Streptomycin, 1946:

British central administration of supplies of a new drug of American origin
with special reference to clinical trials in tuberculosis

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Abstract

This thesis is the first detailed and integrated account of the introduction of the antibiotic drug streptomycin to Britain shortly after the Second World War. Based largely on archives of the Medical Research Council (MRC) and other Departments, it describes how the central government handled imports, production, distribution and clinical research. It provides an alternative to a literature focusing narrowly on the research methods used in the MRC's clinical trials.

Streptomycin, isolated in the USA in 1943, was developed commercially under government control, following the model of penicillin. Laboratory results suggested that streptomycin was potentially useful in treatment of several diseases, including tuberculosis, which was then a major public health problem in many countries. The Ministry of Health anticipated a surge of public demand for this drug, that was then extremely expensive in its country of origin and not yet available in the UK, while there was still little sound evidence of its effect in human disease. The Ministry of Supply agreed to allow industrial firms to develop facilities to produce enough streptomycin for the MRC to ascertain its clinical value; however, domestic production was continually delayed. Following months of frustration of British attempts to procure even small quantities of streptomycin from the USA, finally, in November 1946, American export control authorities released a huge quota of the drug at a cost of £80,000. The Treasury approved the purchase, which was earmarked for research.

Drawing attention to the management of material resources through selective framing of knowledge, this thesis provides a portrait of the work of technical experts within a bureaucratic system, and it reveals how the shortage of streptomycin shaped the existence and form of an important research programme.
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Chapter 1. Introduction

1.1 Overview

In January 1947, the first patients were enrolled in an experiment that would become a landmark in medical history, the clinical trial of the antibiotic streptomycin in pulmonary tuberculosis. Although no one knew for sure whether this substance, discovered in 1943, would turn out to be another 'miracle drug' like insulin or penicillin, many scientists and members of the British public had high hopes. Tuberculosis, the country's leading killer of young adults, might finally be treated more effectively than with months of rest in a sanatorium.

Doctors and patients by the hundreds were trying in vain to obtain streptomycin from the Medical Research Council (MRC), which held almost the whole supply in the country. The government had just imported from the USA a massive stock of the product, 50 kilograms, and decided to sponsor domestic manufacture. The Treasury was preparing to spend £140,000 on streptomycin clinical trials, more than on all of the MRC's other clinical research projects combined. But a year earlier, at the start of 1946, the situation had been very different. Hardly any members of the public had heard of streptomycin. The MRC was unable to procure so much as 500 grams of the substance. And the question of British government subsidies for production was not even on the agenda.

How could the position change so drastically in such a short time? Why did the British government purchase such a huge quantity of the drug? Why did it conduct its own clinical trials at all? The existing historical literature, consisting of brief and fragmentary accounts, does not answer such questions. This thesis provides the first detailed and integrated account of the introduction of streptomycin to Britain. It brings together aspects of the streptomycin story that have been discussed in isolation: imports, production, distribution and research. We shall see that once all these pieces are in place, this will lead to a revision of each of the partial stories that have been written.

I place supplies of streptomycin at the very heart of my account. Hundreds of letters and memos dealt with issues of supply: attempts to import the drug from
the USA, attempts to ensure that stocks of it did not go to waste, uncertainty about whether to boost domestic production. These were among the British Government's primary concerns around streptomycin; by contrast, during the whole of 1946 the now well-known scheme of random allocation of patients in one of the clinical trials was mentioned in a single letter. In the course of providing an account of the introduction streptomycin, I will thus also provide an alternative account of the streptomycin clinical trials, correcting the emphasis in existing literature on that sub-topic.

Streptomycin deserves historical attention for many reasons. It was the second antibiotic to come into widespread use, after penicillin. It was phenomenally expensive at first, coming onto a restricted market early in 1946 at a cost of $16 per gram, worth more than its weight in gold. Its commercial success helped create a boom in the pharmaceutical industry. Along with insulin, penicillin and sulphonamides before it, and cortisone afterwards, it belonged to a relatively small class of substances that were hailed by the general public as 'miracle drugs' and helped to transform doctor-patient relationships. On it were conducted major research programmes, in which methods were used that have served as a model for the evaluation of other medical treatments. It arrived at a key juncture in the history of medicine in Britain, at the end of the Second World War and prior to the implementation of the National Health Service. It was the first effective chemotherapeutic treatment for pulmonary tuberculosis, and, along with the drugs that followed in its wake (beginning with para-aminosalicylic acid in 1948 and isoniazid in 1951), helped cut annual tuberculosis mortality from some 25000 deaths just after the war to a few hundred during the 1970s, and eventually bring about closure of sanatoria that had consumed vast amounts of public expenditure. It was the first effective treatment for two conditions that had hitherto been all but uniformly fatal, namely tuberculous meningitis and acute miliary tuberculosis; the former killed about 500 people per year in Britain, the large majority being young children. It remains the treatment of choice for bubonic and pneumonic plague.

Yet for all the importance of streptomycin, we lack a critical history of this
drug, as the historian of medicine Donald McGraw observed last decade. The winner of the Nobel Prize for the discovery of the drug, Prof Selman Waksman, had written an autobiography and a rather self-congratulatory history of tuberculosis. There were at the time other histories of tuberculosis, sections on streptomycin in many popular histories of antibiotics, and brief memoirs by scientists involved in early American research. All these works concentrated on the discovery and initial development of streptomycin in the USA. Such works as have appeared on streptomycin in the last two decades have continued to look at early development of the drug, and there is still no comprehensive account. Much of the focus remains narrowly on medical scientists even in works that

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2 Selman A. Waksman, My Life with the Microbes (New York: Simon and Schuster, 1954); idem, The Conquest of Tuberculosis, (London: Cambridge UP, 1964); also, idem, "Tenth anniversary of the discovery of streptomycin, the first chemotherapeutic agent found to be effective against tuberculosis in humans", Amer.Rev.Tuberc. 70.1 (Jul 1954), 1-8.


extend to a later period. New books with a social historical approach have shed much light on tuberculosis, but have not gone into detail on streptomycin.

The most balanced existing account of how streptomycin came to Britain consists of a mere five pages in Linda Bryder’s history of tuberculosis in twentieth century Britain, Below the Magic Mountain. It focuses largely on clinical trials, and says nothing about production. Significantly for this thesis, Michael Worboys has criticized the book for treating medical knowledge separately from professional, institutional and administrative changes. The rest of what we know about the international spread of streptomycin from about 1945 onward is largely anecdotal, consisting of snippets about isolated aspects of the story. Waksman characterizes the British reception of the drug as overly skeptical, describing the publicity about toxicity of the drug as exaggerated.

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11 Waksman, Conquest. Only Bryder repeats his claim, and without substantive elaboration.
telephone calls and that there was believed to be a "lively international traffic in contraband streptomycin". One account mentions how a special shipment of streptomycin for George Orwell was arranged early in 1948. A history of the American manufacturer Merck mentions licensing of streptomycin production methods to an unnamed British firm. Davenport-Hines and Slinn, in their history of Glaxo, provide a rare discussion of the economic significance of streptomycin, describing the company's £400,000 investment in production facilities. They do not mention clinical trials of streptomycin at all, nor describe in any detail the company's production efforts prior to 1948.

