Bryder L (2014). The Medical Research Council and treatments for tuberculosis before streptomycin.

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Introduction

Despite being set up in 1913 using a fund specifically earmarked for tuberculosis, the Medical Research Committee (renamed the Medical Research Council (MRC) in 1919) prioritised other areas of medical research. From 1920, the MRC did have three sub-committees concerned with tuberculosis: the tuberculin committee, the bacteriology committee and the occupational phthisis [pulmonary tuberculosis] committee (AS MacNalty, a medical officer in the Ministry of Health, was secretary of all of them). However, none of these committees was primarily concerned with investigating the effects of the treatments in vogue in the 1920s and 1930s – sanatorium treatment, tuberculin, sanocrysin and artificial pneumothorax. The Council did provide some financial assistance to physicians researching treatments in institutional settings, but did little itself to evaluate the effects of these treatments.

The special problem of tuberculosis

The Medical Research Committee was underwritten by a fund which was part of the 'sanatorium benefit' for tuberculosis under the 1911 National Insurance Act. This Act provided insurance for all wage earners against illness and unemployment. Tuberculosis was the only disease specified in the Act for which there was free institutional treatment. Furthermore, tuberculosis was the only health problem for which insurance commissioners were authorised to extend treatment to dependants of the insured, an indication of the seriousness with which this disease was regarded in early twentieth-century Britain.

One and a half million pounds were allocated by the Treasury for the erection of tuberculosis institutions. An additional million pounds were to be expended annually on treatment, a rate of 1s 4d per insured person per annum. One penny per person was set aside for further research (amounting to £56,000 per annum) on the grounds that this would ensure the maximum return from State expenditure. At a time of great optimism about the benefits of scientific research, this clause was added at the last minute as a ‘minor detail’ and was passed through parliament relatively unchallenged (Bryder 1989 p 2). Two years later an editorial in the *British Medical Journal* declared, ‘Amidst the turmoil of controversy regarding the Insurance Act, the fact has almost been lost sight of that it provides the first great contribution from the State towards research in scientific medicine’ (Editorial 1913).

Those managing this fund soon diverted it to other areas of research. The 1913 *BMJ* editorial explained that the ‘main concern of this part of the Act [was] to combat tuberculosis’, but that in many ways this disease was unsuitable for research, chiefly because when a question was addressed, the slow development of morbid lesions delayed the answer. The editorial held that tuberculosis should be regarded as one member of a group of infections, other members of which were more appropriate subjects for research. This opinion, the writer said, was supported by the fact that in institutions largely devoted to general investigations into infections, such as the Rockefeller Foundation and the Pasteur Institute, comparatively little work had been done on tuberculosis (Editorial 1913).

In 1921, MacNalty summarised comments made by Henry Dale (later director of the MRC's National Institute for Medical Research) at a conference on the future of the MRC’s tuberculosis work:

> *At present there appeared to be no real starting point for research in the chemo-therapy of tuberculosis. When in America he inquired into the researches that were being carried on at the Phipps Institute [for tuberculosis research, Philadelphia] on this subject. They comprised tentative experiments on the effect of Methylene-blue and Mercury, but Dr Paul Lewis, the director, agreed that such experiments had not provided a threshold for further researches. The chemo-therapy of tuberculosis was not in the same position as was that of Syphilis when Ehrlich started his experiments on 606.... In his [Dale’s] opinion the Committee must wait for a starting point in this branch of research* (MacNalty 1921 p 9).

However, the Council could have invested more time and money in assessing the effects of the treatments which were being used in the 1920s and 1930s – sanatorium treatment, tuberculin, sanocrysin and artificial pneumothorax.

Sanatorium treatment

The predominant form of treatment of tuberculosis throughout the first half of the twentieth century, in Britain and elsewhere, was 'sanatorium treatment', whereby patients were confined in institutions in which they rested, exercised, ate wholesome food and followed careful routines, all of which were thought to control their disease. As already noted, the 1911 Act had provided such treatment free of charge to all wage earners and their dependants. From 1921, local authorities were required to provide free sanatorium treatment to all tuberculosis patients in their area, and by 1938 Britain had more than 30,000 sanatorium beds (Bryder 1988 p 76).

