

Unravelling the ‘Tangled Web’: Chemotherapy for Tuberculosis in Britain, 1940–70¹

The William Bynum Prize Essay

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Abstract: The introduction and assimilation of chemotherapy to treat pulmonary tuberculosis (TB) during the mid-twentieth century appears at first sight to be a success story dominated by the use of streptomycin in a series of randomised clinical trials run under the auspices of the Medical Research Council (MRC). However, what this standard rhetoric overlooks is the complexity of TB chemotherapy, and the relationship between this and two other ways of treating the disease, bed rest and thoracic surgery. During the late 1940s and 1950s, these three treatment strands overlapped one another, and determining best practice from a plethora of prescribing choices was a difficult task. This article focuses on the clinical decision-making underpinning the evolution of successful treatment for TB using drugs alone. Fears over the risk of streptomycin-resistant organisms entering the community meant that, initially, the clinical application of streptomycin was limited. Combining it with other drugs lessened this risk, but even so the potential of chemotherapy as a curative option for TB was not immediately apparent. The MRC ran a series of clinical trials in the post-war period but not all of their recommendations were adopted by clinicians in the field. Rather, a range of different determinants, including the timing of trials, the time taken for results to emerge, and whether these results ‘fitted’ with individual experience all influenced the translation of trial results into clinical practice.

Keywords: Streptomycin, Tuberculosis, Chemotherapy, 1946–70, Clinical trials

Introduction

Between 1940 and 1970, the introduction and assimilation of chemotherapy to treat pulmonary tuberculosis (TB) presented British medical specialists with a unique set of opportunities and challenges. As Anne Hardy acknowledged in 2003, the history of TB treatment in this timeframe is somewhat under-researched, and this is all the

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¹ ‘The Drugs’, *Tubercle*, 34, 1 (1953), 1–32

more surprising given that it also spans the restructuring of TB services following the introduction of the National Health Service (NHS) in 1948.² One reason for this lacuna may be that the social science approaches dominating medical history research during the final quarter of the twentieth century focused attention on exploring the social and cultural dimensions of medical practice. The concomitant devaluation of traditional progressive narratives meant that the post-war history of TB, which is at its roots a story of biomedical success, did not sit comfortably within prevailing research agendas.³ Treating TB using drugs might also have seemed a straightforward narrative, dominated as it was by the 1976 claim of Thomas McKeown that 'effective treatment began with the introduction of streptomycin in 1947'.⁴ Admittedly, McKeown was writing within a particular political context but his comment perhaps further inhibited research into TB history in the post-chemotherapeutic era, because it implied that this drug was sufficient in itself to treat the disease satisfactorily.⁵ Interpreted as a *fait accompli*, investigating the mid-twentieth-century history of TB might appear an uninspiring and rather pedestrian quest. However, what McKeown's statement masks is the complexity of TB chemotherapy, and the inter-relationship between this and two other methods of treating the disease, bed rest and thoracic surgery. These three treatment strands were not temporally successive but overlapped one another.

In 1940, bed rest was the mainstay of treatment. The introduction of chemotherapy towards the end of this decade coincided with (and initially helped to promote) the rapid post-war expansion of thoracic surgery, with the result that during the early to mid 1950s surgery was thought to deliver the best chance of long-term recovery.⁶ By the mid-1960s, the treatment of TB using only a cocktail of drugs was almost always successful but, as Anne Hardy noted, 'from the first rumours of streptomycin's discovery to the successful incorporation of the drug into clinical practice there was a distinct hiatus, underplayed in historical accounts'.⁷ As will be explored here, the use of streptomycin during the 1940s

² Anne Hardy, 'Reframing Disease: Changing Perceptions of Tuberculosis in England and Wales, 1938 to 1970', *Historical Research*, 2003, 535; For a comprehensive survey of TB historiography, see Linda Bryder, Flurin Condrau and Michael Worboys, 'Tuberculosis and its histories: then and now', in Flurin Condrau and Michael Worboys (eds), *Tuberculosis Then and Now: Perspectives on the History of an Infectious Disease* (Montreal: McGill-Queen's University Press, 2010), 3–23; Although the post-war history of treatment in Britain has been somewhat neglected there has been substantial interest in the use of BCG vaccination to prevent TB, both in the global and national arenas; Niels Brimnes, 'BCG Vaccination and WHO's Global Strategy for Tuberculosis Control 1948–83', *Social Science & Medicine*, 67 (2008), 863–73; Henrice Altink "'Fight TB with BCG": Mass Vaccination Campaigns in the British Caribbean, 1951–6', *Medical History*, 58, 4 (2014), 475–97; Niels Brimnes, 'Vikings against Tuberculosis: The International Tuberculosis Campaign in India, 1948–51', *Bulletin of the History of Medicine*, 81, 2 (2007), 407–30; Christian W. McMillen and Niels Brimnes, 'Medical Modernization and Medical Nationalism: Resistance to Mass Tuberculosis Vaccination in Postcolonial India, 1948–55', *Comparative Studies in Society and History*, 52, 01 (2010), 180–209. See also Sunil Amrith, 'In Search of a "Magic Bullet" for Tuberculosis: South India and Beyond, 1955–65', *Social History of Medicine*, 17 (2004), 113–30, for a discussion of how the evolution of global health policy on TB during the 1950s and 1960s was influenced by trial results in India.

³ Charles Webster's 1976 presidential address to the Society for the Social History of Medicine is a good arbiter of this change in emphasis; see Dorothy Porter, 'The Mission of Social History of Medicine: An Historical View', *Social History of Medicine*, 7 (1994), 345–59.

⁴ Thomas McKeown, *The Modern Rise of Population* (London: Edward Arnold (Publishers) Ltd, 1976), 93.

⁵ McKeown's work is not addressed here but useful overview sources include James Colgrove, 'The McKeown Thesis: A Historical Controversy and Its Enduring Legacy', *American Journal of Public Health*, 92 (2002), 725–9; and Amy L. Fairchild and Gerald M. Oppenheimer, 'Public Health Nihilism vs Pragmatism: History, Politics, and the Control of Tuberculosis', *American Journal of Public Health*, 88, 7 (1998), 1105–17.

⁶ B.J. Bickford *et al.*, 'A Further Report on Lung Resection for Pulmonary Tuberculosis', *Thorax*, 7 (1952), 316.

⁷ Hardy, *op. cit.* (note 2), 553.

was limited not only by its restricted supply and cost, but also because it could not be used safely without the simultaneous administration of at least one companion drug.⁸ Determining best practice from a confusing plethora of treatment options was far from easy and, although the Medical Research Council (MRC) supervised ever more sophisticated clinical trials, a range of factors including the timing of trials, how long it took for results to emerge and whether they ‘fitted’ with clinical experience, and whether results from trials abroad were relevant at home all affected whether or not medical practice subsequently altered.

At the beginning of the twentieth century, TB was still a leading cause of death amongst economically active British adults. Starting with Lloyd George’s National Insurance Act of 1911, a series of legislative measures designed to combat the spread of the disease followed so that by the end of the First World War, a plan for a national scheme of prevention and treatment run by local authorities was in place.⁹ From about the 1890s, sanatorium treatment had been evolving and expanding and, by the 1930s, as Sir Arthur Newsholme described, a short stay was recommended for every newly diagnosed patient to gain ‘hygienic education and training in the methods of life he must hereafter pursue’.¹⁰ This ‘sanatorium treatment’, often funded by local authorities, was an attempt at lifestyle modification where strategies to prevent TB spreading in the home environment were combined with measures aimed at promoting disease quiescence. It was separate from the use of specific interventions, such as total bed rest or procedures to collapse the diseased lung which, although they might take place in a sanatorium, did not form ‘sanatorium treatment’ per se.¹¹ The distinction which had evolved between generic sanatorium treatment and bed rest as a specific therapy is an important one. TB has a tendency to heal spontaneously, and bed rest was thought to promote this process. Around 1940 the significance of rest was underpinned by a scientific explanation based on physiology, which served to lengthen the period of rest recommended by clinicians.¹² This, together with the continuing absence of evidence that any specific dietary regime (other than a nutritious mixed diet if the patient could be persuaded to eat it) had an impact on disease progression, meant that by the mid-1940s bed rest was the primary treatment for TB, backed up by additional palliative or active interventions.¹³ At the same time, there was a growing emphasis on the importance of healing the lung cavity itself. As X-ray facilities increased, external measurements of toxicity such as elevated temperature or pulse rates

⁸ This was highlighted by Helen Valier; ‘At home in the colonies: the WHO-MRC trials at the Madras Chemotherapy Centre in the 1950s and 1960s’, in Condrau and Worboys, *op. cit.* (note 2), 214.

⁹ Linda Bryder, *Below the Magic Mountain: A Social History of Tuberculosis in Twentieth-Century Britain* (Oxford: Clarendon Press, 1988), 36–45.

¹⁰ Sir Arthur Newsholme, *Medicine and the State: The Relation Between the Private and Official Practice of Medicine with Special Reference to Public Health* (London: George Allen & Unwin Ltd, 1932), 208–9. See also Michael Worboys, ‘The sanatorium treatment for consumption in Britain, 1890–1914’, in John V. Pickstone (ed.), *Medical Innovations in Historical Perspective* (Basingstoke: Macmillan, 1992).

