The MRC randomized trial of streptomycin and its legacy: a view from the clinical front line

J Crofton

J R Soc Med 2006 99: 531

The MRC randomized trial of streptomycin and its legacy: a view from the clinical front line

J Crofton

J R Soc Med 2006;**99**:531–534

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

During the Second World War, I served for eighteen months with Professor Guy Scadding in a military hospital in the Middle East.[1] At the end of the war, Professor Scadding resumed his previous academic and clinical jobs at the Brompton Hospital and the Postgraduate Medical School, and I worked part-time for him as an unpaid clinical assistant at his outpatient sessions. After I was appointed as a registrar at the Brompton Hospital in September 1946, Professor Scadding suggested that I should become a half-time member of the Medical Research Council (MRC) Tuberculosis Unit, with responsibility for coordinating the Brompton Hospital component of the MRC trial of streptomycin for pulmonary tuberculosis (Scadding was a member of the committee appointed to oversee the trial). Thus it was that I came to be involved in a study that is widely regarded as a milestone in the history of clinical trials.

BACKGROUND OF THE TRIAL

Following the immense success of penicillin, much research had been going on to detect other potential antibiotics from other fungi that might be effective against bacteria, such as the tubercle bacillus, against which penicillin had proved ineffective. This was important because tuberculosis was the most important cause of death of young adults in Europe and North America. An American soil biologist, Selman Waksman, had been systematically testing soil fungi, and one of his assistants, Albert Schatz, had isolated two fungi that produced streptomycin. This had proved very effective against tubercle bacilli, first in the test tube,[2] then in tuberculosis of guinea pigs. Preliminary experience in patients with tuberculosis looked similarly promising. There was much publicity, but the drug was still very expensive. An exhausted postwar Britain had few dollars, and the government was only prepared to purchase a limited quantity of the drug for testing on patients in the UK.

13 Spylaw Bank Road, Colinton, Edinburgh EH13 0JW, UK

E-mail: eapretty@breathemail.net

To decide how these tests would be carried out, the MRC set up an advisory committee chaired by Dr (later Sir) Geoffrey Marshall, a senior Brompton Hospital and Harley Street consultant. Philip D'Arcy Hart, director of the MRC Tuberculosis Research Unit, was appointed secretary to the committee. Austin Bradford Hill, Professor of Medical Statistics at the London School of Hygiene and Tropical Medicine, was one of the members of the committee.

The committee decided that there should be a series of multi-centre trials at tuberculosis units throughout the UK. The initial trials involved patients with the most serious forms of the disease - miliary and meningitic (both previously almost uniformly fatal), and very advanced pulmonary tuberculosis (with a high but not uniform mortality). Any recovery of patients with miliary or meningitic tuberculosis proved convincingly the worth of the new drug in those conditions.[3] In contrast, patients often recovered from pulmonary tuberculosis, even from very advanced disease.

THE MRC TRIAL OF STREPTOMYCIN FOR PULMONARY TUBERCULOSIS

Given the uncertain prognosis of pulmonary tuberculosis and the limited supply of the drug, Bradford Hill proposed that it would be unethical not to assess what advantage streptomycin offered in this form of the disease compared with the current standard treatment—bed rest. This view was accepted.

It was decided to limit the patients participating in the trial to those aged between 15 and 30 with 'acute progressive bilateral pulmonary tuberculosis of presumably recent origin, bacteriologically proved and unsuitable for collapse therapy'. Both the streptomycin and control group would receive the standard treatment for this type of disease—bed rest. As there were more patients with pulmonary tuberculosis than there were hospital or sanatorium beds to accommodate them, those allocated to bed rest alone in the trial received priority for admission. If streptomycin proved valuable these patients would receive it later, when supplies improved. Meanwhile, they would avoid any unknown ill effects of the new drug.