Reports on this form of treatment were not encouraging, however. The MRC provided assistance by paying for a clerk to follow up patients who had been treated at the King Edward VII sanatorium at Midhurst from 1914, and published the results of the research in 1919. The report compared the death rate following sanatorium treatment with that expected by age and sex among the general population. It concluded that 'sanatorium treatment did not in fact restore the patients who formed the subject of the investigation to the average condition of health enjoyed by the general population'. (Bardswell 1919 introduction). An MRC report published in 1924 concluded that 'enduring arrest' was expected from 'early cases' treated by sanatorium treatment, but also noted that no comparison had been made with a control group not treated in a sanatorium (Hartley 1924). A 1937 report on sanatorium treatment stated that it really depended on 'the willingness or capacity of the patient to continue on the routine of life he had been taught during his residence' (Trail 1937). Most general assessments were negative; for instance, of the 3,000 patients discharged after sanatorium treatment under the London County Council in 1927, 2,280 (76 per cent) were dead by 1932 (Bryder 1988 p 178). It was in that context that physicians were scrambling to find treatments, although with little assistance from the MRC.

Tuberculin Committee

One treatment which the MRC assessed in its early years was tuberculin, establishing a Tuberculin Committee for this purpose. Robert Koch had discovered the bacterial cause of tuberculosis, the tubercle bacillus, in Germany in 1882. In 1890 he proclaimed 'tuberculin', derived from a culture of the bacillus, as a cure for tuberculosis. However, doubts were soon cast on the value of tuberculin, and it eventually transpired to be more valuable as a diagnostic than a therapeutic tool. Nevertheless it continued to have supporters as a therapy in Britain and elsewhere. The MRC's first annual report for 1914-15 announced that it had provided 'clerical and visiting assistance' to researchers at two sanatoria where tuberculin was being investigated (MRC Annual Report 1914-1915 p 24). The MRC reported in 1919 that tuberculin had 'no appreciable effect either for good or ill' (Bardswell 1919 pp 4, 52), and noted that 'the value of tuberculin is completely negative' (MRC Annual Report 1917-1918 p 19). Despite this, the following year, the Minister of Health asked the MRC to research the claims for its efficacy made by the Tuberculin Dispensary League. The Tuberculin Committee published a detailed account of the 107 cases treated by tuberculin and presented to it by the League, and concluded: 'the longevity of cases treated by this tuberculin method is equally seen in cases untreated by tuberculin' (Editorial 1923).

The MRC backed its own candidate for developing a variation to tuberculin, Georges Dreyer, Professor of Pathology at the University of Oxford. MRC secretary Walter Fletcher wrote in 1923:

> *MacNalty is making a short report upon the progress of Dreyer's work in producing an improved Tuberculin… in my opinion, and in that of far better judges than myself, this work gives enormous promise. There are already practical results to show which, to my mind, far outweigh any that have been claimed, whether justly or unjustly, for our friend Spahlinger* [who produced tuberculin]*'* (Fletcher to Newman 1923).

MacNalty's report concluded that Dreyer's researches were 'of far reaching importance and if confirmed and maintained are calculated, in the near future, to revolutionise not only the treatment of tuberculosis but that of other bacterial diseases…' (MacNalty 1923).

In a confidential report for members of the MRC only, the results of this research on 80 patients with tuberculosis (at the London and Brompton hospitals) were described as 'sensational' (Fletcher memorandum 1923). Fletcher declared, 'If these early results are confirmed and extended, the whole landscape will be changed'. He even gave the new antigen a name, 'diaplyte' meaning 'washed out', in eager anticipation of this new era.

The following year, however, Fletcher was forced to admit that:

> *Professor Dreyer's new vaccine for tuberculosis, the discovery of which was heralded with such acclamation last summer, has failed to give the results expected of it. In very few cases have patients shown any improvement under the treatment* (Fletcher 1924).

While tuberculin continued to have its supporters in Britain (for example Sir Robert Philip, Professor of Tuberculosis at Edinburgh University), the MRC Tuberculin Committee focused its efforts on establishing a test for the detection of tuberculosis in cattle, with grants from the Empire Marketing Board; this was eventually run jointly with the Agricultural Research Council. On the use of tuberculin as a treatment, the MRC reported in 1927:

> *From time to time the [Tuberculin] Committee receive through the Council representations from outside which urge the need for new investigations of the clinical value of tuberculin in the treatment of human tuberculosis. The Committee have carefully considered these requests, but believe that no useful purpose would be served by meeting them. Since Koch first prepared tuberculin nearly forty years ago medical practitioners throughout the world have used it in every kind of tuberculosis and by a great variety of methods. Numerous reports of these trials are available. .. If tuberculin administration were so safe and infallible a method of cure as some advocates of it assert, it would by now, as a result of all this work, have definitely established a claim to supersede all other methods of treatment* (MRC Annual Report 1926-1927 p 96).