¹¹ L.S.T. Burrell, *Recent Advances in Pulmonary Tuberculosis* (London: J & A Churchill Ltd, 1937), 187–8.

¹² Rest slowed the metabolism reducing the need for oxygen in the bloodstream. This decreased the breathing rate, which in turn lessened the flow of bacterial toxins around the body so limiting disease spread; R.Y. Keers and B.G. Rigden, *Pulmonary Tuberculosis: A Handbook for Students and Practitioners* (Edinburgh: E & S Livingstone Ltd, 1945), 145–8. Here, the authors stressed the primacy of rest in the ‘modern treatment of the disease’, which would result in a ‘considerably longer period than has hitherto been customary in the average British sanatorium’, 146–7.

¹³ See Brice R. Clarke, *Causes and Prevention of Tuberculosis* (Edinburgh: E & S Livingstone Ltd, 1952), 123–7; for a review of diet in the treatment of TB. As the author noted, none of the regimens proposed had ‘shown any remarkable results’, 123.

were overtaken by the greater importance attached to internal radiographic changes.¹⁴ The closure of lung cavities came to be seen as one of the principal determinants of treatment success, superseding the earlier twentieth-century emphasis on the importance of physical markers such as weight gain.

Attempts to rest the lung by collapsing it also became more sophisticated as the twentieth century progressed. Although Linda Bryder presented evidence to support the theory that collapse therapy in general did little to influence eventual outcomes, this runs counter to the experience of clinicians at the time.¹⁵ Neville Oswald, writing in 1979, described how in the late 1940s 'various forms of collapse therapy were applied with confidence', but added that 'their overall value will probably never be known'. Apart from anything else, he argued, the variation in individual response to differing regimes of rest and/or surgery meant that statistical evaluation was difficult.¹⁶ This seems to be a realistic appraisal of a complicated scenario. Unequivocal evidence of the therapeutic value of artificial pneumothorax was difficult to substantiate – for example, in 1922 an MRC-commissioned report had revealed that specialist opinion differed on every aspect of the procedure except that it produced improvement in the majority of cases in which it was used.¹⁷ L.S.T. Burrell, one of the authors of this report, argued in his 1937 textbook that aside from factors which might influence success at individual level – social circumstances, personality and willingness to commit to a long-term treatment option – it was difficult to draw firm conclusions from case studies in the absence of comparative 'control' cases.¹⁸ The problems associated with evaluating specific interventions were reiterated in 1948 by Frederick Heaf and N. Lloyd Rusby who reproduced F.J. Bentley's 'seven deadly sins' of case analysis – namely, to draw general conclusions from too few cases; to write up only certain cases and not others; to report on cases in too short a timeframe; to evaluate the procedure using unmatched controls; to use imprecise definitions of treatment outcomes; to fail to trace all of the participants in the series; and to report the detail of each case inadequately.¹⁹ Such difficulties over the statistical evaluation of treatment meant that clinical experience and judgment assumed primacy. In 1945, even when faced with evidence from large studies that collapsing the lung did not improve prognosis, R.Y. Keers and B.H. Rigden argued that this was so at odds with their own clinical experience that such results should be questioned.²⁰

¹⁴ L.E. Houghton, 'Planning of long-term treatment', in T. Holmes Sellors and J.L. Livingstone (eds), *Modern Practice in Tuberculosis: 1* (London: Butterworth & Co., 1952), 147.

¹⁵ Bryder, *op. cit.* (note 9), 179–83. Bryder suggested that the introduction of collapse therapy (particularly artificial pneumothorax) principally served to raise specialist prestige because of the additional skill the procedure required. Specialist consensus, however, was that with suitably selected cases, by 1945 well-equipped sanatoria expected to achieve at least an 80% five-year survival rate for patients with established pneumothorax; W.E. Snell, *British Thoracic Association: The First Fifty Years* (London: British Thoracic Association, 1978), 36–7.

¹⁶ Neville Oswald, 'Tuberculosis', *British Medical Journal*, 2 (1979), 189.

¹⁷ R.Y. Keers, *Pulmonary Tuberculosis: A Journey down the Centuries* (London: Baillière Tindall, 1978), 158–9.

¹⁸ Burrell, *op. cit.* (note 11), 289–97. Burrell's comments were mirrored by Keers, who wrote that for pneumothorax therapy 'the accumulation of readily comparable statistics [was] virtually impossible'; R.Y. Keers, *op. cit.* (note 17), 159.

¹⁹ Frederick Heaf and N. Lloyd Rusby, *Recent Advances in Pulmonary Tuberculosis*, 4th edn (London: J & A Churchill, 1948), 233–4. These concerns still resonate – for example, an 'editor's choice' article in the *BMJ* in 2010 highlighted the fact that although there had been 4600 participants in the trial of the drug reboksetine, only the outcomes for 1600 had subsequently been published; Trish Groves, 'Evidence Debased Medicine', *BMJ*, 341 (2010), c5715.

²⁰ Keers and Rigden, *op. cit.* (note 12), 175.

Despite the testimonies of physicians, historians have tended to be critical of the medical responses to TB in Britain pre-1940.²¹ To give just one example, the value of institutional segregation has been consistently downplayed, with emphasis placed instead on the non-effectiveness and fiscal inefficiency of sanatorium treatment.²² Both the motives of medical practitioners and their medical practices have been criticised, with F.B. Smith suggesting that pre-war specialists were enveloped in a culture of self-interest and professional aggrandisement.²³ As will be revealed here, there is little evidence that Smith's characterisation is readily translatable to the third quarter of the twentieth century where the hallmark, rather, would seem to be one of medical endeavour.

Chemotherapy for Tuberculosis: The MRC Trials of Streptomycin, 1947

By the end of the Second World War, then, treatment for TB comprised a prolonged period of bed rest supplemented by collapse therapy for some. Treatment was individualised to the patient within the constraints of available resources, and there was even an air of 'hope and therapeutic promise' for the years ahead.²⁴ However, 'the complacency of the specialty . . . was shattered by the simultaneous arrival of anti-tuberculosis drugs and the means of assessing their effectiveness' – in the form of the 1947 MRC trials of streptomycin.²⁵ The rationale for these trials was articulated by Philip D'Arcy Hart in his 1946 Mitchell lecture to the Royal College of Physicians, which was printed in full in the *British Medical Journal*. D'Arcy Hart, who worked for the MRC, set out a comprehensive review of the attempts to treat TB using drugs, including the newly discovered streptomycin. Setting the context for his talk, D'Arcy Hart explained that the search for a 'cure' rather than for effective palliation had been heightened by the 1910 success of salvarsan in treating syphilis, and reinvigorated by the discovery of penicillin in 1940. Notwithstanding these successes, as far as TB was concerned there was a substantial history of repeated chemotherapeutic failure with the result that bed rest and collapse therapy remained the favoured active treatments.²⁶ D'Arcy Hart, however, accepted that streptomycin (which had been extracted from a soil microbe in 1943 by a United States team directed by Selman Waksman) did have chemotherapeutic potential, despite some substantial drawbacks. The drug had to be administered by injection, and there were side effects associated with its use. It was in short supply except in the United States, it was

²¹ This critical stance has been noted by Fairchild and Oppenheimer, *op. cit.* (note 5), 1107; and by Nancy Tomes, 'The White Plague Revisited', *Bulletin of the History of Medicine*, 63 (1989), 470–7.

²² F.B. Smith, *The Retreat of Tuberculosis, 1850–1950* (Beckenham: Croom Helm, 1988), 130, 239; Neil McFarlane, 'Hospitals, Housing, and Tuberculosis in Glasgow', *Social History of Medicine*, 2 (1989), 83–5. A later précis of local authority provision can be found in John Welshman, *Municipal Medicine: Public Health in Twentieth-Century Britain* (Berne: Peter Lang, 2000), 124–5.

²³ Smith, *op. cit.* (note 22), 240, 244–5; Tomes, *op. cit.* (note 21), 470 described both Smith and Bryder as viewing 'doctors as agents of their own self-interest, acting in accordance with their economics, class, and professional needs'.

²⁴ Snell, *op. cit.* (note 15), 37.

²⁵ Oswald, *op. cit.* (note 16), 189.