On a single aspect of the British streptomycin story is there an established account, which describes the pioneering clinical trials, the clinical researchers and the medical statistician Bradford Hill. As Harry Marks has remarked in the context of other literature on clinical trials, when methodological innovations take centre stage "a peculiar narrative results in which history is blindly driven forward by scientific progress." His criticism can aptly be applied to this body of

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17 Harry M. Marks, "Notes from the underground: The social organization of therapeutic research", in Russell C. Maulitz and Diana E. Long (ed), *Grand...
literature, which will be examined more thoroughly in the chapter on clinical trials. For the purposes of addressing the more general themes raised in the current chapter, we should note that these works agree that a link existed between the MRC's research and economic circumstances, but our picture of that link is very incomplete, and often misleading.\textsuperscript{18} The huge cost of the research programme is never mentioned, and the industrial angle is all but forgotten. In much of this literature, published papers and personal recollections have been taken at face value, and the claims reported in one account are then repeated in another with little refinement, so that familiarity has taken the place of hard evidence. As a consequence, in half a century, the MRC's original public portrayal of the trials has remained virtually unchallenged.

Like Marks, I found that oral history interviews were of little use in constructing a narrative history, although they provided valuable insights into the medical research culture of the time. (See notes on sources in the Bibliography.) As practitioners of oral history have noted, the oral tradition cannot be relied upon for factual detail.\textsuperscript{19} Physicians involved in streptomycin research have, for example, told me on several occasions that the public demand for streptomycin was not particularly intense, and that one of the key members of the streptomycin clinical trials committees had nothing to do with streptomycin.\textsuperscript{20}

Instead, this study sticks close to documentary primary sources. It is based largely on archives of the MRC and other British Government Departments, supplemented by American federal government and university sources, and an industry source. To illuminate the state of scientific and medical fields, I have


\textsuperscript{18} The picture consists almost solely of the argument that a shortage of streptomycin made it ethically justifiable to leave some experimental patients untreated.


turned to published papers, on the understanding that they should not necessarily
be taken at face value. I closely contextualize these primary sources. As we shall
see, the customary civil service ethic provided license for official external
communications to mislead the public, while internal communications presume the
reader’s membership in an exclusive organizational culture. Thus documents of
both kinds are readily intelligible only through familiarity with the period context.

It follows from my intensive approach to sources that a tight limitation on
the period of the thesis has been necessary. I focus on quite a short time span,
from January 1946 to January 1947, with a few threads traced back or followed
forward as necessary. During this period the system was set in place that led to
further purchases of the drug for research and treatment, and to implementation
and eventual publication of the trials.

Likewise I limit the scope of this study to how British central
administration dealt with streptomycin, as I will discuss further below. I focus
unapologetically on the Whitehall bureaucrats who, in an era of centralized
planning, simply carried more weight in the story of streptomycin supplies than
did other historical actors. (See the biographical appendix.) In particular, the
current study makes only a limited attempt to tackle patients’ issues. Sheila
Rothman’s monograph exemplifies a welcome recent trend in history of medicine
towards considering "the patient’s perspective".21 Her justification for her
project, however, conflates two independent choices of the historian: the topic of
study (patients or doctors), and the values applied to it, ie, whether to historicize
or to take for granted the "language and constructs of medicine".22 A study
focusing on "innovative physicians and prize-winning investigators,... eminent
hospitals... and therapeutic advances",23 which is in part what I undertake, need
not adopt a celebratory or uncritical attitude. Patients’ experiences per se were, I

21 Sheila M. Rothman, Living in the Shadow of Death: Tuberculosis and the
social experience of illness in American history, (Baltimore: Johns Hopkins UP,
1995).

22 Rothman, p.1.

23 ibid.
argue, simply not consequential in the resolution of the historical struggles at stake here—however crucial they were to the patients and their families themselves, and however illuminating they might be about broader cultural themes of illness and death. As Rothman and others have noted, if we look for a shifting balance of power, we see the mid-twentieth century as one of the zeniths in doctors’ power to act without attending to their patients’ voices. During my period, the authority to declare whether a treatment for tuberculosis was efficacious, whether a clinical experiment was scientifically valid, or how government’s public health resources should be allocated, rested firmly under the control of elites, and this study focuses unapologetically on those elites. What mattered within a hierarchical system like the English civil service was how the people in charge of the health care system perceived patients’ experiences, beliefs and desires. If any further justification were needed for this choice of scope, a full and representative picture of patients’ contemporary experiences would require sources that are almost by definition dispersed far from the documentary traces of their interactions with officialdom. On my narrower view of patients, the official sources are genuinely revealing.

Since most of the narrative to be presented here is new to the public record, discussion of the specific relations among the four main threads (imports, production, research and distribution) must be saved for later, but we may note that similar threads can be seen in the case of penicillin, about which there is a substantial body of historical literature on research, production and distribution—there is little on early imports and exports per se. Penicillin was invoked as the primary model for the handling of streptomycin. Penicillin involved many of the same drug companies on both sides of the Atlantic, an overlapping set of government officials, similar media promotion and similar public pressures for access to treatment. Streptomycin thus provides an important comparison case. The historian David Adams has described the distribution of penicillin to American civilians during the war, but does not relate this to the research that was the

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rationing body's primary responsibility. The official history of the MRC's wartime research mentions in passing that the need for a mechanism for controlling penicillin distribution was one reason for setting up the MRC's Penicillin Clinical Trials Committee. In the case of insulin in the early 1920s, the MRC ran clinical trials of insulin in Britain after it had been proven to save lives in Canada and the USA. But we are still in need of accounts of how research is linked to distribution of drugs at the early "experimental" stage.

It should be emphasized that during the period up to the end of 1946, much of what is now known about streptomycin remained uncertain. It was unclear whether the drug would be effective against tuberculosis in the long term, or indeed how effective it was in the short term. It was not altogether clear whether such side effects as had been observed were the result of the drug itself or of impurities from the manufacturing process. Researchers in the USA had found the emergence of strains of bacteria resistant to streptomycin, and this would eventually become one of the major clinical limitations of the drug, but relatively little was known about this at the time. In addition to these points of uncertainty that were generally shared, it must be emphasized that particular pieces of new information did not, in general, become available to key people—let alone to marginal players—at the same time. During the period examined in this thesis, research was proceeding at a very rapid pace—some 2000 research papers on streptomycin were published between its discovery in the autumn of 1943 and the summer of 1948—and the


rumour mill was active. Reconstructing what anyone believed about streptomycin at any given time is difficult: it cannot be read off automatically from the existence of a research paper on the topic. Knowledge was socially localized in specific communities. This story, in other words, deals with compartmentalized knowledge. This thesis depicts social worlds where information was often shared grudgingly, where delays and breakdowns of communication were the norm, where an elite civil service jealously guarded its own authority.

Knowledge and power were intimately related: the concentration of expertise within a small elite made it possible for selective framing of knowledge to be used to advantage in struggles over industrial planning, drug distribution and trade, as we shall see in numerous incidents throughout the thesis. This study will reveal how expertise helped to shield Whitehall from accountability for decisions about streptomycin. We shall find echoes of this pattern in the gradual accretion of a standard account about streptomycin clinical trials, one that through selective framing has obscured our view of how the British government handled streptomycin. It is time for an integrated account.

1.2 Outline of chapters

This Introduction has provided an overview of the key themes and a discussion of existing secondary literature, other than that on clinical trials, which is addressed in Chapter 6. We now turn to an outline of the remaining chapters. Chapter 2 focuses on the rapid development of scientific knowledge about streptomycin, particularly as a potential chemotherapy for tuberculosis. I describe early research on streptomycin from the discovery of the substance in 1943 up to the end of 1945. Making reference to an MRC scientist's lecture to elite physicians, I describe the long history of failed treatments for tuberculosis, and the new wave of research at the end of the war. The machinations behind a prestigious lecture series, the Harben Lectures, reveal the cooling of the MRC's attitude towards publicity about streptomycin. Finally, the content of the Harben Lectures is summarized, to explain and illustrate the excitement about streptomycin within the scientific and medical communities in the summer of 1946.
The fundamental political and public health background to the streptomycin purchase is laid out in Chapter 3, on demand and distribution. A typology of public requests is presented. Issues of fairness and the lack of a shared standard of appropriate research are highlighted by an incident involving a powerful official seeking streptomycin for a family member with leukaemia. A scheme of distribution through emergency broadcast appeals for the drug heightened tensions over who should have access. The government's response to the ensuing heavy demand bypassed sophisticated arguments about the need for properly controlled research, in favour of a crude but effective attempt to raise public fears that the drug was toxic.