Dr Marc Daniels was appointed to coordinate the trial, and he, D'Arcy Hart and Bradford Hill—supported by a highly efficient trial manager, Mrs Charlene Agnew—were

the team responsible for the design, coordination, analysis and reporting of the study. Daniels had had experience of coordinating multicentre investigations in tuberculosis;[4] four years previously, D'Arcy Hart had been responsible for the first well controlled clinical trial done under the aegis of the MRC;[5] and Bradford Hill had set out the principles of clinical trial design in a book based on a series of articles published in the Lancet.[6] The success of the trial owes much to this very powerful team.

When a consultant physician identified a potentially eligible patient, the patient's details were sent to Marc Daniels at the national coordinating centre for the trial. If the patient was judged to meet the eligibility criteria, admission was arranged to the next available hospital bed in the nearest participating centre. Each gender in each centre was allotted a numbered series of envelopes, bearing only the name of the hospital. Each envelope contained a card indicating 'S(treptomycin)' or 'C(ontrol)'. The numerical order of the envelopes was based on a series of random numbers. When a patient was approved for the trial the next envelope for that centre and gender was opened. Streptomycin and control patients were usually admitted to different wards but otherwise treated exactly the same.

Neither group of patients knew that they were in a trial, which remained confidential throughout its 15-month duration. Progress was assessed with monthly chest X-rays, graded by three specialists who remained ignorant of (blind to) the identities of the allocation of patients to streptomycin with bed rest or bed rest alone. Any difference of opinion, usually slight, was resolved by discussion. Monthly direct smear and culture of sputum was also reported by bacteriologists who also remained blind to the treatment group. Fever, weight and sedimentation rates were also recorded regularly.

Organization of the trial was facilitated because an act of parliament in 1911 had made tuberculosis the responsibility of local authorities, which had adopted the model of tuberculosis outpatient clinics associated with hospitals or sanatoria introduced by Sir Robert Philip in Edinburgh. Clinicians were reassured about the ethics of entering patients for the trial both by the prestige of the chairman of the oversight committee, Sir Geoffrey Marshall (who had been one of Winston Churchill's doctors), and by the lack of any effective alternative treatment. I suspect it was also Geoffrey Marshall's prestige which ensured that I had no serious difficulty with the other consultant physicians at the Brompton Hospital. My job as a clinician was to ensure strict adherence to the admission criteria, proper random allocation, organization of the standard investigations and diligent completion of the case records.

There were many personal advantages of my involvement in the study. By my frequent contact with Marc Daniels (who became a close friend) I soon learnt what was required and ensured that it was implemented. Importantly, it introduced me to a study design—the randomized controlled trial—that I would go on to use extensively during the rest of my career. In addition, the Brompton Hospital was a small, friendly place, so I came to know all the consultants and their teams. I went on their ward rounds and attended the excellent clinical meetings, and so learned a lot about tuberculosis and other chest diseases. I also worked very closely there with the bacteriologist, Denny Mitchison, who was later to head his own Medical Research Council Tuberculosis Bacteriology Unit.

The results of the trial showed that streptomycin was helpful. During the first six months after admission to the study, there were four deaths among 55 patients who had been allocated streptomycin, compared with 15 among 52 patients allocated to bed rest alone, and this difference was reflected in radiological and other improvements. During the subsequent six months, the radiological and mortality differences were less marked (there eight more deaths in the streptomycin group and nine more in the groups treated with bed rest alone).

There was no formal indication of the results to the participating centres until the trial was completed and analysed. I personally learnt of the results through my frequent contacts with Marc Daniels. I presume he conveyed these informally to other centres before they were published in the *BMJ*. Of course, I soon saw the different results in the two groups among the patients at the Brompton Hospital. I also saw the initial improvement in patients in the streptomycin group, and often their subsequent deterioration when their bacilli became drug resistant.