²⁶ Philip D'Arcy Hart, 'Chemotherapy of Tuberculosis: Part I'; *British Medical Journal*, 2 (1946), 806–10; 'Part II', 849–55. See Alan Yorke Yoshioka's thesis, 'Streptomycin, 1946: British Central Administration of Supplies of a New Drug of American Origin with special reference to Clinical Trials in Tuberculosis' (unpublished PhD thesis: University of London, 1998) for a comprehensive analysis of the procurement of streptomycin and its early trials.

expensive and there had been few systematic clinical trials. Most problematic of all, TB bacilli rapidly became streptomycin-resistant, both *in vitro* and *in vivo*.²⁷

D'Arcy Hart's initial reservations about streptomycin were shared by both Selman Waksman and H.C. Hinshaw, who had been involved in early clinical trials in the United States. In 1947, Hinshaw stated that 'over-enthusiastic evaluation' of streptomycin was 'a tragedy', and that it should not be seen as a satisfactory replacement for existing treatment options. Waksman agreed, but added that nevertheless, streptomycin had potential.²⁸ First reports of streptomycin in the British medical press also echoed this cautionary stance; in 1946 *Public Health* reported only that it seemed more promising than anything found so far, but it was 'too soon to say more'.²⁹ To some extent, even before D'Arcy Hart's lecture, the way was open for the subsequent MRC-run investigations into the clinical efficacy of streptomycin. The medical profession was aware that there was no specific chemotherapeutic cure for TB, just as they were aware of the need for the evaluation of existing treatment options even if finding suitable control cases was difficult. Producing statistically verifiable evidence of treatment efficacy from a respected source which could be replicated when translated into medical practice was a necessity, but also had the potential to transform the dominant paradigm of treatment, based on clinical experience and observation, into one based on statistical evidence from clinical trials.³⁰ The MRC felt that it was ideally placed to organise and run the rigidly controlled trials needed to investigate the efficacy of streptomycin for TB, and the government's purchase of fifty kilograms of the drug from the United States in 1946 enabled them to prove it.³¹

The MRC conducted three trials of streptomycin, each designed to evaluate the use of the drug in different clinical scenarios. Apart from the well-documented trial into pulmonary TB, which recruited patients from January 1947 and published its report in October 1948, there were also trials into the treatment of TB meningitis in young children, and tuberculous broncho-pneumonia.³² However, the different trials had very different outcomes and this influenced their assimilation into clinical practice. The trial into TB meningitis also recruited patients from January 1947. No patient controls were included because as this condition was almost invariably fatal, it was considered unjustifiable to deny patients access to anything which might help them. By August 1947, trial results

²⁷ D'Arcy Hart, Part II, *op. cit.* (note 26), 852–3; Streptomycin caused nausea and vomiting, rashes and numbness, usually transient in nature. However, its effect on vestibular function, affecting sight and balance was more serious; Medical Research Council, 'Streptomycin in Tuberculosis Trials Committee: Streptomycin Treatment of Pulmonary Tuberculosis', *British Medical Journal*, 2 (1948), 778; Yoshioka argued that the British government had over-emphasised the toxicity of streptomycin in an attempt to minimise demand, but it is hard to entirely accept his theory; 'Streptomycin in Postwar Britain: A Cultural History of a Miracle Drug', *Clio Medica*, 66 (2002), 204.

²⁸ 'Tuberculosis and the Health Act', *British Medical Journal*, 2 (1947), 105.

²⁹ 'Streptomycin in the Treatment of Tuberculosis', *Public Health*, 59 (1946), 175. See also Bryder, *op. cit.* (note 9), 255.

³⁰ Helen Valier and Carsten Timmermann argued that controlled trials 'must be understood as both a tool to produce knowledge persuasive enough to direct best clinical practice, and as a powerful means to discipline research workers in disparate settings'; 'Clinical Trials and the Reorganization of Medical Research in post-Second World War Britain', *Medical History*, 52 (2008), 494.

³¹ For context on the role of the MRC in the treatment and evaluation of TB, see Linda Bryder, 'The Medical Research Council and Treatments for Tuberculosis before Streptomycin', *Journal of the Royal Society of Medicine*, 107, 10 (2014), 409–15. On the legacy of the MRC in developing clinical trial protocols, see Iain Chalmers, 'UK Medical Research Council and Multicentre Clinical Trials: From a Damning Report to International Recognition', *JLL Bulletin: Commentaries on the History of Treatment Evaluation*, (2013), <http://www.jameslindlibrary.org> (accessed 17 December 2014).

³² Yoshioka, *op. cit.* (note 26), 168.

were so promising that the Ministry of Health released supplies of streptomycin to treat this disease even though the stock of the drug was so limited. Although in this instance clinical practice changed immediately in response to MRC trial results, this proved the exception rather than the rule.³³ The most well-known MRC trial of streptomycin, which investigated its use as a treatment for pulmonary TB, is usually discussed within the context of its contribution to the development of trial procedures rather than from the perspective of the trial results.³⁴ It is credited with being the first randomised controlled trial in the world, because it used a statistically based random sampling method devised by Professor (later Sir) Austin Bradford Hill to determine which patients were in the control group (who were treated conventionally using bed rest), and which patients were in the streptomycin group (who received the drug as well as bed rest). David Greenwood has argued that this trial was not novel because of the randomisation process itself. Randomisation had already been used in trials in the United States during the 1930s, and by the MRC in a trial of patulin to treat the common cold in 1943–4. What differentiated it was that the allocation of patients to each arm was done by means of sealed envelopes, which completely removed the element of selection bias from the clinicians involved.³⁵ It is emphasised here that all patients in the trial received treatment in the form of bed rest, which was regarded as the best available therapy at the time. The patients in the streptomycin arm of the trial were given the drug as a supplementary measure.

The criteria for trial entry were very strict; disease of recent origin, affecting both lungs, in those aged between eighteen and twenty-five. For this particular group, the only other suitable treatment at the time was bed rest.³⁶ The MRC Trials Committee was able to side-step many of the moral and ethical issues connected with deciding who should receive drug treatment and who should not, because the control group were in any event getting the best available treatment promptly. As emphasised already, the small amount of streptomycin available to the MRC was used as an adjunct to, rather than a replacement for, existing treatment, and this had the added advantage of meaning that any difference in outcomes between the two groups could be attributed solely to effect of the drug.³⁷ Due to the strict entry requirements, it was not easy to find trial participants. As well as the co-operation of individual physicians, the MRC had to obtain permission from local authorities to use their patients because the trial recruited patients before the NHS was operational. Originally, patients were to be drawn from three hospitals in or around London but, to find sufficient participants, the MRC had to approach authorities in Wales, Scotland and Leeds, and extend the age range to thirty. Eventually, 109 patients who complied

³³ Medical Research Council, 'Streptomycin in Tuberculosis Trials Committee, Streptomycin Treatment of Tuberculous Meningitis', *The Lancet*, 251 (1948), 582–3.

³⁴ This bias has been highlighted by Valier, *op. cit.* (note 8), 213–4; and by Yoshioka, *op. cit.* (note 26), 2, 184–5, whose own work is, perhaps, an exception to this trend. Valier & Timmermann, *op. cit.* (note 30), 494, for example, focused on the role played by the controlled trial in the future development of medical research in Britain after the Second World War.

³⁵ David Greenwood, *Antimicrobial Drugs: Chronicle of a Twentieth Century Medical Triumph* (Oxford: Oxford University Press, 2008), 163.

³⁶ The trial protocol permitted the induction of an artificial pneumothorax at any time in any patient in either group if thought likely to be beneficial, and this intervention was used for five control-group patients, Medical Research Council, *op. cit.* (note 27), 770.

³⁷ Yoshioka, *op. cit.* (note 26), 6, reported that the government had imported a 'massive stock of the product, 50 kilograms'. Considering that thirteen to fourteen kilograms would have been needed for the fifty-five patients in this trial alone, irrespective of the amount needed for the two other trials, the argument of the MRC that this was a very limited amount seems valid.

with the trial criteria were selected. The results at the six-month point revealed that although streptomycin slowed disease progression, it did not achieve cavity closure. Most improvement was seen in the first two to three months of treatment, but one unexpected finding was the 'impressive clinical improvement . . . seen in some of the patients treated by bed rest alone', and this served to underscore the value of conventional treatment. As the report makes clear, no cures had been achieved. Moreover, the development of bacterial resistance, coupled with vestibular (inner ear) side-effects meant that 'a full measure of caution before prescribing streptomycin for any particular patient' was advised.³⁸ Whilst applauding the organisation of the trial itself, a *British Medical Journal* leader in October 1948 reiterated that streptomycin should not be used without an appreciation of its toxicity and the possible risk to public health if resistant organisms entered the community.³⁹ These were serious clinical disincentives, so initially, as Keers remarked, the drug 'appeared to have little to offer the patient with chronic pulmonary tuberculosis'.⁴⁰

Tuberculosis Treatment, 1948–54

The introduction of the National Health Service (NHS) in July 1948 disrupted TB services, and unsettled many clinicians. When its structure was being planned during the 1940s, some specialists thought that the integration of the curative, preventive and social elements of care for those with TB should be maintained, whilst others argued that local authority control had resulted in the development of a specialty isolated from mainstream hospital medicine.⁴¹ Aneurin Bevan, the Labour Minister of Health from 1945, had considered the option of using the existing local authority model to deliver his new service but the difficulty in ensuring equality of access to health care has been cited as one of the reasons why he did not do so.⁴² In the event, responsibility for the diagnosis and treatment of TB passed to the new hospital service, controlled by Regional Hospital Boards, whereas responsibility for care and after-care, and for prevention remained at local government level. As Watkin acknowledged, the arrival of the NHS in and of itself did not spark any changes in treatment but, although local circumstances differed, the amount spent on TB within the newly organised hospital service undoubtedly increased the creation of opportunities to explore and adopt treatment changes.⁴³ Additionally, the regional structure of the hospital service meant that good practice and limited facilities such as those for thoracic surgery were more easily shared. Nevertheless, at the time, the separation of health

³⁸ Medical Research Council, *op. cit.* (note 27), 770, 780–1.