Chapter 4 lays out the attempts to minimize the shortage by stimulating British production. It compares this briefly with American policy. It explains why the Ministry of Supply approved priorities for streptomycin production in June 1946, and goes on to show how the production plan was tailored to the MRC's stated requirements.

Chapter 5 describes early attempts to procure the drug from abroad. I compare American requests and official responses with the British case described in Chapter 3. Relaxation of American export restrictions in the autumn of 1946 resulted from enhanced production and the market conditions in the USA, while Canadian production made it possible for a small sample to be sent for standardization purposes. The British government's process of accepting the first export allocation illustrates the priorities of the Treasury.

Chapter 6 describes the planning of clinical trials, the aspect of the British streptomycin story that has been the subject of almost all the attention to date. I review, in light of the new archival evidence, features of the experimental design that have been discussed in the secondary literature, such as the scheme of control groups and the careful definition of cases. I show how the government's supply concerns can help explain these features, along with the MRC's insistence that only large-scale research could provide sound knowledge of the properties of streptomycin. I also clarify that the MRC delegated limited responsibility to its clinical committees, and the relationship between tuberculosis research and other projects involving the drug. In an epilogue, I chronicle the evolution of the
standard story of the streptomycin clinical trials.

The culmination of the thesis, however, is not the design of the trials but the decision that allowed the trials to take place at all, namely the approval in mid-November 1946 of the purchase of a large quantity of American streptomycin. This key economic event is examined in Chapter 7. First I describe the principles of Treasury oversight of the MRC, in relation to the new political climate. I also examine the question of whether the government would commit to purchase the initial output of British streptomycin producers. I describe the American offer. I analyze in detail a crucial document, in which the MRC explained its case to the Treasury. Finally I describe the interdepartmental meeting about the purchase, and its aftermath.

A concluding chapter recapitulates these events in chronological order, to remind the reader of connections between contiguous events. I draw some connections with bodies of historical literature on tuberculosis, clinical trials and the pharmaceutical industry. Finally I offer an assessment of the British government's streptomycin programme.
Chapter 2. The Research Background: Chemotherapy of Tuberculosis

My colleagues and I view the present status and future possibilities of chemotherapy in clinical tuberculosis with hopeful enthusiasm, being ever mindful of the fact that neither streptomycin nor any of the other known substances that have proved effective in experimental animals can fully qualify as the long awaited curative drug.

William Feldman, Harben Lectures, 17 July 1946.¹

The need for caution has been learned from bitter experience of the past failures with gold, copper and tuberculin, and from the false promise given by animal experiments with the sulphones.

Philip Hart, Mitchell Lecture, 9 July 1946.²

In the summer of 1946 many British medical practitioners first heard authoritative and detailed descriptions of the new antibiotic, streptomycin. Several public lectures presented findings from studies of the drug’s use in the treatment of tuberculosis. The lectures placed the recent results on streptomycin in the context of a long and error-filled tradition of attempts to find effective drug therapies for this disease. The speakers represented elite medical research institutions: Dr Philip Hart from the Medical Research Council (UK), and Dr William Feldman from the Mayo Clinic in Minnesota. Despite the caution with which these two scientists characterized the existing evidence on streptomycin, one can imagine the responses among the members of the various audiences. Specialists attended a meeting of the Tuberculosis Association in Oxford which the presiding officer looked back on as


the most exciting moment in his professional life. Members of the august Royal College of Physicians heard that streptomycin seemed "more promising than any previous chemotherapeutic agent" against tuberculosis. Medical Officers of Health in the audience at the Royal Institute of Public Health and Hygiene saw dramatic diagrams illustrating the high survival rate of tuberculous guinea pigs treated with streptomycin, contrasted with that of their untreated counterparts. Such experimental data, in conjunction with recent clinical reports, gave new and firmer grounds for hope for the eventual control of a disease which was blamed for some 25,000 deaths annually in Great Britain. This figure was still greater than that for any other infectious disease, despite the huge decline which had occurred in reported tuberculosis mortality rates over the course of the previous century, steady progress having been interrupted only by the two world wars. The causes of this decline have long been debated by historians and epidemiologists, but there is a consensus that treatment with drugs was not a major contributing factor until after World War II.

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4 Hart, Mitchell Lecture, p.852.

5 Feldman, Harben Lectures, p.347.


8 The literature on this topic is vast. For the claim that an improving nutritional level was responsible, the best known exponent is Thomas McKeown. For a polemical challenge to the McKeown thesis, instead crediting public health preventive measures and services at the local authority level, see Simon Szreter, "The importance of social intervention in Britain's mortality decline c.1850-1914: a reinterpretation of the role of public health", Social History of Medicine 1.1 (1988), 1-39. For a sophisticated assessment of such arguments in relation to relatively reliable local data, see Anne Hardy, The Epidemic Streets: Infectious disease and the rise of preventive medicine, 1836-1900, (Oxford: Clarendon Press, 1993), pp.211-266.
2.1 The first research on streptomycin

Streptomycin was first described in a paper published in January 1944, entitled, "Streptomycin, a substance exhibiting antibiotic activity against gram-positive and gram-negative bacteria". Credit for the discovery of streptomycin has been the subject of bitter controversy, which erupted late in the 1940s and therefore need not detain us for long. The microbiologist Milton Wainwright has shown conclusively that around November 1943, Albert Schatz, who was then a postgraduate student at Rutgers University, first isolated the substance now known as streptomycin, and showed that it inhibited the growth of various bacteria in vitro. His supervisor, Professor Selman A. Waksman, directed the research programme, however, and it was Waksman who has generally received the scientific credit for discovering streptomycin, including the 1952 Nobel Prize. Streptomycin was a metabolic byproduct of one of the actinomycetes, namely Actinomyces griseus—often known alternatively as Streptomyces griseus, in accordance with Waksman's taxonomy; the actinomycetes were organisms classified between fungi (like Penicillium) and bacteria. As the physiologist


11 As the original streptomycin discovery paper remarked, the organism which produced the substance was "similar, in most of its cultural characteristics as well as in its morphology, to Actinomyces griseus", which it pointed out had been isolated some 28 years previously, footnoting a paper by Waksman himself. Schatz
Julius Comroe has pointed out, streptomycin was originally of interest primarily for its action against gram-negative bacteria, which were generally not susceptible to treatment with penicillin or sulphonamides and were responsible for a number of serious diseases. These included *Salmonella* food poisoning and some urinary tract infections which were of concern to the US Army and Navy. The tubercle bacillus, which was gram-positive, received only a fleeting mention in the first publication on streptomycin. The second research paper on streptomycin, published in August 1944, reported its effect in mice infected with five organisms, including fowl typhoid and a species of *Salmonella*, but made no mention of the tubercle bacillus. But soon the potential of the new substance to treat tuberculosis became a major focus of research.