DRUG RESISTANCE AND SIDE EFFECTS

The study was also important for what it told us about the development of resistance to streptomycin, and about the drug's side effects. Disappointingly, at six months, tubercle bacilli could still be cultured from the sputum of 47 of the 55 patients treated with streptomycin, compared with 50 of the 52 patients in the control group. Although surviving patients in the control group deteriorated faster than those in the streptomycin group, deterioration occurred in the streptomycin group as well, and this coincided with the development of streptomycin resistance in the bacilli, especially after the fourth month of treatment. Although the initial intention had been to continue daily streptomycin for the whole 6 months, this later deterioration and the development of bacterial resistance in the streptomycin group led the MRC to decide to discontinue treatment after only four months.

The difference between the groups became clear to me through ongoing observation of the patients at the Brompton Hospital. The trials had made clear that

streptomycin treatment could not be relied on to cure tuberculosis because of the development of bacterial resistance. And so it was for another new anti-tuberculous drug—para-aminosalycylic acid (PAS)—if it was given alone.[7] The development of resistance in individual patients was, at that time, a new phenomenon. It had not occurred with penicillin. We soon learned that a combination of streptomycin and PAS proved far more effective than either alone in treating tuberculosis, and reduced the development of resistance.[8]

Toxic effects of streptomycin can be severe,[9] but although they were observed in many patients in the MRC trial, in none were they considered sufficiently severe to necessitate discontinuing treatment. By far the most important toxic effect was damage to the inner ear, causing giddiness.[10] We encountered two other ill effects of streptomycin. These may have been due to the cruder drug produced by early manufacture because they were not seen later. One was very minor, a mere sense of tingling around the mouth, usually very short term. But the other—nausea and vomiting—was more disturbing. It developed in a number of patients after about six weeks of treatment. Because of the timing of its onset, a colleague, Reg Bignall, and I speculated that it might be a hypersensitivity reaction to streptomycin, and we thought it would be worth seeing whether it could be relieved with an antihistamine drug. Our double blind trial proved the point[11] and stimulated others to try antihistamines for sea sickness.[12]

THE LEGACY OF THE MRC STREPTOMYCIN TRIAL

For many of those of us who had been involved in the MRC streptomycin trial, randomized trials became a way of life, and provided much of the evidence upon which rational treatment policies came to be based. In addition to testing new drugs, new combinations of drugs, and new drug regimens, trials were also designed to assess the value of bed rest and treatment in hospital, and the preventive potential of vaccines. Indeed, when Archie Cochrane was pondering which of the specialities within medicine had made most determined efforts to base policies and practices on the results of reliable research he had no hesitation in awarding the 'gold medal' to the tuberculosis specialists.

The MRC streptomycin trial certainly left a personal legacy for me. In 1952, I left the Brompton Hospital to take up the chair of respiratory diseases and tuberculosis at the University of Edinburgh. There was a substantial tuberculosis epidemic in Scotland at the time, and I became responsible for 400 tuberculosis beds. Other consultants were appointed soon afterwards, and our group participated in subsequent MRC tuberculosis trials (for example, MRC 1955[13]). In addition, through the Tuberculosis Society of Scotland (later Scottish Thoracic Society), we were the first group in the world to test some treatment policies for tuberculosis in randomized trials. We assessed whether the long accepted policy of bed rest during treatment was of value, and found no evidence that it was.[14] We looked at the effects of adding corticosteroids to anti-tuberculous drug therapy.[15] We assessed the effects of variable dosage of the third of the new anti-tuberculosis drugs—isoniazid.[16] And we evaluated a preventive policy of drug treatment for tuberculosis of doubtful activity.[17]

Randomized trials like these were of great practical importance in developing effective treatment strategies, but they were not intellectually challenging. Our major intellectual challenge in tuberculosis research was to identify the causes of failed drug treatment. This was proved to be due to drug-resistance resulting from bad or risky therapy, or failed adherence to therapy. The results of randomized trials, taken together with detailed investigation of drug resistance in individual patients and proper organization of services, enabled our team in Edinburgh to achieve 100 per cent cure rates for pulmonary tuberculosis, the commonest form of the disease and one which had not long before killed half the patients who developed it.[18]

These results were better than anyone had achieved anywhere in the world, indeed far better than we ourselves had expected, and for a number of years our figures were not believed. Perhaps because of this, during the years that we were developing our services, we received large numbers of visitors from abroad. Most of them were more interested in learning about the treatment methods we had based on the results of our studies.