³⁹ 'Streptomycin in Pulmonary Tuberculosis', *British Medical Journal*, 2 (1948), 791.

⁴⁰ Keers, *op. cit.* (note 17), 217.

⁴¹ John Geddes, 'Prevention', in Frederick Heaf (ed.), *Symposium on Tuberculosis* (London: Cassell, 1957), 122. Keers, *op. cit.* (note 17), 188.

⁴² Alyson Pollock, 'Where Should Health Services Go: Local Authorities Versus the NHS?', *BMJ*, 310 (1995), 1580–4. See also Rudolf Klein, *The New Politics of the NHS: From Creation to Reinvention* (Oxford: Radcliffe Publishing, 2006) 5–21. An example of the diversity of hospital provision pre-1945 can be found in Martin Powell, 'Hospital Provision before the National Health Service: A Geographical Study of the 1945 Hospital Surveys', *Social History of Medicine*, 5, 3 (1992), 483–504.

⁴³ Brian Watkin, *The National Health Service: The First Phase 1948–74 and After* (London: George Allen & Unwin, 1978), 1. Although he was referring to the situation in Scotland, Christopher Clayson described this as a 'flood of fortune', which 'permitted the rapid expansion of the tuberculosis service'; 'One Hundred Years of the Co-ordinated Service for Tuberculosis', *Proceedings of the Royal College of Physicians Edinburgh*, 18 (1988), 45.

and welfare services caused deep concern and division within the profession, with some predicting that it would be hugely detrimental for patient and practitioner alike.⁴⁴

The results of the MRC trial into the use of streptomycin for treating pulmonary TB were published in October 1948, at a time when the speciality was grappling with the reorganisation of their services between NHS and local authority structures. However, as acknowledged in the Memorandum of the Ministry of Health's Standing Advisory Committee on Tuberculosis (published in *The Lancet* in February 1949), the trial results did not make it any easier for clinicians to determine at what stage in the disease or treatment process a course of streptomycin would be most effective. The Memorandum had been written to help specialists decide when and how to use the drug, but it ended by warning that 'indiscriminate use of streptomycin carries with it definite dangers both to the individual and to the community'.⁴⁵ The use of streptomycin was therefore limited initially not only because supplies of the drug were still controlled by the Ministry of Health, and because there were fears over bacterial resistance, but also because its clinical application was unclear. When streptomycin was released for use by all practitioners on 1 November 1949, a *British Medical Journal* leader stressed that this could lead to it being 'either wasted or used in such a way as to do positive harm'. In comparison with penicillin, streptomycin was both more harmful and less potent, and the decision to use it was 'emphatically one for the expert only'. It was a 'fragile' weapon, different to other drugs, with the demarcation between its benefits and disadvantages 'ill-defined'. The leader continued, '[d]octors possess in streptomycin something quite peculiar and not to be regarded in the same light as any other drug'.⁴⁶ This comparison between the properties of penicillin and streptomycin provides a useful opportunity to reflect on how different the assimilation into medical practice of these two drugs was. Penicillin, suitable for use in a wide range of scenarios, quick to work and with few side effects was adopted rapidly. Streptomycin, in scarce supply, and problematic both in terms of side effects and bacterial resistance, was not. Within the context of the conquest of infections by effective, safe anti-microbial agents – 'the golden age of medicine' – streptomycin may therefore have seemed no wonder-drug.⁴⁷

In the meantime, reports of the efficacy of a second drug, para-aminosalicylic acid (PAS), being used to treat TB in Sweden, had resulted in the MRC conducting a second clinical trial in 1948.⁴⁸ Three groups of patients, all with the same tightly defined disease parameters as in the original trial, were recruited from eleven hospital centres. One group received streptomycin, another PAS and the third received both drugs. This time, there was unequivocal bacteriological evidence that the administration of streptomycin with PAS considerably reduced the emergence of drug-resistant strains of *M. tuberculosis*.⁴⁹ In contrast to the top-down approach of the original trial of streptomycin, this trial resulted from a bottom-up need for assessment because PAS was already entering clinical practice

⁴⁴ G. Lissant Cox's letter, 'Whither Tuberculosis?', *British Medical Journal*, 2 (1948), 1118, generated a huge amount of correspondence on this topic which lasted well into 1949.

⁴⁵ 'Streptomycin in the Treatment of Tuberculosis: An Official Memorandum', *The Lancet*, 253 (1949), 274–5.

⁴⁶ 'The Uses of Streptomycin', *British Medical Journal*, 2 (1949), 1098–9.

⁴⁷ See, for example, Allan M. Brandt and Martha Gardner, 'The golden age of medicine?' in Roger Cooter and John Pickstone (eds), *Companion to Medicine in the Twentieth Century* (London: Routledge, 2003).

⁴⁸ Jürgen Lehmann, 'Para-Aminosalicylic Acid in the Treatment of Tuberculosis', *The Lancet*, 1 (1946), 15.

⁴⁹ 'Treatment of Pulmonary Tuberculosis with Para-Aminosalicylic Acid and Streptomycin', *British Medical Journal*, 2 (1949), 1521. 'The Prevention of Streptomycin Resistance by Combined Chemotherapy: A Medical Research Council Investigation', *British Medical Journal*, 1 (1952), 1157–62.

outside specialist control and before any formal evaluation of its efficacy.⁵⁰ The second MRC trial had much more important consequences for the introduction of chemotherapy into clinical practice than the first. The interim trial report was published in December 1949, and once the spectre of drug-resistant organisms entering the community had been overcome, combinations of streptomycin and PAS were being prescribed in 1950 and used routinely by the end of 1951.⁵¹ Initially, treatment with streptomycin and PAS was thought to postpone death, not to prevent it, and any long-term effect on mortality rates was not anticipated. A *Tubercle* correspondent in April 1951 reported rather gloomily that there were patients of his treated with the drugs 'who would have died during 1950 but are now going to die in 1951'. The following month, a Birmingham specialist wrote that although TB mortality in the city had dropped by twenty per cent in 1950 compared to 1949, 'probably the result of the intensive use of Streptomycin and PAS', this improvement 'may be temporary in character'.⁵² Although there was a dramatic drop in TB mortality across the country, the Chief Medical Officer argued that treatment advances should not lead to the neglect of the 'fundamental principles of rest, both physical and mental, diet and close understanding of the patient as an individual'.⁵³

Initial assessment of the value of chemotherapy using streptomycin and PAS was hampered by its 'confused' introduction.⁵⁴ A *Tubercle* editorial of 1950 discussed how, although there was no doubt of their value, there was no accepted protocol for dosages or duration, or any sense of which patients might benefit most from drug therapy. Rather than leaving this to the MRC to investigate, it was suggested here that 'physicians must publish their results each adding his quota so that firm opinions will emerge'.⁵⁵ This meant that by the beginning of the 1950s, clinicians had access not only to the information gained from the tightly-controlled MRC clinical trials, but also some sanction to report their individual prescribing regimens with the ultimate aim of determining best practice in the field. As the potential benefits of drug treatment for TB became clearer, the search for new drugs intensified, and by the beginning of the 1950s the focus of activity had moved away from single academic researchers with modest grants towards teams of chemists working in a commercial pharmaceutical environment.⁵⁶ This was a win-win situation, as the pouring of drug company money into research had the potential to benefit both the company in terms of financial reward, and the patient, in terms of access to better drugs with less toxicity. This intensive activity resulted in the simultaneous recognition of the anti-tuberculous properties of isoniazid by three pharmaceutical companies early in 1952 – Squibb and Hoffmann La-Roche in the United States, and Farbenfabriken Bayer in Germany. It was in a spirit of optimism, albeit still tempered with caution that in April 1952 *Tubercle* announced that clinical results from two derivatives of isonicotinic acid

⁵⁰ See, for example, Birmingham Central Library holding MS 1523/15/1, Birmingham Regional Hospital Board Tuberculosis Services Committee, 1 September 1948, Minute 59, where the Committee had been asked for advice on using PAS to treat TB.

⁵¹ Maxwell Caplin, J.J. Griffiths and C.P. Silver, 'Respiratory Tuberculosis in East London', *Tubercle*, 37 (1956), 233–42.

⁵² 'Mortality Decline', *Tubercle*, 32 (1951), 93, 116.

⁵³ Cmd 8582, Report of the Chief Medical Officer on the State of the Public Health for the year ended 31 December 1950, 78.

⁵⁴ Snell, *op. cit.* (note 15), 45 'different physicians used these drugs in different dosage for different periods and for different reasons'.

⁵⁵ 'Streptomycin and PAS', *Tubercle*, 31 (1950), 73.