The scientific literature on streptomycin accumulated rapidly over the next several years. Waksman compiled a bibliography which contained nearly 1200 entries in its first edition, published in 1948, and 5550 in the 1952 edition. In 1944, there were 9 scientific papers on streptomycin; in 1945, at least 55; and in 1946, more than 236. American journals and American researchers accounted for the overwhelming majority of these papers during the first three years. Much of this research was published in the fortnightly house journal of the Mayo Clinic, one of the USA's leading clinical referral centres, located in the town of

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14 These figures are derived from a count of the first 500 entries in the book, which is in rather rough chronological order.
Rochester, Minnesota. The first researchers to work with streptomycin, other than members of Waksman's group itself and Merck & Co (the firm that developed streptomycin commercially), were two investigators at the Mayo Clinic, Dr William H. Feldman and Dr H. Corwin Hinshaw. They published in September 1945 the first report on the use of streptomycin in human tuberculosis. Their first such patient was a young woman with pulmonary tuberculosis, whose treatment began on 20 November 1944. The Mayo study covered 34 patients. Sixteen of them had pulmonary tuberculosis, in which they said the drug "did not appear to have any rapidly effective curative action", but there tended to be prompt improvement of recently-developed lesions. They described their series as obviously inadequate in size, and said that a "more extensive and more closely controlled study" was underway. Certain other extra-pulmonary forms of tuberculosis were recommended for study, in preference to the more common forms of chronic pulmonary tuberculosis, in which they predicted that striking benefit would be unlikely. They emphasized that care in a sanatorium and collapse therapy were thoroughly proved to be effective therapies, and should in no instance be abandoned in favour of agents whose efficacy was still not conclusively


16 Comroe, p.961. According to Wainwright's historical investigations, the first person to be cured with streptomycin was a 2 year old boy who was treated by Dr W. Richards for a heavy urinary infection, septicaemia and meningitis at New York Babies' Hospital. Wainwright did not identify the type of meningitis. The boy's treatment was declared a success in a letter to Waksman dated 27 September 1944. See Wainwright, Miracle Cure, pp.126-127.

demonstrated. A few months earlier, in May 1945, the first clinical report on streptomycin dealt with its use in five cases of typhoid fever, to which I will refer in Section 3.2. The first review of clinical uses of streptomycin in conditions other than tuberculosis, published in November 1945, described the Mayo Clinic’s results with 45 patients. Eight patients with bactaeremia due to gram-negative organisms recovered. They considered their results "good" in ten of thirteen cases of urinary tract infections. They suggested that streptomycin might prove of value in certain pulmonary infections such as Klebsiella pneumonia. Four cases of influenzal meningitis were treated, with apparent eradication of infection, although one of the patients died later of complications. On the basis of 30 patients, Heilman and colleagues at the Mayo Clinic concluded, "In any of the cases studied, serious and uncontrollable toxic reactions were not encountered following administration of fairly large amounts of streptomycin in single or repeated injections. In some instances, streptomycin has been administered to patients for a considerable time without evidence of toxic reactions." Hinshaw and Feldman described streptomycin’s toxicity as low, in September 1945, and said that serious reactions were rare. Fever was observed after injection with some lots of the drug, which were judged unsuitable for clinical use and therefore reserved for animals; this had been common with early lots of penicillin as well. As they wrote, the reactions were less severe in recent months than when the first patients were treated with relatively impure material. They found one case of transient deafness, and several cases of vertigo after prolonged administration of the drug. For a while there was much uncertainty as to whether the toxic effects were due to


streptomycin itself or to various contaminants arising from the manufacturing process.\textsuperscript{22} By the end of 1945 there were many laboratory studies but little clinical data in print. In light of what was to come in the UK, I remind the reader that the Mayo studies also stressed uncertainty and advised caution with the apparent purpose of discouraging requests for the drug. Even the best-informed scientists in the USA held considerable uncertainty about the effects of streptomycin and about the best way to use it.

2.2 The Mitchell Lecture

Hart spoke before the Royal College of Physicians (RCP) on Tuesday 9 July. At the time he was on the external staff of the MRC, working at one of the Council's research outposts, the National Institute for Medical Research Farm Laboratories, in Mill Hill in the northwest of London. His Mitchell Lecture took the form of a historical overview of the trends in tuberculosis research which, from the MRC's point of view, made it advisable for doctors to take a cautious attitude towards streptomycin. His expressed intent was to trace the development of the chemotherapeutic aspect of tuberculosis treatment, so that the physician, and particularly the non-specialist, might see in perspective the successes which he forecast.\textsuperscript{23} That is, while some members of the RCP practised in tuberculosis sanatoria and could be presumed to have some familiarity with the rise and decline of tuberculosis remedies, the majority of physicians treated tuberculosis as only a small part of their work. We might construe this as an assumption that those who lacked specialist knowledge would be more susceptible to fads and fancies.\textsuperscript{24} Hart


\textsuperscript{23} Hart, Mitchell Lecture, p.805.

\textsuperscript{24} Tuberculosis treatment was not necessarily unusual in this respect, although some writers have tended to characterize the field as a hotbed of quackery. See eg David Cantor, "Cortisone and the politics of drama, 1949-55," \textit{Medical Innovations in Historical Perspective}, ed. John V. Pickstone (New York: St. Martin's, 1992), 165-184; c.f. F.B. Smith, "Gullible's travails: tuberculosis and
thus pointed out that he was omitting discussion of what he referred to as innumerable 'consumption cures'. Instead, he focused on the more than 60 substances which recent scientific reports had said were active against tubercle bacilli (the bacteria responsible for tuberculous infection and disease). The term "chemotherapy", as Hart noted, was used with a variety of senses, which had shifted in prevalence over the years. He took as its defining characteristic that its objective must be to attack the parasites, say, protozoa or bacteria, within the body of the host organism, either by destroying them outright or weakening them sufficiently that they became vulnerable to the host's own defensive powers. The credibility of the chemotherapeutic approach to tuberculosis was probably at a low point by 1935, Hart suggested. But in that year it was reported that the synthetic substance sulfanilamide was able to control previously intractable infections in mice, caused by bacteria known as streptococci. Three years later, researchers at Johns Hopkins University in Baltimore claimed some degree of inhibition of tuberculous infections in guinea pigs (the experimental animal of choice for tuberculosis research), when large and frequent doses of sulphanilamide

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26 These publications were listed in the annual Index Medicus. His survey did not dwell on the developments in thoracic surgical treatment, such as artificial pneumothorax.

27 Hart said that all were agreed that the term excluded both therapy by means of immune bodies (such as tuberculin), and purely symptomatic treatment. According to Paul Ehrlich, who coined the term, a key criterion of chemotherapy was "specific" action, the direct targeting of infective organisms. Hart, however, argued that some cases of apparently indirect action were properly regarded as examples of chemotherapy, one such being gold therapy, which had been prominent in tuberculosis treatment. Chemically synthesized agents such as sulphonamides, and compounds obtained from natural or biological sources were included; he made no sharp distinction between substances on the basis of origin, because it was widely expected that antibiotics might be produced by synthesis instead of by fermentation. Hart, Mitchell Lecture, p.805.

28 Despite the common root of their names, there was no notable microbiological connection between streptococci and streptomycin.
were given.\textsuperscript{29} Such developments encouraged the further investigation of the chemotherapeutic approach. Hart said that some of the sulphones (a group of synthetic substances which were chemically similar to the sulphonamides) gave striking results in the inhibition of tuberculous disease in guinea pigs, but that the majority of clinical trials were unfavourable. One of his explanations was that low tolerance for the drugs and the risk of toxic symptoms such as anemia made it difficult to administer dosages which would have an adequate effect on the disease.\textsuperscript{30} Hart’s list included other organic compounds which were developed within a few years into a standard combination therapy for tuberculosis.\textsuperscript{31}

The climax of Hart’s lecture was his discussion of streptomycin, which he introduced as one of the antibiotics. The term "antibiotic", in its modern sense of a substance produced by one micro-organism and found to be inhibitory to the growth or activity of another species of micro-organism, was proposed in 1941 by Selman A. Waksman, Professor of Microbiology at Rutgers University in New Jersey. In 1940 and 1941 the chemotherapeutic properties of penicillin were announced by researchers from the Dunn School of Pathology at Oxford University, led by Howard Florey and Ernst Chain. In December 1945, a Nobel Prize went to these two men along with Alexander Fleming from the Wright Institute of Microbiology at St Mary’s Hospital in Paddington, who had first identified the bactericidal properties of penicillin, in 1929.\textsuperscript{32}


\textsuperscript{31} In addition to streptomycin, these were \textit{p}-aminosalicylic acid (later abbreviated PAS), which was put to clinical trial starting in 1948; and nicotinamide, a close predecessor of a drug which reached the stage of clinical trial in Britain in 1952, namely isonicotinic acid hydrazide (known as isoniazid or INH).