Sanocrysin

Another treatment for which the MRC helped fund investigations was 'sanocrysin', an injectable salt with a gold content of 37 per cent. This was first used as a treatment for tuberculosis in Denmark in 1923, following experiments on calves. In 1924 the MRC reported that it was inviting doctors of the university medical clinics in London (including St Thomas's, St Mary's and London hospitals), the Professor of Therapeutics in Edinburgh, and the Chief Medical Officer of the Welsh National Memorial Association (a voluntary anti-tuberculosis organisation) to conduct clinical trials of the drug (Fletcher to MacLean 1924). The researchers subsequently reported that, given the unpredictability of tuberculosis, it was difficult distinguish between the effects of the treatment and the course the disease would have taken without the drug (Sanocrysin trials 1924-26).

From 1925 the MRC also provided assistance to Professor Lyle Cummins in the laboratory of the King Edward VII Memorial Association in Cardiff, who was more optimistic about sanocrysin's potential. The culmination of this research was that the MRC reported in 1927 that sanocrysin was of some benefit to carefully selected cases, but it did not indicate how these cases were to be identified (MRC Annual Report 1926-1927 pp 94-95). That same year Andrew Morland, the medical superintendent of a Swiss sanatorium and later based at University College Hospital London, commented on the difficulty of assessing the efficacy of sanocrysin. He speculated that any improvement was unconnected with the treatment and might have occurred in spite of it. He presented his results 'with the knowledge that the figures given cannot pretend to scientific accuracy but merely represent our clinical judgement on the cases involved' (Morland 1927).

It was clear that treatment for tuberculosis was proving difficult to assess using observational data. In a controlled trial in the United States, Amberson and his colleagues (1931) matched patients with tuberculosis into two clusters and, by tossing a coin, decided which of the groups would receive sanocrysin. Treatment outcomes were judged by observers who were kept unaware of the group to which patients had been assigned. No beneficial effects of sanocrysin were detected, and it was clear from the trial that the drug had some very nasty adverse effects. Diaz and Neuhauser (2004) have suggested that this study sounded the death knell of gold therapy throughout America.

In Britain, however, the drug became part of the armamentarium used to treat tuberculosis. Neither the drug's toxicity nor the methodological advance illustrated by the controlled trial done in the United States appear to have influenced the research methods used in Britain to evaluate the effects of sanocrysin. The annual reports of local medical officers of health in London reveal that the drug was used regularly at most tuberculosis dispensaries between 1932 and 1938 for 'suitable cases'; for example the London County Council reported in 1934: 'Treatment by gold salts is still considered beneficial in certain cases', but again, without specifying how suitable cases should be identified (London's Pulse). This treatment was provided on the advice of medical authorities at the Brompton Hospital for Diseases of the Chest, the major tuberculosis hospital in London, with the relatively high cost being met by local councils. Brompton's Hospital Research Fund funded a survey of 153 tuberculosis patients treated with sanocrysin between 1926 and 1928. In his report published in *The Lancet*, HE Mansell concluded there had been 'promising results' but also advised that 'there is need for further controlled investigation' (Mansell 1932), by which he meant further investigations, which should be 'controlled'. The MRC did not respond to this request.

In its 1936 annual report, the MRC outlined the research activities of Sir Gilbert Morgan, Director of the Chemical Research Laboratory of the Department of Scientific and Industrial Research, Teddington, Middlesex, declaring:

> *Observations have been continued on the chemotherapeutic action in tuberculosis of a gold compound prepared by Sir Gilbert Morgan … Encouraging results have been obtained in laboratory tests of this product, but it is as yet too early to assess its clinical value; it is being tried in cases of phthisis' (MRC annual report 1935-1936 p 107).*

A decade later, Philip D'Arcy Hart (Tansey 2006), secretary of the MRC's Committee on Tuberculosis in Wartime,

wrote of sanocrysin that:

> *The laboratory groundwork on the curative effect of sanocrysin was insecure, and the drug was heavily sponsored for general therapeutic use without adequately critical clinical trials… the clinical benefit was not dramatic or constant enough to dispense with balanced controls.* (Hart 1946).