⁵⁶ Keers, *op. cit.* (note 17), 220 described pharmaceutical companies as 'humming with activity'.

showed promise. 'We imagine', said the editorial, 'that they will before long be available in this country for trial.'⁵⁷

The assessment of new drugs to treat TB was becoming ever more complex, since they needed to be judged against the now proven contribution that streptomycin and PAS made to treatment regimens. To be adopted, new agents would need to display high efficacy; but as Marc Daniels and Austin Bradford Hill described in their 1952 report into chemotherapy for TB, the MRC possessed suitable trial protocols, expertise and experience to carry out the necessary investigations. Their Trials Committee started work on the evaluation of isoniazid in March 1952. Isoniazid was a dream preparation compared to streptomycin and PAS. It was easy to take in tablet form, simple to manufacture and, because it had already been synthesised by two doctoral students in 1912, it was off licence and therefore cheap. The Committee's interim report, published in October 1952, acknowledged that these factors, combined with the demonstrable efficacy of the drug, made it an attractive prescribing choice especially for cases currently being treated at home. It did, however, suffer from the by now customary major disadvantage that drug resistance developed quickly, and in a high proportion of cases treated. To combat this difficulty, further trials investigating various combinations of isoniazid with either streptomycin or PAS had already commenced.⁵⁸

At the beginning of 1953, a *Tubercle* editorial highlighted the 'tangled web' of TB chemotherapy. It was acknowledged that although the combined effect of the drugs gave 'very wonderful results', the best way of using them was unclear. Indeed, the sentiment expressed was that 'anyone with a strongly expressed opinion, however poorly supported by evidence, is likely to get his way'.⁵⁹ The MRC trials into the best use of isoniazid continued and the second report, published in March 1953, presented a bewildering array of prescribing choices. A combination of isoniazid and streptomycin or isoniazid and PAS had been found to be as effective as the current 'best' regimen of streptomycin and PAS. This left the way clear for individual physicians to use whichever combination of drugs they thought most appropriate, based upon personal experience, a consideration of what might suit each patient best and whether the treatment was to be administered at home or in hospital. Whatever eventual choice was made, on one point the MRC Committee was clear – single drugs should not, under any circumstances, be prescribed because of the certainty that drug resistance would arise if this was done. Two of the three available drugs – streptomycin, PAS and isoniazid – should always be used.⁶⁰ As J.G. Scadding remarked in 1954, although there had been large-scale trials, 'many problems remained unsolved'. Scadding was an eminent clinician. At the time he was the Director of Studies at the Institute of Diseases of the Chest at Brompton and a member of the MRC Tuberculosis Chemotherapy Trials Committee. Even with these antecedents, he was not able to unreservedly recommend any particular combination of drugs. Although

⁵⁷ 'A New Remedy', *Tubercle*, 33 (1952), 97. Initially two drugs were trialled, isoniazid and a second, closely related compound which was subsequently shown to be hallucinogenic.

⁵⁸ Marc Daniels and A. Bradford Hill, 'Chemotherapy of Pulmonary Tuberculosis in Young Adults: An Analysis of the Combined Results of Three Medical Research Council Trials', *British Medical Journal*, 1 (1952), 1167; Medical Research Council, 'The Treatment of Pulmonary Tuberculosis with Isoniazid: An Interim Report to the Medical Research Council by their Tuberculosis Chemotherapy Trials Committee', *British Medical Journal*, 2 (1952), 744–5: 735.

⁵⁹ 'The Drugs', *op. cit.* (note 1), 1.

⁶⁰ Medical Research Council, 'Isoniazid in the Treatment of Pulmonary Tuberculosis: Second Report to the Medical Research Council by their Tuberculosis Chemotherapy Trials Committee', *British Medical Journal*, 536, 1 (1953).

streptomycin was the most toxic drug in terms of side effects, when used in combination with isoniazid he thought it the most effective regimen clinically. Isoniazid and PAS together seemed to be best at preventing the development of bacterial resistance and, because both drugs could be taken by mouth, it was 'an attractive combination'. It is therefore a measure of how difficult it was to decide between the drugs in the mid-1950s that Scadding went on to recommend streptomycin with PAS as his preferred prescription option. As for the length of treatment, Scadding maintained that the extent and chronicity of disease, the potential for surgical intervention and the circumstances of each patient made it impossible to derive even general rules for how long this should be – it should remain a clinical decision for the individual physician to make. He did, however, note that some patients had received prolonged drug treatment 'with very impressive results' – again without defining how long this prolonged period had been.⁶¹ By this time, the MRC appeared to be losing interest in running any more chemotherapy trials. Instead, because there was now considerable evidence that clinicians co-operated with clinical trials and understood the importance of following protocols, the MRC's Tuberculosis Research Unit indicated that it was happy to circulate their trial methodology to 'encourage and aid the development of this important and growing field of clinical medicine'.⁶² It is almost as if having inculcated the profession suitably, the MRC was passing the baton of responsibility for future trials back to clinicians in the field.

The arrival of chemotherapy did not spell the end of surgical treatment for TB; initially, the reverse was the case. As Birath *et al.* wrote in 1950, 'before long it was clear that one of the chief indications for the combined use of PAS and streptomycin was precisely in the surgical treatment of tuberculosis'. There were two reasons for this. Firstly, a short course of chemotherapy in the pre-operative period improved the general condition of the patient prior to surgery. Secondly, during the operation and post-operatively, the drugs limited the spread of infection.⁶³ The role of streptomycin in providing routine 'cover' during thoracoplasty (lung collapse) operations had actually been investigated by the MRC between January and September 1948. The results of the trial, not published until 1951, indicated that although streptomycin did reduce the occurrence of persistent wound infections, it did not have any effect upon the number of patients who were sputum-negative three months later. Therefore, it was recommended that streptomycin should not be used by surgeons routinely, but reserved for use when there was a definite clinical need.⁶⁴ This appears to be a classic example of when the results of an evidence-based MRC trial *never* entered clinical practice. The results just took too long to enter the public domain, and by the time they did, using streptomycin as operative 'cover' had become an established routine, tried, tested and valued in the field and this practice continued.⁶⁵ It

⁶¹ J.G. Scadding, 'Clinical Use of Antibacterial Drugs in Pulmonary Tuberculosis', *British Medical Bulletin*, 10, 135 (1954), 137–9.

⁶² Wallace Fox, 'Recent Developments in Controlled Trials in Pulmonary Tuberculosis', *British Medical Bulletin*, 10, 108 (1954), 113.

⁶³ G. Birath *et al.* 'Para-amino-salicylic Acid (PAS) and Streptomycin in the Surgical Treatment of Pulmonary Tuberculosis', *Thorax*, 5 (1950), 65. Birath and his colleagues gave daily doses of either 1g of Streptomycin or 10g PAS one week before and two weeks post-operatively. I.A. Sarot, 'Extrapleural Pneumonectomy and Pleurectomy in Pulmonary Tuberculosis', *Thorax*, 4 (1949), 205.

⁶⁴ Medical Research Council, 'Prophylactic Streptomycin in Thoracoplasty Operations', *Thorax*, 6 (1951), 24. The trial had been carried out when streptomycin was in short supply and expensive, and fears over bacterial resistance were at its height. Even though the final report acknowledged the changed clinical scenario brought by the simultaneous administration of PAS, the recommendation stood.

⁶⁵ See for example, B.J. Bickford *et al.* 'Lung Resection for Pulmonary Tuberculosis', *Thorax*, 6 (1951), 30. D.C.

is also the case that the MRC was more interested in investigating long-term outcomes – that is, whether or not using streptomycin made a difference to the ultimate recovery of the patient. Surgical teams were much more concerned with short-term outcomes – patient survival on the operating table and the prevention of post-operative wound infections, so that the patient could be handed back to medical colleagues for ongoing care.

Long Term Treatment Outcomes: 1954–60

Although during the early to mid-1950s bed rest, surgery and chemotherapy were still all important elements of treatment, by the end of that decade a fundamental change had occurred. By 1959, John Crofton was able to argue that the ‘right use of modern methods of chemotherapy’ had finally made the prospect of a cure a reality.⁶⁶ In the intervening years, surgical treatment for TB had reached its zenith and then rapidly dropped from favour, and the absolute requirement for bed rest to promote recovery had been challenged. At the beginning of this short timeframe, chemotherapy and bed rest were not considered to be curative therapies, but adjuvant therapies which assisted the natural healing process. The use of chemotherapy postponed death by attacking the infective organism, whilst bed rest gave the body a chance to recover, and so these two treatment strands had a synergistic potential.⁶⁷ Thoracic surgery perhaps was different in as much it targeted the tuberculous cavity itself by removing it or collapsing the lung around it, and there had been an expectation in the early 1950s that new surgical procedures – which included either total or partial excision of a diseased lung – might eventually prove curative.⁶⁸ By 1957, however, surgery was already beginning to be seen not as a primary treatment option, but as a secondary, preventive option to guard against relapse.⁶⁹ Although these developments occurred within the context of rapidly decreasing TB mortality, they stemmed principally from the extension of chemotherapy from a short-term to a long-term intervention, not as the result of clinical trials, but of clinical observation. It could be argued that chemotherapy might never have been considered as a definitive therapeutic option had it not been for a shortage of beds and thoracic surgeons during the late 1940s and early 1950s.⁷⁰ By the end

Beatty and A. Weiner described how originally they had planned a controlled trial to run between April 1948 and April 1951 giving some patients streptomycin and others not, but from April 1950 onwards they had decided to give all patients operative cover (1g of streptomycin and 20g PAS daily for 2 days pre-operatively and 21 days post-operatively) as ‘the benefits of streptomycin . . . were such that it would not have been justifiable to withhold it’; in ‘The Influence of Streptomycin on the Incidence of Pleural Effusion Complicating the Division of Adhesions’, *Thorax*, 8 (1953), 70.