\textsuperscript{32} The best of the numerous general historical books on penicillin is Gladys M. Hobby, \textit{Penicillin: Meeting the challenge}, (New Haven: Yale, 1985).
described penicillin as virtually lacking toxicity and having very high efficacy in systemic infections by susceptible organisms.\(^{33}\) The tubercle bacillus, however, was not significantly affected by penicillin, it had been found in several in vitro and animal experiments.\(^{34}\) Hart listed a large variety of antibiotic substances which had been tested for activity against the tubercle bacillus; many of these were isolated from moulds, while some came from bacteria, such as licheniformin from \textit{Bacillus licheniformis},\(^{35}\) and some from the actinomycetes.\(^{36}\) So far, Hart said, he knew of only two antibiotics for which complete investigations of anti-tuberculosis potential had been made: streptomycin (which had been studied in Waksman's laboratory in 1941, but was rejected on grounds of excessive toxicity and failure to control experimental tuberculosis in the guinea pig) and streptothricin.\(^{37}\)

Hart's cautionary tone is best illustrated with his extended discussion of sanocrysin, a gold salt which was introduced in 1924. He dubbed the period from 1925 to 1935 the 'gold decade', on the basis of the frequency of papers about sanocrysin. By the end of the war, he said, only a few stalwart believers used the

\(^{33}\) The first fatal allergic reaction to penicillin was reported in 1949. Whorton, p.131.

\(^{34}\) Hart, Mitchell Lecture, p.851.

\(^{35}\) Hart and his colleague R.K. Callow were studying licheniformin at the National Institute for Medical Research Farm Laboratories.

\(^{36}\) This family yielded antibiotics such as actinomycin and micromonosporin. Seven such antibiotics from actinomycetes were known in November 1944, according to a paper by the Rutgers researchers. Selman A. Waksman, Elizabeth Bugie, and Albert Schatz, "Isolation of antibiotic substances from soil microorganisms, with special reference to streptothricin and streptomycin", \textit{Proc. Staff Meet. Mayo Clin.} 19.23 (15 Nov 1944), 537-548. Of these substances, only streptomycin and streptothricin were said by them to "deserve careful consideration as chemotherapeutic agents", at p.537.

drug, in a few conditions. He drew from the sanocrysin story several lessons for chemotherapeutic assessments:

(1) The laboratory groundwork on the curative effect of sanocrysin was insecure, and the drug was heavily sponsored for general therapeutic use without adequately critical clinical trials. (2) The drug's toxicity relative to presumed effective dose was at first underrated. (3) The clinical benefit was not dramatic or constant enough to dispense with balanced controls...

We shall see how the MRC argued that similar problems ought to be avoided in the testing of streptomycin. Hart's historical lecture emphasized that it was difficult to produce sound laboratory results in tuberculosis treatment, and harder still to extrapolate from such findings to knowledge about how useful a drug would be in clinical use. This cautious perspective was shared by Feldman and Hinshaw, who had since 1940 published the most widely cited scientific reports on experimental treatment of tuberculosis in guinea pigs. They wrote in 1944 the first experimental report on streptomycin in animal tuberculosis. It was for that work, and for the Mayo clinical research on streptomycin which began to appear in 1945, that the MRC sought to bring Feldman on a tour of Britain.

2.3 Preparations for the Harben Lectures

38 Hart, Mitchell Lecture, p. 808.

39 Hart, Mitchell Lecture, p. 809.

40 Hart argued that certain methodological safeguards were desirable, one being a control group of patients, who were not treated with the drug in question. In the testing of sanocrysin, one of the rare clinical trials to use such controls had yielded discouraging findings, as Hart pointed out. See J. Burns Amberson, B.T. McMahon and Max Pinner, "A clinical trial of sanocrysin in pulmonary tuberculosis", American Review of Tuberculosis 24 (1931), 401-435.

The MRC attempted early in 1946 to stir up British medical interest in streptomycin. In striking contrast to events later in the year, no reservations about this endeavour were exhibited during the winter months. Despite the lack of familiarity at MRC headquarters with the state of the art in tuberculosis treatment, this project was presented to the Royal Institute of Public Health and Hygiene (RIPH) as a priority. It is quite possible that the prestige associated with the field of new antibiotic drugs explains the MRC's actions.

At the beginning of 1946, William Feldman informed Sir Ernst Chain at Oxford that he would be very interested in visiting Britain to give a number of lectures on his work. Chain mentioned this in a letter to Sir Edward Mellanby, the top administrator at the MRC, following a meeting they had had on 21 January. Chain wrote, "I am certain that his visit will be very stimulating to many workers in this country and should attract considerable interest." Feldman was identified as "a pathologist by profession and one of the soundest experimentalists in the field of experimental tuberculosis", in which he had been responsible for studies of promin and streptomycin. The very next day, the president of the Royal Institute of Public Health and Hygiene, H.H. Gerrans, asked Mellanby to nominate a speaker for the institute's annual Harben Lectures. These lectures, on some aspect of public health and science, were normally held during the final three months of the year; however, Mellanby urged the Institute to move ahead their date. Passing on Chain's recommendation, Mellanby wrote to Gerrans, "it is rather an urgent matter that he [Feldman] should come here soon and, if his visit could take place in June, it would be a very great advantage to medicine in this country." Mellanby described streptomycin as an "exciting" development, one

42 Chain to Mellanby, 24 Jan 1946, FD1/3258.
43 ibid.
44 ibid.
46 Mellanby to Gerrans, 22 Feb 1946, FD1/3258. In light of the purported urgency, it is rather curious that it took a month, and a reminder from Chain, for Mellanby to respond to Gerrans' initial request. Chain to Mellanby, 21 Feb 1946,
in which "scientific and medical men would take a great interest". Chain was told of the RIPH's approval of the invitation, and he was asked for "some information about the matter as they seem to know little about him [Feldman] from reputation". His reply was effusive about Feldman's reputation among pathologists and bacteriologists, and described as the most suitable scientist who might provide "full information on the present state of the treatment of various forms of tuberculosis by streptomycin".

In April, Gerrans relayed Feldman's stated desire to "visit certain Research Laboratories and Tuberculosis Sanatoria, in order to obtain an impression of the work which is now going on here [in Britain]". Though Mellanby had been Secretary since 1933, he declared himself unfamiliar with the tuberculosis field, in a letter to Harold Himsworth, to whom he turned for advice. A week after receiving this request, Himsworth described himself as having "no inside knowledge of the quality of work going on in that field". He in turn recommended asking Philip Hart or else the Oxford bacteriologist and pathologist, A.Q. Wells. Only then did Mellanby write to ask for advice from Hart, who had been the secretary of the MRC's Committee on Tuberculosis in Wartime. Hart provided a list of clinical sites which Feldman might visit. Not suprisingly in light of his prominence in the Socialist Medical Association, he specially marked

FD1/3258.

