripheral within the MRC at the time, in areas such as experimental epidemiology with animals, surveys and industrial research. This work involved at various times Philip D'Arcy Hart and Austin Bradford

Hill.<sup>56</sup> Without the need for patient cohorts or multi-centre studies, and lacking a positive concept of a population, statistical expertise was not initially required by the TTC. Later, the potential of statistics in clinical trials may have impressed itself through Snodgrass and Anderson's reports to the TTC on the use of the novel antibiotics Prontosil and sulph-anilamide for erysipelas.<sup>33,34</sup> These made use of statistical concepts, such as chi-square and standard error, a point emphasised by the authors who made explicit that the evidence supporting their conclusions had been assessed statistically. Austin Bradford Hill, who was employed by the MRC and had published a successful series of articles on statistics in the *Lancet*,<sup>28,57</sup> was invited to join the TTC, but he was too late, and too junior, to have had any influence on the design of clinical trials supported by the TTC.

The presence of John Ryle on the TTC is also of note. Frustrated by what he saw as the limitations of laboratory science in medicine, he was appointed Regius Professor of Physic at Cambridge in 1936 and went on to become a leading advocate of social medicine. In his new post, Ryle opposed the 'seductive efficiency of laboratory medicine',<sup>58</sup> advocating instead an empirical, observational approach to medicine.<sup>59</sup> In considering populations, and bringing observation and patient experience to the fore, the modern approach to clinical trials lies closer to Ryle's model than to experimental physiology. Within the TTC though, Ryle was unable to advocate his concept of social medicine because of the committee's orientation towards experimental physiology.

The wider social context of Britain in the 1930s was also important in shaping the methods chosen by the MRC. At a time of major decline in British industry, the establishment of the TTC was a direct response to pressure from the ABCM for support at home and internationally, as Keith Williams has shown.<sup>2</sup> And although the industry was never represented on the TTC, in practice much of its operation can be seen as a response to the industry's requirement for rapidly produced scientific endorsement of new drugs. Experimental physiology was largely sufficient as a way to do this; trials comparing different drugs were only required when the efficacy of a British version of a drug was being compared with a foreign preparation. Such trials were rare, and were designed as far as possible to produce objective physiological data on which to make comparisons.

As with America,<sup>15</sup> World War II marked a watershed in the understanding of how best to test therapeutic drugs in the UK. Before the war, the TTC model prevailed and it was generally sufficient to understand the effectiveness of a drug in terms of its physiological

action. After the war, physiology remained, but it became increasingly important to understand the effectiveness of therapeutic drugs in terms of their population (group)-based, clinical outcomes.

The reasons for this change are varied and have yet to be fully explored, but a beginning has been made.<sup>60</sup> The reasons include growing confidence in the use of statistics in medical research following the success of Bradford Hill's book;<sup>28,57</sup> the institutionalisation of social medicine following the appointment of John Ryle to the chair of Social Medicine at the University of Oxford in 1942;<sup>61</sup> the growth of epidemiology and social medicine accompanying the establishment of the NHS in 1948;<sup>62</sup> and, following the success of antibiotics, growing interest of pharmaceutical companies in treatments for non-infectious diseases.<sup>63</sup> In different ways, these developments contributed to an increasing focus on populations (groups) as both the source of and target for knowledge about the effectiveness of medicines. Looking back now at its work, the TTC should not be seen as having failed because it did not anticipate the future, but as successfully producing knowledge in a way that was about to become redundant.

#### Declarations

**Competing interests:** None declared

**Funding:** None declared

**Ethical approval:** Not required

**Guarantor:** BT

**Contributorship:** Sole authorship

**Acknowledgement:** I am grateful to Professor Steve Sturdy and Professor Vivian Quirke for their comments on earlier drafts.

**Provenance:** Invited contribution from the James Lind Library.

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