⁶⁶ John Crofton, ‘Chemotherapy of Pulmonary Tuberculosis’, *British Medical Journal*, 1 (1959), 1610.

⁶⁷ George Day, ‘Sanatorium Treatment Today’, *Tubercle*, 36 (1955), 52.

⁶⁸ B.J. Bickford *et al.* ‘A Further Report on Lung Resection for Pulmonary Tuberculosis’, *Thorax*, 316, 7 (1952). As Bickford *et al.* had recorded earlier, the idea of removing diseased lung tissue from the body had ‘a natural appeal both to the surgeon and the patient’: Greenwood, *op. cit.* (note 35), 27.

⁶⁹ A.L. d’Abreu, ‘Respiratory tuberculosis: surgical treatment’, in F.R.G. Heaf (ed.), *Symposium on Tuberculosis* (London: Cassell, 1957), 465; B.J. Bickford *et al.*, ‘A Critical Review of the Results of Lung Resection for Pulmonary Tuberculosis’, *Thorax*, 12 (1957) 152. Papers from *The Treatment of Pulmonary Tuberculosis: A Conference held at King Edward VII Sanatorium, Midhurst, May 11th and 12th, 1962* (Edinburgh: E & S Livingstone Ltd, 1962) amply illustrate the decline of surgery for TB.

⁷⁰ For example, although the Birmingham Regional Hospital Board faced significant challenges in 1948 their most serious initial problem was identified as ‘perhaps the shortage of sanatoria beds in the face of mounting incidence of tuberculosis . . . regarded as urgent to the point of desperation’ and this meant many patients started their treatment at home; Birmingham Regional Hospital Board, *Birmingham Regional Hospital Board 1947–66: A Chronicle of the Activities of the Birmingham Regional Hospital Board since their inception in 1947, indicating the Principal Trends in Society and Medicine which have influenced their Policy* (Birmingham: National Health Service, 1966), 8.

of 1954, however, there was a 'growing feeling that the initial treatment has become so successful that the necessity for ultimate surgery may be questioned'.⁷¹ 'Initial treatment' in this context meant the combination of bed rest and chemotherapy, and at first the need for rest was the dominant paradigm. Chemotherapy had been assimilated into existing patterns of established treatment as an addition to the fundamental tenet of bed rest, rather than a replacement for it. Patients who had started their treatment at home during the early 1950s out of necessity (because of a lack of institutional bed-space), were by 1954 being maintained on chemotherapy for ever lengthening periods. This led to the observation that by the time their turn for thoracic surgery came they no longer needed it, and this almost incidental finding turned out to have great clinical significance.⁷²

The timescale by which chemotherapy emerged as a curative option for TB can be pinpointed fairly accurately because there are at least two detailed accounts of its introduction into clinical practice during the 1950s. One comes from a review of prescribing practice at the Brompton Hospitals by A. Foster-Carter, and the other from a review of practice in Birmingham by V.H. Springett.⁷³ Although there was no smooth or universal introduction of this new approach to using chemotherapy, nevertheless the speed with which long-term therapy emerged indicates a flexible and dynamic response by individual doctors to a rapidly changing clinical scenario. Springett and Foster-Carter worked very differently. Whereas in Birmingham Springett worked as part of a team of chest physicians with a corporate policy on treatment, Foster-Carter described the Brompton *modus operandi* as 'a benevolent anarchism . . . complete individual autonomy is allowed and each clinician is a law unto himself'. Analysis of the treatment methods here were therefore the 'average opinion of a number of clinicians' and based on personal experience rather than agreed drug protocols. The models of clinical organisation represented by these two consultants show how heterogeneity of provision in medical services is brokered not only by the availability of physical resources, but also by esoteric factors such as individual personality and corporate culture. The Brompton information is useful just because it showed a range of opinion – and the take-up of chemotherapy reported is of particular relevance. The decline in mortality from TB, argued Foster-Carter, gradual between 1900 and 1949, decreased sharply in 1950, 'co-incident with the arrival of two-drug chemotherapy' and indicative of its 'immense power'. Chemotherapy did not start at Brompton until 1950, and then only for about half of their patients. Isoniazid was not prescribed until 1953, and then not for all patients and only for short periods. During 1954 patients routinely received streptomycin, PAS and isoniazid for between six and nine months. By 1955, chemotherapy with isoniazid and PAS for up to two years, with a starting supplement of streptomycin was being prescribed for most.⁷⁴ Foster-Carter's timescales for the introduction of chemotherapy were mirrored in Birmingham, where surgical facilities for treating TB were extremely limited, and this means that it is possible to determine with a high degree of certainty both when and why the surgical treatment of TB began to lose its attraction.⁷⁵

⁷¹ 'Sanatorium Treatment', *Tubercle*, 35 (1954), 265.

⁷² Day, *op. cit.* (note 67), 52–3; 'Unnecessary Surgery?', *Tubercle*, 36 (1955), 393–4.

⁷³ A.F. Foster-Carter, 'The results of treatment of pulmonary tuberculosis in communities in recent years', in *The Treatment of Pulmonary Tuberculosis*, *op. cit.* (note 69), 21–6; V.H. Springett, 'Ten-Year Results During the Introduction of Chemotherapy for Tuberculosis', *Tubercle*, 52 (1971), 78–9.

⁷⁴ Foster-Carter, *op. cit.* (note 73), 23.

⁷⁵ Springett, *op. cit.* (note 73), 73–4. See also James Grant, E.L. Feinmann and K.M. Martischig, 'A Study of Control Methods in Tuberculosis', *Proceedings of the Royal Society of Medicine*, 54 (1961), 703, which shows a

Compelling evidence of the efficacy of long-term chemotherapy was provided by the work of J.D. Ross and D.T. Kay, in 1955. Ross and Kay tracked a series of patients discharged between 1952 and 1954, and found no statistically significant difference in relapse rate between patients treated conservatively with rest and chemotherapy alone, and patients who had gone on to have surgery. However, they did find a significant difference between the rate of relapse and the length of chemotherapy prescribed, and concluded that treatment success depended upon extended drug use and not upon whether surgery was subsequently undertaken.⁷⁶ Ross and Kay were members of Professor (later Sir) John Crofton's Edinburgh team, recognised for its expertise in treating TB using long-term chemotherapy. Crofton was an outstanding physician; he had moved to Edinburgh in the early 1950s and re-organised TB services in the city into an integrated system covering both in-patient and out-patient care. Crofton's aim was that every Edinburgh patient should have access to 'good' chemotherapy and, supported by his team, he was able to achieve impressive results.⁷⁷ Although studies such as that of Ross and Kay highlighted the potential value of long-term chemotherapy, uncertainties remained over how long treatment should be continued, and whether it would ultimately be successful. Prompted by the Research Committee of the British Tuberculosis Association – because specialists were already advocating and prescribing ever-longer drug treatment courses – the MRC decided to conduct a further trial into chemotherapy for TB. Commencing in January 1956, over a two-year period almost three hundred patients were recruited and given chemotherapy for varying lengths of time from six months to three years. As well as determining the optimum length of treatment, the trial aimed to validate statistically a clinical observation which was already starting to influence medical practice. Once again, though, rather than leading the way for treatment advances the results from the trial lagged behind clinical developments. By the time the report was published in 1962, its recommendation that treatment should be continued for two years to prevent relapse attracted little attention, because by then it merely confirmed existing practice.⁷⁸ John Crofton's statement at the British Medical Association's annual meeting in 1958 that the 'right use of modern methods of chemotherapy now makes it possible to aim at 100% success in the treatment of pulmonary tuberculosis' appears to have had a great impact on colleagues elsewhere.⁷⁹ Crofton's results were subsequently replicated by clinical teams in Birmingham and Manchester, both of whom, it seemed, wanted to substantiate his claims by validating his success rates using their own patient populations.⁸⁰ Long-term chemotherapy had already been the treatment of choice for some five years by 1960, but it is argued here that it was only when Crofton's treatment success rates had been achieved in other centres that the real 'eureka' moment occurred for specialists – TB could be cured if

similar timescale for the evolution of chemotherapy in Gateshead.

⁷⁶ J.D. Ross and D.T. Kay, 'A Review of 138 Cases of Closure of Tuberculosis Lung Cavities Under Chemotherapy', *Thorax*, 11 (1956), 6–8.

⁷⁷ John Crofton, 'Tuberculosis Undeafed', *British Medical Journal*, 2 (1960), 685–6; Crofton, *op. cit.* (note 66) 1610–4.

⁷⁸ Medical Research Council Tuberculosis Chemotherapy Trials Committee, 'Long-Term Chemotherapy in the Treatment of Chronic Pulmonary Tuberculosis with Cavitation: A Report to the Medical Research Council by their Tuberculosis Chemotherapy Trials Committee', *Tubercle*, 43 (1962), 203.

⁷⁹ J.D. Ross, 'The Antibacterial Therapy of Tuberculosis', *Tubercle*, 39 (1958) 47; Crofton, *op. cit.* (note 66), 1610.