47 Mellanby to Gerrans, 22 Feb 1946, FD1/3258.

48 Mellanby to Chain, 25 Feb 1946.

49 Chain to Mellanby, 2 Mar 1946, FD1/3258.

50 Gerrans to Mellanby, 9 Apr 1946, FD1/3258.

51 Mellanby to Himsworth, 10 Apr 1946, FD1/3258. Mellanby also wrote for advice to Chain but there is no record of any reply.

52 Extract from Himsworth to Mellanby, original file not stated, 17 Apr 1946, FD1/3258.

the individuals on his list who he said were knowledgeable about "broader aspects" of the tuberculosis problem. Hart’s list included the Wellcome Research Laboratories in Beckenham, and Imperial Chemical Industries (ICI) in Manchester-- neither of which, interestingly, became commercial manufacturers of streptomycin. Mellanby deleted these industrial firms when he made a copy of Hart’s list to be passed on to Feldman.55

In March, however, Mellanby’s enthusiasm for the visit had cooled. At that time, omitting to mention his earlier boosterism, he told Howard Florey that it was at Chain’s instigation that he had recommended inviting Feldman. Mellanby said, moreover, that he was "not sure that this was really wise".56 The reversal of Mellanby’s apparent attitude is easily explained by a visit paid to him by Sir Wilson Jameson, the Chief Medical Officer (CMO) at the Ministry of Health. Mellanby recalled the incident in a later note to J.M. Mackintosh, 57

Jameson as Dean at London School of Hygiene and Tropical Medicine (LSHTM). He wrote, "[Y]ou remember that Jameson remonstrated with me for arranging for Feldman to lecture at the Royal Institute of Public Health and Hygiene."57 It is most likely that Jameson persuaded Mellanby that to stir up public interest in streptomycin would be politically dangerous because demand for the drug would be impossible to satisfy, as had been the case for a time with penicillin.58 Thus, Mellanby explained, he did not intend replying directly to the RIPH, and asked Mackintosh, who knew Feldman well, to be the go-between for

54 Hart to Mellanby, 29 Apr 1946, FD1/3258. He named his colleague Glover as best able to recommend experimental sites if Feldman wished to look at the animal side. By this time Hart was confirmed to deliver the Mitchell Lecture the week before Feldman’s talks.

55 Mellanby to Mackintosh, 6 May 1946. This might be explained by a desire on Mellanby’s part to avoid revealing to the American visitor what he considered the backward state of the British pharmaceutical industry.

56 Mellanby to Florey, 12 Mar 1946, FD1/6751.

57 Mellanby to Mackintosh, 6 May 1946, FD1/3258.

58 An extensive search has failed to locate any record of Jameson’s remarks.
the MRC's recommendations regarding Feldman's tour.59

On 18 June, the President of the Tuberculosis Society of Scotland wrote to Mellanby, with an invitation to the American speaker,60 but after the exchange of a series of letters, this request reached Feldman early in July, when he said it was too late for him to accept any further engagements.61 Feldman presented a series of three lectures before the Royal Institute of Public Health and Hygiene (RIPH), on the evenings of 15 to 17 July, and spoke at the Tuberculosis Association meeting which took place in Oxford from 18 to 20 July.

2.4 The Harben Lectures

One cannot overemphasize the importance of establishing by careful animal experimentation certain basic information before any drug is used to treat a tuberculous human being... The experimentalist must accept a definite responsibility in this matter and be prepared to resist the enthusiasm of the adventuresome colleague who may insist on using promising drugs prematurely in treating tuberculous patients.62

William Feldman's series of lectures emphasized the methods used in the search for effective chemotherapy of tuberculous disease in humans. It was difficult enough to estimate how useful any substance would be in the clinic on the basis of evidence from animal experiments; however, results of in vitro tests, he argued, simply did not correlate well with the results of tests on living animals. In the first of his three lectures, Feldman set out four requirements in laboratory studies of anti-tuberculosis chemotherapy: the substance should be well tolerated

59 ibid.
60 Dick to Mellanby, 18 Jun 1946, FD1/3258.
61 Chain to Mellanby, 8 Jul 1946, FD1/3258.

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and not have too bad side effects; it should turn a virulent infection into a nonprogressive infection and extend the life of the animals; it should eliminate (or at least render avirulent) the organism from the animal’s organs such as lungs, liver, spleen and lymph nodes; and finally, it should produce results in a 'reasonable' length of time, such as six months in guinea pigs. He argued that research would progress fastest if time and effort were saved for substances fulfilling these criteria. He also listed a number of factors which had to be considered in evaluating the soundness of experimental claims, such as evidence that an infection had actually taken hold, evidence that therapeutic effects were permanent, and confirmation of results by others. According to his suggested set of experimental procedures, an initial screening would be done on a small number of animals, divided into treated and control groups. If the findings looked promising, a 'crucial experiment' would follow, using a larger number of animals in which an infection was established for several weeks before treatment was begun.

The topic of acquired resistance to drugs, which became of great concern later in the case of streptomycin, was mentioned briefly. Feldman noted that information regarding the development of drug-fastness by tubercle bacilli had been found only recently. Youmans and colleagues at the Mayo Clinic announced in March 1946 that they had compared the resistance of strains of tubercle bacilli which had been isolated from eight patients, before and after treatment with streptomycin. In seven of the patients' strains, they found, the resistance increased 500 to 1,000 fold. Feldman said that when he and Hinshaw had tested certain sulfones, the question of drug-fastness was not seriously considered, but added that if resistance did develop, it did not apparently interfere with suppression of disease in the animals.

According to the criteria set out in Feldman's first lecture, the streptomycin experiments must surely have appeared highly credible to the audience at the

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63 Feldman, Harben Lectures, p.278.

Royal Institute. His final lecture presented striking evidence that streptomycin halted the progression of tuberculosis in guinea pigs. In his and Hinshaw’s first experiment with streptomycin, four guinea pigs were treated and compared with seven untreated controls after 54 days, and the differences in the amounts of tuberculosis were "impressive". The second experiment was similar in design but used 20 treated animals and 10 untreated controls. The disease in the untreated animals was widely disseminated, they found, in contrast to the near absence of disease in the treated ones. The conclusion of these two experiments together was that streptomycin was undoubtedly able to suppress consistently a potentially lethal infection in guinea pigs, and that the substance was well tolerated. Thus the third and crucial experiment was done, with 49 guinea pigs. Treatment was delayed until seven weeks after inoculation with tubercle bacilli, and liver biopsies and tuberculin tests established that infection had taken place. After treatment for 166 days, more than half of the treated animals showed no macroscopic or microscopic tuberculosis, they said. More than a third of the treated group converted to a negative tuberculin test by the end of their experiment, it was reported. Only two of the 25 treated animals died; in contrast, 19 of the 24 controls died, and upon necropsy all of the untreated animals showed extensive tuberculosis. The mortality and necropsy results were illustrated with striking black-and-white graphics: schematic diagrams contrasted heavy black marks on the organs of the guinea pigs in the control group with the predominantly white symbols of lack of infection in the treated animals. Furthermore he dealt with all the other factors that he had presented in the first lecture as possible grounds for discounting an experimental claim, by pointing to the results of three further experiments, one of which was still in progress.

The lecture ended with a summary of their clinical results with 75 tuberculous patients. Most of them had what were considered intractable forms of

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65 His second lecture surveyed the experiments, many of them done at the Mayo Clinic, on a variety of substances such as promin, diason, promizole. He concluded that the sulphone drugs were an unpromising avenue for research into synthetic agents, on the grounds that he believed their toxic properties were inherent in the family. p.321.
the disease, and their condition deteriorated during a pre-treatment period of
observation. That is, there were no simultaneous untreated control patients
reported in the study. Even in fatal cases of miliary or meningeal tuberculosis,
treatment had extended the patients' lives considerably, and their lesions were
found to be contracted. Only tentative conclusions about streptomycin in clinical
tuberculosis were offered by Feldman, but he said it was possible to report certain
favourable trends which were fairly consistent. In closing he stressed the virtue of
patience. Many listeners, however, must have been persuaded that the substance
was worth trying in their own medical practices.