He also said that investigation had been rendered difficult because of the increasing popularity of artificial pneumothorax as the preferred treatment (Hart 1946).

Artificial pneumothorax and thoracoplasty for 'collapse therapy'

In the 1920s and 1930s, following trends in Germany and America, collapse therapy was a popular method of treating pulmonary tuberculosis in Britain. The intention was to collapse the infected lung, allowing it to rest and heal. 'Artificial pneumothorax' achieved this temporarily by introducing air into the pleural cavity; 'thoracoplasty' permanently collapsed the lung by removing part of the rib cage. The MRC provided small grants to medical practitioners working in tuberculosis institutions who wished to assess such treatments.

In 1922 the MRC published a report on artificial pneumothorax. It covered 150 cases, among which 62 per cent had shown improvement. One of the authors, tuberculosis specialist LST Burrell, opined, 'I know of no one who has tried it seriously, and then discarded it' (Burrell 1922 p 7).

In 1936 the MRC published a report of the London County Council's experience with artificial pneumothorax. Six hundred and seventy seven cases had been followed up for periods varying from three years to 13 years and compared to a control group of 3,329 patients treated conservatively and followed for up to five years. The report noted that approximately 10 per cent of all patients undergoing residential treatment for pulmonary tuberculosis in 1934 were considered suitable for artificial pneumothorax. If the procedure was useful, this would only raise the general level of the results by approximately 4 per cent, as judged by survival after five years in all pulmonary tuberculosis patients under treatment. The conclusion reached was that it would continue to be of 'vital importance to properly selected individual sufferers', again, without indicating how to make such selections (Bentley 1936 preface and p 91).

In 1933, the MRC also provided an 'expenses grant' to the Joint Tuberculosis Council (JTC, an organisation of tuberculosis specialists) to investigate 'the late results of artificial pneumothorax treatment of pulmonary tuberculosis' (MRC annual report 1933-1934 p 109; Burrell 1933). The results of the research were eventually published in a supplement to *Tubercle* in February 1937 (Joint Tuberculosis Council 1937), where it acknowledged the £200 grant from the MRC towards the cost of the inquiry. The JTC had followed 3021 cases of pulmonary tuberculosis treated by pneumothorax in 42 institutions in Britain and Northern Ireland over several years. In its report the JTC referred to the problems it had with constructing a control group:

> *Such scientific control is the main difficulty in the estimation of every new treatment; in this inquiry such difficulty is particularly great and is, the Committee believe, the main reason why the results are inconclusive.*

The two 'control' groups they had relied on were 1,329 cases in the same hospitals 'in whom attempts to induce pneumothorax failed or were abandoned for any reason within three months', and 2,750 cases treated at the King Edward VII Sanatorium, Midhurst, between 1911 and 1929, of whom less that 1 per cent had received artificial pneumothorax.

A commentary on the study in *The Lancet* (1937) concurred, 'The difficulty has been to provide adequate controls'. Of the first control group, the commentator pointed out, 'It is arguable, to say the least, that this "A.P.-failed" group is likely to show poor results'. Nor did *The Lancet* editorialist consider the second control group comparable, as it was composed of a different social class with better facilities for continuing care following treatment (Editorial 1937). The JTC itself had noted that those at Midhurst were 'certainly of better social class, and can therefore command a higher standard of after-care than the average in this investigation'. This different clientele had been noted in a 1919 MRC report which pointed out that 'those belonging to … the working or industrial classes, are not eligible for treatment at the King Edward VII Sanatorium' (Bardswell 1919 p 7). *The Lancet* noted another difference in the two groups, with Midhurst having been specifically endowed to treat 'early and curable cases'. Again, the JTC had acknowledged that there was 'a considerable degree of selection in the cases accepted for treatment at Midhurst … the majority care cases with a reasonably good prospect of recovery', limiting their value as a control group. *The Lancet* editorial concluded:

> *Few if any clinicians with much experience of pneumothorax treatment doubt its value in suitable cases, and it is impossible to avoid a feeling of disappointment that four years' painstaking and comprehensive work should have failed to establish a statistical basis for this conviction* (Editorial 1937).