⁸⁰ H.E. Thomas al, '100% Sputum-Conversion in Newly Diagnosed Pulmonary Tuberculosis', *The Lancet*, 276 (1960), 1185–6; J.R. Edge *et al.* 'An Assessment of Antibacterial Treatment used Alone or in Association with Surgical Operation in the Treatment of Pulmonary Tuberculosis', *Thorax*, 16 (1961), 262.

the right treatment was correctly prescribed, reliably taken and taken for long enough. This gave doctors enormous personal responsibility for treatment success and made them more accountable for treatment failures. As Crofton spelled out the 'slightest error on the part of either doctor or patient may result in disaster. In no disease is the result of conscientious doctoring more rewarding. In none is the result of carelessness or ignorance more tragic for the patient.'⁸¹ At a clinical level for the individual patient, long-term chemotherapy forced a re-evaluation not only of the place of surgery, but also the importance of rest in bed.

Re-evaluating Bed Rest, 1950–60

The primary requisite for bed rest to promote recovery was initially unchallenged by the introduction of long-term drug treatment. However, the realisation that many patients on chemotherapy felt better quite quickly meant that the need for rest even as a supplementary treatment component soon demanded scrutiny. Two Bedford physicians, N. Wynn-Williams and R. Douglas Young, started to investigate the feasibility of ambulant long-term chemotherapy treatment prompted by reports of successful treatment from countries where facilities for bed rest were negligible. They compared the results from one group of patients diagnosed between January 1954 and June 1955, where bed rest was standard, with those from a second group of patients who had been diagnosed between July 1955 and June 1956. They had encouraged patients in this second group to get up and return to work as soon as they could. Although there were some differences between the cohorts – the earlier group had received less effective chemotherapy and more surgery – Wynn-Williams and Young justified their decision to deliberately curtail bed rest for the second patient cohort in part because it reduced the 'unhappiness and personality changes so often caused by long absence from home and employment'. The authors were quite careful not to suggest that rest was without value in treatment; rather, they emphasised that it was possible for patients to do equally well without it, and they called for 'a properly controlled trial to evaluate the place of bed-rest' to be undertaken.⁸²

It is possible that when Wynn-Williams and Young's paper was prepared for publication in 1957, they were unaware that the Tuberculosis Society of Scotland had such a trial well underway. The interim report of the Scottish trial, which recruited patients over a similar timescale between May 1954 and July 1956, was published later in the same year. Although John Crofton was the most senior member of the trial Research Committee, even he initially encountered some difficulty in persuading his colleagues to co-operate. This was due to ethical concerns over the trial protocol, because, as he explained, 'everybody thought that you needed at least three months' bed rest'.⁸³ The trial randomised patients into two groups, both given isoniazid and PAS – drugs easy to take at home. One group then rested in bed, either at home or in hospital, while the other group continued at work. Although the conclusion of the interim trial report was that patients with less severe disease

⁸¹ Crofton, *op. cit.* (note 66), 1613. Ross contended that chemotherapy failed for four basic reasons – the use of the wrong drugs, the use of the right drugs but in insufficient doses, interrupted treatment schedules or treatment regimes that were too short. Of these, three were due to physician error, but the interruption of treatment was almost always attributable to the patient, particularly when drugs were given on an out-patient basis; Ross, *op. cit.* (note 79), 47.

⁸² N. Wynn-Williams and R. Douglas Young, 'How Much Rest in Pulmonary Tuberculosis?', *Tubercle*, 38 (1957), 338–9.

⁸³ D.A. Christie and E.M. Tansey (eds), *Short-Course Chemotherapy for Tuberculosis* (Witness Seminar Transcript, Wellcome Witnesses to Twentieth Century Medicine, Vol. 24, The Wellcome Trust, 2004), 33.

did as well at work as those on bed rest, it was acknowledged that workplace treatment was not straightforward. This was because being at work tended to make patients underestimate the seriousness of their condition, which in turn led to less adherence to their treatment regimen. It was therefore recommended that treatment at work should be reserved for 'highly co-operative patients with mild disease' to minimise the potential for workplace infection.⁸⁴ The conclusion of the Scottish report is much more robust than that of Wynn-Williams and Young, probably because it was conducted as a randomised controlled trial rather than as an investigation into successive cohorts of patients. Whereas the Bedford physicians had been diffident about dismissing the value of rest during treatment, the Scottish report stated unequivocally that those at work could do as well as those treated conventionally with bed rest, provided they took their medication regularly. This meant more responsibility for the physician in terms of patient management, because not only did they have to decide which drugs to give and for how long, they now had to assess the likelihood that individual patients would take their drugs reliably.

When the final report of the Scottish study was published in *Tubercle* in 1960, far more emphasis was given to the failure of patients to take their drugs. This was now viewed as a serious drawback of long-term chemotherapy, and was considered to be the only reason why the condition of a handful of patients had actually deteriorated during the trial. The recognition that patients were more likely to comply with treatment if they were bed-bound rather than working complicated clinical management, because although it was evident that bed rest was not necessary for medical reasons, for some patients it appeared to be necessary for psychological or cultural reasons to ensure treatment compliance.⁸⁵ The over-riding concern of physicians was that patients took their drugs regularly, and whether they were in bed or not was becoming a secondary issue. Shortly after the publication of this final report, Philip D'Arcy Hart wrote to the editor of *Tubercle* to express his concern that the trial literature review had made no mention of the World Health Organization's (WHO) 1959 report from the Tuberculosis Chemotherapy Centre in Madras.⁸⁶

The Madras Study

Randomised controlled trials in Madras, reported at length in a WHO Bulletin in 1959, had been designed to gain information on several different aspects of TB treatment, but it was the investigation into the comparison of home and hospital treatment which attracted most attention at the time.⁸⁷ As far as this strand of the trial was concerned, the study's conclusion was that under the particular conditions under which it was carried out, the results obtained in the home treatment group were so nearly equivalent to those of the sanatorium group that most cases could now be treated at home 'provided that certain minimum requirements were met'. These minimum requirements were eminently achievable in Britain; they included an adequate drug supply, a system for checking they had been taken, community support of patients by health and social workers, and welfare

⁸⁴ D.T. Kay, 'The Treatment of Pulmonary Tuberculosis at Work: A Controlled Trial. An Interim Report by the Research Committee of the Tuberculosis Society of Scotland', *Tubercle*, 38 (1957), 380–1.

⁸⁵ D.T. Kay, 'The Treatment of Pulmonary Tuberculosis at Work: A Controlled Trial. Report from the Research Committee of the Tuberculosis Society of Scotland', *Tubercle*, 41 (1960), 170.

⁸⁶ 'Treatment with Rest', *Tubercle*, 41 (1960), 397.

⁸⁷ Tuberculosis Chemotherapy Centre, Madras, 'A Concurrent Comparison of Home and Sanatorium Treatment of Pulmonary Tuberculosis in South India', (Abstract) *Tubercle*, 40 (1959), 468–70. The Madras Centre had been set up in 1956 as a joint venture between the Indian Council of Medical Research, the Madras State Government, the World Health Organization and the MRC.

support for those in need.⁸⁸ The Madras trial participants had been drawn from a deprived community in urban Madras, and, as Sunil Amrith has pointed out, this result was of great potential importance for shaping the future direction of WHO's global policy on TB. Perhaps the biggest non-clinical legacy of the Madras study was the recognition that providing adequate chemotherapy was available, and its administration was supervised, the underlying social determinants of TB – poverty and deprivation – were of secondary importance.⁸⁹

Analysing the clinical legacy of the Madras trials is more complex, particularly when considering the impact the trials had on practice in the UK. Helen Valier and Carsten Timmermann highlighted the fact that the 1959 Madras trial results provided convincing evidence that patients 'could be safely treated at home and with chemotherapy alone' – but this was already known by UK clinicians.⁹⁰ Long-term chemotherapy, administered at home was well established, and it had been recognised that rest in bed for extended periods was unnecessary. Helen Valier contended that entrenched attitudes by physicians militated against results from Madras having any influence at home – but it could be argued that medical practice had already altered in advance of those results being published, and this may have rendered some of the trial results irrelevant in the British context.⁹¹ That there is a debate to be had is clear, as the transcript of a Wellcome Witness Seminar in 2004 shows. Whilst Kenneth Citron's assessment of the Madras study was that it had been 'fundamental to our routine practice' leading directly to the closure of TB hospitals by the end of the 1960s, Peter Davies contended instead that people had 'taken the wrong message out of Madras'. He continued, the 'lesson of Madras is close supervision'.⁹² By the beginning of the 1960s in the UK, successful treatment was almost entirely dependent upon correct medication being prescribed by the practitioner and taken reliably by the patient. This led to the initial treatment for TB being much *more* likely to take place in hospital at the end of the 1950s than it had been earlier in the decade, albeit in the context of an active clinical scenario for triple therapy lasting two or three months rather than one of long-term admission for rest. By 1959, both Crofton in Edinburgh and Springett in Birmingham admitted almost all their patients to hospital in this initial treatment phase, to ensure they received and took the correct medication. Springett articulated his reasons for this as being both to supervise treatment, and to accommodate cultural expectations; with the 'social background in this country', he wrote, 'people who are seriously ill . . . expect to be in hospital'.⁹³ Hospital admission was brokered by a gamut of clinical, social, cultural and

⁸⁸ Tuberculosis Chemotherapy Centre, Madras, *op. cit.* (note 87), 470. The study actually found it harder to ensure continuity of treatment amongst the sanatorium group, (where there were self-discharges and absconding patients), than amongst the home group.