2.5 Recapitulation

The isolation of streptomycin was announced in January 1944. Papers
concerned with biochemistry, pharmacology, bacteriology and experimental
pathology and other aspects of the drug began to accumulate at an accelerating
pace. A few clinical reports on streptomycin appeared during 1945. By the start of
1946, tuberculosis was one of the potential uses of the drug in which the interest
had become strongest. However, the leading researchers agreed that it would take
at least six months and a large number of patients to yield definitive clinical results
in the pulmonary form of the disease. This conclusion was based on past
experience with other anti-tuberculosis drugs such as sanocrysin, in which, the
experts said, initial optimistic claims had been poorly founded. Early in 1946 the
MRC arranged for Feldman, one of the top American tuberculosis
experimentalists, to visit the UK. Intervention from the Ministry of Health in
March 1946 sharply cooled the MRC's enthusiasm for promotion of the drug. The
threat was that public interest in the drug would translate into demands for access,
which could not yet be met. Feldman's public lectures presented, in a persuasive
manner, evidence of the drug's effectiveness against tuberculosis both in guinea
pigs and in humans. Even before the MRC held any supplies of streptomycin of its
own, it began to face the difficult problem of managing the drug's distribution in
Britain.
Chapter 3. Demand and Distribution

For the time being we are able to say that we have no streptomycin. Later on we shall have to take the line that the limited supplies as yet available are all earmarked for cases within the scheme of clinical trials.

Dr A. Landsborough Thomson, Under Secretary, Medical Research Council, to Sir Jack Drummond, Research Director, Boots Pure Drug Company Ltd, 4 Nov 1946

Statements which are intended or are likely to become public...
are of course always made on the responsibility of the Minister, and usually with his personal approval; all the most important will in fact be made by him, whenever possible, in Parliamentary debate or in replies to questions. The rule here is simple. Nothing may be said which is not true: but it is as unnecessary as it is sometimes undesirable, even in the public interest, to say everything relevant which is true; and the facts given may be arranged in any convenient order. It is wonderful what can be done within these limits by a skilful draftsman.

H.E. Dale CB, The Higher Civil Service of Great Britain

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1FD1/6760.

2H.E. Dale, The Higher Civil Service of Great Britain, (Oxford: Oxford UP, 1941), pp.104-105. The writer, formerly Principal Assistant Secretary, Ministry of Agriculture and Fisheries, should not be confused with Sir Henry Dale, director until 1942 of the National Institute for Medical Research.
The collective principle asserts... that medical treatment and care... should be made available to rich and poor alike in accordance with medical need and by no other criteria... It insists that no society can legitimately call itself civilised if a sick person is denied medical aid because of a lack of means.

Aneurin Bevan, *In Place of Fear*, 1952

3.1 Introduction

In the autumn of 1946, a Mr Jones from the *London Daily Mail* approached one branch of government after another, in search of a new drug, streptomycin. His son was suffering from tuberculosis, and as we have seen in the previous chapter, there were reports that streptomycin was an effective treatment for this disease. By that time, several pharmaceutical firms in the USA were manufacturing streptomycin, and so Jones contacted the American Embassy in London and the US State Department in Washington DC, asking them for help in obtaining some of the drug. The British Supply Office (BSO), the British government’s procurement branch in Washington, was notified of the request, apparently by the American authorities. In turn the BSO informed the British Commonwealth Scientific Office (BCSO), a small governmental bureau which handled scientific liaison between American research organizations and their counterparts in Britain, Canada, Australia and other Commonwealth countries. An official from the BCSO, Mrs Vivian Connell, passed her news of the case on to the MRC. At some point during this run-around, Jones was told to contact the Medical Research Council (MRC) back in London. According to an agreement that had been reached during the summer, the MRC held responsibility for allocating whatever streptomycin was to be had in Britain— which then amounted to minuscule quantities, on the order of a few grams at most. Official letters written to members of the public in the autumn said that streptomycin was not yet


available in Britain, that in any event its medical value was quite uncertain and that there were dangerous side effects. Frank Green, the third-ranked official at MRC headquarters, recorded in an annotation upon Connell's letter that he had explained this situation in a telephone conversation with Jones. Green declared, "He was completely reasonable about it."\(^5\)

Green's remark encapsulates the government's attitude to public requests for streptomycin throughout the late 1940s. On the one side, numerous individual members of the public earnestly sought the drug for themselves or for the treatment of their loved ones. On the other side, that demand by the masses encountered rational management by a state bureaucracy, in which the MRC's scientific authority played a central role. For members of the public to be 'reasonable' about streptomycin, in Green's idiom, was for them to accept the logic presented by the MRC: that the drug could not yet be obtained by the enquirers, and moreover that it was in the best interests of the enquirers that this should be so. While the MRC had strong arguments to justify the way it dealt with material supplies, because of the lack of availability of the drug in the country, and the genuine uncertainty surrounding the value of the drug, the means that it used to persuade the public to go along with this scheme were manipulative, as we shall see below.

It may be helpful to place streptomycin distribution into a wider context of the distribution of other new or expensive medical treatments. The allocation of life-saving medical treatments to individual patients has long been a troublesome issue. In many cases it has been dealt with by central administrative control. Insulin was rationed by the MRC in the 1920s.\(^6\) Distribution of streptomycin, both in the USA and the UK, was primarily modelled after that of penicillin. The first mass-produced penicillin was devoted exclusively to use by the armed forces in both countries. In July 1943, all supplies of penicillin for American civilian use

\(^5\)Undated annotation, on ibid.

were put under the direction of the Committee on Chemotherapeutic and Other Agents (COC), an organ of the National Research Council. The COC, which we shall encounter again in Chapter 4, operated along explicitly utilitarian principles. Ten months later, in May 1944, responsibility was transferred to the new Office of Civilian Penicillin Distribution, which made use of a nationwide system of depot hospitals. The drug became commercially available in the USA in March 1945. Early British output of penicillin was reserved for clinical trials by the MRC, then in the late spring of 1944, the Ministry of Health set up its Penicillin Clinical Advisory Committee and Penicillin (Civilian Supplies) Committee. The former was concerned to draw up clinical instructions on the types of case for which penicillin was to be used when it became available for civilian cases, and on the methods of administration. The latter, chaired by one of the two Deputy Chief Medical Officers (DCMOS), Sir Weldon Dalrymple-Champneys, was to determine the distribution of the supplies available for civilians. Penicillin was owned by the Ministry of Supply, and made available free of charge to the universities and teaching hospitals. In June 1946 penicillin became available on prescription in Britain, by purchase from commercial chemists. Throughout the official planning of penicillin distribution, it was assumed that control would give way to market distribution; that is, there was never a hint that the industry, under controls during wartime, would be permanently nationalized. Other treatments have followed similar paths. Cortisone was centrally controlled at the end of the 1940s.

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8Adams, pp.131-152.

9Penicillin. Notes of a meeting in Mr McGregor’s Room on Mon 26 Jun 1944 to consider office arrangements in connection with questions arising on Penicillin, MH58/358.