However, some of our visitors were interested in the methods we used in designing and running our randomized clinical trials. On this score, I think we may have had some impact in two countries. In 1957, Professor Hans Jacob Ustvedt of Oslo invited me to lecture to the Norwegian Medical Society on the techniques of controlled trials. Somewhat later, Professor Marion Zierski of Lodz, head of the main postgraduate training centre for tuberculosis in Poland, invited me for a lecture tour there about designing, running and analysing clinical trials. I like to believe that, together with the MRC Tuberculosis Research Unit, we helped to promote the adoption of a study design for which the MRC streptomycin trial is often seen as a symbol.

REFERENCES

1 Scadding JG. Reflections on my studies of the effects of sulphonamide drugs in bacillary dysentery in Eqypt, 1943–1944. (Text of a manuscript sent to Iain Chalmers in June 1999). *J Roy Soc Med* 2006;**99**:423–6

2 Schatz A, Waksman SA. Effect of streptomycin and other antibiotic substances upon *Mycobacterium tuberculosis* and related organisms. *Proc Soc Expt Biol Med* 1944;**57**:244–8

3 Medical Research Council. Streptomycin treatment of tuberculous meningitis. *Lancet* 1948;**1**:582–96

4 Crofton J. Marc Daniels (1907–1953). The James Lind Library (www.jameslindlibrary.org), 2005

5 Medical Research Council. Clinical trial of patulin in the common cold. *Lancet* 1944;**2**:373–5

6 Hill AB. *Principles of Medical Statistics*. London: Lancet, 1937

7 Swedish National Association against Tuberculosis. Therapeutic Trials Committee. Para-aminosalicylic acid treatment in pulmonary tuberculosis. *American Review of Tuberculosis* 1950;**61**:597–612

8 Daniels M, Hill AB. Chemotherapy of pulmonary tuberculosis in young adults; an analysis of the combined results of three Medical Research Council Trials. *BMJ* 1952;**1**:1162–8

9 Bastian H. Down and almost out in Scotland: George Orwell, tuberculosis and getting streptomycin in 1948. The James Lind Library (www.jameslindlibrary.org), 2004

10 Bignall JR, Crofton JW, Thomas JAB. Effect of streptomycin on vestibular function. *BMJ* 1951;**1**:534–59

11 Bignall JR, Crofton J. Antihistamine drugs in the treatment of nausea and vomiting due to streptomycin. *BMJ* 1949;**1**:13–14

12 Glaser EM, Hervey GR. The prevention of seasickness with hyoscine, Benadryl and Phenergan. *Lancet* 1951;**2**:749–53

13 Medical Research Council. Various combinations of isoniazid with streptomycin or with PAS in the treatment of pulmonary tuberculosis. *BMJ* 1955;**1**:435–45

14 Tuberculosis Society of Scotland. The treatment of pulmonary tuberculosis at work. *Tubercle, Lond* 1960;**41**:161–70

15 Horne NW. Prednisolone in the treatment of pulmonary tuberculosis. A controlled trial. Final report to the Research Committee of the Tuberculosis Society of Scotland. *BMJ* 1960;**2**:1751–6

16 Scottish Thoracic Society. High and low isoniazid dosage in the combined drug treatment of pulmonary tuberculosis. *Tubercle, Lond* 1962;**43**:130–8

17 Scottish Thoracic Society. A controlled trial of chemotherapy in pulmonary tuberculosis of doubtful activity, 5-year follow-up. *Tubercle, Lond* 1963;**44**:39–46

18 Stewart SM, Crofton JW. The clinical significance of low degrees of resistance in pulmonary tuberculosis. *Amer Rev Resp Dis* 1964;**89**:811–29