⁸⁹ Amrith, *op. cit.* (note 2), 126–7. However, as Amrith draws out, although the WHO went on to 'initiate parallel projects in 'crowded slums' in Tunis and Nairobi, modelled on Madras', this was in the face of conflicting evidence from a second trial of chemotherapy in which it was involved, this time in Bangalore. Here, successful treatment depended much more on both socio-economic conditions and on drug availability across the whole area; 122–3.

⁹⁰ Valier and Timmermann, *op. cit.* (note 30), 501; Crofton, *op. cit.* (note 66), 1613; 'Tuberculosis', *The Lancet*, 272 (1958), 1278.

⁹¹ Valier, *op. cit.* (note 8), 226.

⁹² Christie and Tansey, *op. cit.* (note 83), 32, 66–7.

⁹³ Crofton, *op. cit.* (note 66), 1610; V.H. Springett, 'The Results of Treatment of Pulmonary Tuberculosis in Communities in Recent Years', *The Treatment of Pulmonary Tuberculosis*, *op. cit.* (note 79), 31. Springett wrote that in 1956 almost all patients started chemotherapy at home; by 1959, they were almost all admitted to hospital; *op. cit.* (note 73), 76. Sanatorium treatment for TB was still very much part of popular culture during the 1960s, for example, espoused in Bill Naughton's 1963 play 'Alfie', which was made into a film in 1966.

public health reasons and perhaps this is why the results from Madras, important though they were for the WHO, did not really impact on clinical practice at home. Specialists already knew that treatment could be successful but they also knew that it could fail and they were not prepared to take any unnecessary risks.

Chemotherapy into the 1960s

Identifying the specifics of treatment failure and attempting to circumvent them proved challenging for clinicians during the 1960s. Medical discourse had moved from discussions over which drugs should be used and for how long, to discussions over strategies to promote regular drug-taking. The problem of ensuring that medicine was taken reliably for long periods was compounded for TB patients by the unpalatability of one of the three standard drugs, PAS. It was estimated that in the home environment, between a quarter and a half of patients did not take this drug reliably.⁹⁴ This was highlighted in a retrospective study of treatment failures in Birmingham in 1960 – by checking through what drugs had been administered where, failure to take PAS at home emerged as the most likely cause of relapse.⁹⁵ During the Madras study, Wallace Fox had found that the dependability of self-medication had been governed not by whether or not the patient attended clinic regularly, but by a whole range of social, medical and cultural factors – from unpleasant side effects to not wanting to take drugs on religious fast days. In addition to those who could give specific reasons for not taking their medication, there was a large group who were unable to give any reason at all.⁹⁶ Increasingly, specialists began to acknowledge that for treatment to succeed, both long-term support and a good doctor-patient relationship were essential. Linked to this was an awareness of the need for an easily supervised treatment regimen, acceptable to the patient, with minimal side effects and, as a leading article in *Tubercle* in 1968 exposed, although trial results had been extensively studied, analysis of the outcomes in routine clinical practice had been ‘grossly neglected’.⁹⁷ Shortly afterwards, in 1969, Graham Poole and Peter Stradling published details of a chemotherapy regimen ‘designed for effective foolproof antituberculosis treatment’. Poole and Stradling argued that they were not prepared to see effective treatment jeopardised by patients’ ‘frailties’. Delivered entirely on an out-patient basis, initial treatment with streptomycin, PAS and isoniazid was followed by streptomycin and isoniazid three times a week for fifteen months. As streptomycin had to be injected by a health professional, this was, effectively, a fully supervised home treatment course.⁹⁸ Other clinicians were prepared to give the final choice to their patients. For example, in his 1969 paper, Satinder Lal argued that in considering treatment plans, ‘the patient’s point of view must be taken into account’. Patients admitted with TB to the Fairfield Chest Unit in Bury between 1965 and 1968 had therefore been considered for

⁹⁴ Wallace Fox suggested that cultural determinants operated, because although most hospital patients in the UK took prescribed PAS, physicians in the United States, in Europe and most particularly in France experienced great difficulty in persuading their in-patients to do so; ‘The Problem of Self-administration of Drugs: With Particular Reference to Pulmonary Tuberculosis’, *Tubercle*, 39 (1958), 273.

⁹⁵ Harold E. Thomas, ‘A Retrospective Study of Cases of Pulmonary Tuberculosis Developing Drug Resistance’, *Tubercle*, 41 (1960) 44. This study led directly to a decision to admit Birmingham patients with lung cavities to hospital for six months.

⁹⁶ Fox, *op. cit.* (note 94), 273.

⁹⁷ ‘Results of Treatment’, *Tubercle*, 49 (1968), 235.

⁹⁸ Graham Poole and Peter Stradling, ‘Intermittent Chemotherapy for Tuberculosis in an Urban Community’, *British Medical Journal*, 1 (1969), 82–4.

inclusion in a trial which gave them a treatment choice. After an initial period on all three drugs, patients were given a choice between continuing with isoniazid and streptomycin, or isoniazid and PAS. Of the 70 trial participants, 67 (95.8%) chose to continue with streptomycin, despite the fact that this involved their travelling to a clinic for injections. Lal concluded that the survey confirmed 'once again' the difficulty patients experienced in taking PAS, a difficulty regarded as 'a major cause of default in the drug therapy of tuberculosis'.⁹⁹ In this instance, giving patients a choice had resulted in most having a fully supervised treatment plan – but by patient choice rather than by clinician choice. By the late 1960s, then, although there was some standardisation of dosage, and an accepted average treatment time of about eighteen months, there was nevertheless diversity in the actual drugs prescribed according to geographical location. The fact that the different strategies used all gave good results in the communities where they were offered suggests that the commitment of the supervising physician, and the relationship built up with their patients, were more important determinants of success than the actual combination of drugs prescribed or their place of delivery.

Conclusion

The standard rhetoric of streptomycin as the definitive treatment for TB from 1947 masks both the history and the success of two other methods of treatment used during the 1940s and early 1950s, bed rest and surgery. As has been highlighted here, fears over the risk of streptomycin-resistant organisms entering the community meant that initially its clinical application was limited. Combining it with other drugs lessened this risk, but even so, during the very early 1950s the principal use of streptomycin was as an adjunct to surgical treatment. The potential for chemotherapy as a curative option was thus not immediately apparent; rather, it was an incremental but rapid transition which occurred in the middle years of the 1950s, within the context of shortages of institutional beds and operating theatres. The MRC ran a series of controlled trials during the 1940s and 1950s, to investigate drug combinations, and their clinical application. Although some of the results obtained influenced clinical decision-making rapidly, such as in the case of TB meningitis treatment during the late 1940s, others did not. Determining best practice depended not only on the results of these trials – important though they were – but also on the results of clinical observation. To influence practice, trials needed to produce authoritative, timely, statistically robust evidence which 'fitted' with physician experience. Once chemotherapy as a stand-alone treatment for TB became established, ensuring that drugs were taken reliably on a long-term basis emerged as one of the most difficult aspects of clinical management. Experience was that home treatment, unless highly supervised, could fail, and although results from Madras indicated that it could be as successful as treatment in hospital, in the British context this was a risk that some specialisms were unwilling to take. It has been argued here that the pivotal lesson from Madras as far as clinical practice was concerned was that close supervision of patients on long-term chemotherapy was essential, not that sanatorium or hospital admission was unnecessary. The NHS was designed with equity of provision very much in mind. In many ways, as far as TB is concerned, its arrival can only be regarded as serendipitous in that funding for treatment increased. Untangling the web of different chemotherapy options was a conundrum and in the absence of definitive guidance, the resulting diversity of clinical practice reflected

⁹⁹ Satinder Lal, 'Patients' Preference of Drugs in the Treatment of Tuberculosis', *Tubercle*, 50 (1969), 270–1.

not only the availability of resources, but also the individual proclivity of the treating physicians. Different consultants developed their own clinical management styles and their favourite drug regimes, often tailored to their patient populations. The conclusion drawn here is that after the inception of the NHS, geographical location determined provision – what was offered, by whom and to whom, where and how – much as it had done pre-1948.

Historians have tended to be critical of the work of TB specialists during the first half of the twentieth century with doctors portrayed as wasteful of both opportunities and resources, career- rather than care-orientated. Such a characterisation is not readily translatable to the third quarter of the twentieth century. In a fast-changing clinical and epidemiological scenario, the over-riding desire of clinicians would appear to have been for treatment to succeed, and for this to happen there needed to be not only clinical expertise, but personal empathy between doctor and patient. As Kurt Toman wrote in 1976, successful treatment for TB depends upon ‘mutual human relations’, where the clinician has ‘an understanding of the patient’s non-medical problems, his way of life, work, religion, wants, fears and attitudes towards . . . medicine’.¹⁰⁰

¹⁰⁰ K. Toman, *Tuberculosis Case-Finding and Chemotherapy* (Geneva: World Health Organization, 1979), 214–5.