This provoked a response from Andrew Morland, who wrote that the commentary 'raises the whole question of the applicability of statistics to clinical problems'. He lamented, 'In the investigation you describe, a committee of experts spent four years in the classification and follow-up of a very large number of patients treated by artificial pneumothorax, and compared their fate … with control material which was admittedly not strictly comparable. The result was disappointingly inconclusive.' He thought it would be a good thing to have 'statistical backing to clinical judgement' but believed the cause of the error in this case was easy to pinpoint - that the control group consisted of patients with a substantially better prognosis treated conservatively than the artificial pneumothorax group. He concluded that statistical methodology did not have anything to contribute to this particular clinical problem (Morland 1937).

Morland's letter provoked a response from Austin Bradford Hill (1937a), who expressed concern that Morland 'passes from this criticism of the particular to a criticism of the general, and says that the investigation "raises the whole question of the applicability of statistics to clinical problems"'. This was a question, Hill said, which concerned him closely because he was attempting to show 'how simple statistical methods can be applied with advantage to many clinical problems' (Hill 1937b). He suggested that the clinical trials should have been conducted when the treatment was still in an experimental stage:

> *The time for a test of a new method of treatment is clearly in its early days when opinions upon it differ, and equivalent patients, treated and untreated, are available for study. Too often that critical moment is lost and we fall back later upon second-best comparisons.*
>
> *Dr Morland says that there is now 'a relatively small group of patients in whom pneumothorax is tried without delay as experience has taught us that their prognosis will be much improved thereby'. That conclusion is itself statistical even though it is not given numerical expression. It must be based on a mental, subjective, comparison, of similar types of patients to whom A.P.T [artificial pneumothorax] was applied or not applied. The two groups must have existed; the clinician must have been able to define them as of similar type to reach the conclusion; is it too much to believe that if the critical moment had been seized an objective, numerical assessment could have been obtained by suitable statistical methods?*

Conclusion

Dale had suggested in 1921 that tuberculosis was a notoriously difficult disease to study, and it did not appear to be an attractive area of research in the 1920s and 1930s. From 1930, the MRC had a scholarship for tuberculosis research, the Dorothy Cross scholarship, but the Council struggled to find candidates for it. Indeed, only the obstinacy of the donor, Mrs Cross, who had lost two of her children as young adults to pulmonary tuberculosis in the 1920s, prevented the MRC from extending the scholarship to other fields of medicine, as it had done with the original tuberculosis fund (Bryder 1989 p 13). When the MRC set up a Committee of Tuberculosis in Wartime in 1941, this was not concerned with treatment, but with epidemiology and prevention, which were considered more fruitful avenues to pursue or more urgent in wartime (MRC report 1939-1945).

So, despite being financed from a tuberculosis fund, the MRC did not prioritise evaluative research on the purported treatments for the disease. There was no plan and no research design. Although small grants were given to individuals and institutions to assess methods of treating tuberculosis, these assessments were not conducted in any systematic way, a record of failure comparable to that of the Council's Therapeutic Trials Committee (Bryder 2010). Although no well designed prospective trials had been conducted within the field of tuberculosis, debate about research methods began in the late 1930s, with Bradford Hill intent on defending the statistical method, even if it had been unsuccessfully applied by the Council up to that time.

The introductory section of the 1948 report of the MRC's controlled trial of streptomycin for pulmonary tuberculosis referred to the 'exaggerated claims made for gold treatment, persisting over 15 years' (MRC 1948), noting that only one controlled trial of gold treatment had been located (Amberson et al. 1931), and that this had showed 'negative therapeutic results'. The report of the streptomycin trial, which Bradford Hill and D'Arcy Hart would almost certainly have drafted, commented further that the trial reported by Amberson and colleagues (1931) was the 'only report of an adequately controlled trial in tuberculosis we have been able to find in the literature' (MRC 1948). The MRC had not ventured to sponsor any such trial itself since its inception in 1913. D'Arcy Hart's and Bradford Hill's comments marked the end of three decades of failure by the Council to adopt the scientifically robust methods that had been used, for example, in India and America to evaluate treatments, and the beginning of a golden era of MRC clinical trials (Chalmers 2013).

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