Kidney dialysis and organ transplants continue to be rationed in Britain. Access to the novel anti-retroviral drugs and treatments for opportunistic infections has been restricted since they were introduced in the late 1980s. AIDS activists have challenged, with some success, the frequent requirement that patients seeking such drugs enrol in randomized controlled trials.\textsuperscript{11}

The American medical ethicist John Kilner has set out a typology of 15 criteria which are now widely used by hospitals in choosing between patients seeking limited life-saving medical resources.\textsuperscript{12} The streptomycin story illustrates several kinds of arguments that members of the public believed officials would find persuasive. Although the principle of "free and universal" care was established in the National Health Service, it is significant that a concept of the individual's right to health care was not yet explicit in public discourse around penicillin and streptomycin. We do see, however, appeals to the paternalist duty of the state to take care of those who had risked their lives in the armed services. Factors which had some currency in the 1940s include having family members who were financially dependent on the patient, and willingness to accept treatment. Tuberculous meningitis involved two factors which in many people's eyes heightened the priority of treatment. It was prevalent in infants and young children. And imminent death was at stake, in that prior to the advent of streptomycin, the disease had been all but uniformly fatal within six weeks of diagnosis.

One factor, ability to pay, was especially sensitive in the period after the Second World War. While voluntary hospitals had almoners who assessed patients' ability to pay and provided free or subsidized treatment when it was deemed necessary, patients admitted to the hospitals run by local authorities often had to find their own resources. Many members of the community fell in the gap between National Health Insurance (NHI) and charitable provision of care; 43\% of the


The population was covered by the NHI in 1938. The financial situation was somewhat less onerous in the case of tuberculosis than in other diseases, because sanatorium and hospital treatment was covered under the NHI. A system of allowances, known as Memo 266/T, was implemented in September 1943, at the recommendation of the Dawson Committee on Tuberculosis in War-Time, of which we may recall that Hart was the Secretary. These allowances were no higher than the level of Public Assistance, although arguably they avoided its stigma. Moreover they were restricted to so-called 'curable' cases of pulmonary tuberculosis, thus excluding 90% of those on the tuberculosis registers. The cost to the Treasury of tuberculosis allowances for the fiscal year 1944-45 was £650,000. Petitioners for streptomycin often recognized that the drug might be prohibitively expensive.

Central to the political and economic problem was the question of scientific authority and expertise. How should competing claims for streptomycin be arbitrated? In fact this would be a difficult exercise under the best of circumstances, and one of the remedies was to attempt to avoid having to choose on a case-by-case basis. A bureaucratized, routinized rule-based system made it easier to say no. In part this was an attempt to rule out the exercise of political and economic privilege. As the Minister of Health put it in his political testament of a few years later, quoted at the start of this chapter, medical need ought to be the only criterion for allocation of treatment— not ability to pay, and not political 'pull'. But for that medical need to be judged fairly by the physician or surgeon in clinical practice, there had to be some shared standard of medical knowledge. Did a child with tuberculous meningitis need streptomycin, or was it unlikely to do him (or her) any good? If so, how much did he need and how should it be injected? One problem with trying to set a standard was that there was not

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necessarily a consensus within the medical profession as to what knowledge was reliable and who was qualified to speak. It seems fair to suppose that in the eyes of many lay people of the time, all doctors were experts; however, divisions in the profession have long been familiar to insiders. In particular there has long been a gulf between consultants and general practitioners. But as well, meritocratic ideals have been invoked by reformers in an attempt to displace the traditional patrician authority of the part-time consultant at the great voluntary hospitals, and replace it with authority grounded in scientific knowledge. Several different kinds of authority competed over the distribution of streptomycin: in the end, medical-scientific expertise appears to have been dominant, although wealth and connections sometimes prevailed.

One of the bywords of the time was "efficiency", and officials showed a persistent concern that materials not go to waste, as Adams has described in an analogous situation a few years earlier, of a shortage of penicillin in the USA. The government desired that sound knowledge about the properties of streptomycin be obtained before the drug became widely available. Streptomycin was extremely expensive, and potentially valuable for research purposes since the level of knowledge about it was still so low. Research would be a "reasonable" application of the drug. But for the substance to be handled by doctors having no practical experience of using it, in cases where there was no laboratory evidence to suggest that it had more than a speculative chance of success, that was considered wasteful by the authorities. The Ministry of Health (MoH) and the MRC thus attempted to dissuade members of the public from pursuing supplies of the drug. Keeping a lid on demand might avert political controversy over the fact that there was nowhere near enough streptomycin in the country to meet all the demands that were made. In the climate of the time, the combination of short supplies and

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15For an American analogue, see the discussion of therapeutic reformers in Marks, The Progress of Experiment.

16Adams, "The greatest good to the greatest number".

17A similar situation had arisen prior to the enactment of the Therapeutic Substances Act, 1925, with insulin being "lavishly and wastefully used", in the eyes of the central authorities. See Bliss, Discovery of Insulin, p.173.
intense demand was potentially explosive—though, in the end, the situation remained stable. The situation may briefly be compared with rationing of food and other commodities, which became more intense after the end of the war and provoked considerable resentment in some quarters. Demand for food was politically significant because of aggregation over large population and many commodities rather than the intensity of anyone’s desire for any individual item; demand for streptomycin, however, was understandably seen by many members of the public as a matter of life and death.

The currently prevailing image of British society under Attlee emphasizes the slogan, "fair shares for all". The political journalist and historian Peter Hennessy characterized the welfare philosophy resulting from the Second World War as "equality of benefit for all as a bonding of common citizenship". What tends to be underemphasized is that principles of egalitarianism applied at most to ends, and not to means. What constituted a 'fair share' was determined by an elite which showed little respect for the decision-making capacity of the people who constituted the 'all' of the slogan. In a phrase that captures the patronising tone of the Attlee period, the minister Douglas Jay wrote:

Housewives as a whole cannot be trusted to buy all the right things, where nutrition and health are concerned. This is really no more than an extension of the principle according to which the housewife herself would not trust a child of four to elect the week’s purchases. For in the case of nutrition and health, just as in the case of

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education, the gentleman from Whitehall really does know better what is good for people than the people know themselves. That is, we shall see that the streptomycin story illustrates that Whitehall remained fixed in patterns of paternalist management of the masses; this is particularly evident with respect to the distributive aspect of the story. However effective and fair was the distribution of the drug, given the constraints of the time, the approach taken demonstrated a lack of trust in members of the public.

Issues regarding the management of streptomycin remained, for the most part, outside the domain of parliamentary politics. Isolated questions were asked in the House of Commons, but these uniformly failed to come to grips with the government's strategy for dealing with the situation. The government's tactic of exaggerating the danger of the drug and overplaying the uncertainty about its effectiveness was not challenged. Instead the questions revolved around timing, around individual cases, and these were effectively met with the utilitarian arguments that the stock of the drug should not be fragmented by granting exceptions on humanitarian grounds. If this claim was not greeted with universal satisfaction, at least there was little outright protest. What did transpire, however, was a practical response in the form of a distribution network, coordinated by mass media, handling the quantities of streptomycin which came into the country through unofficial channels.

The MRC continually asserted that streptomycin ought only to be issued under careful control. If the drug came into general use before sound knowledge had been obtained of its properties, they feared, much of it would go to waste. Although there were some medical conditions such as pulmonary tuberculosis in which the long-term clinical benefit was still to be established conclusively, at least there was solid laboratory evidence of its effectiveness in tuberculous animals. Animal modelling, according to the understanding which prevailed in scientific circles, gave reasonable grounds for hope that streptomycin would be useful in human tuberculosis. In other conditions, such as various cancers, there was also uncertainty about the value of streptomycin, but it was of a different kind in the eyes of the MRC staff. No one had bothered to prove that the drug was
useless in these latter conditions, but for the administrators, the onus lay on applicants to show that their request to try the drug was based on more than blind hope. Especially while the drug remained in very short supply, the MRC would attempt to ensure that it was allocated according to what they considered the best scientific evidence. This of course came into direct conflict with the views of some members of the public, for whom the term 'miracle drug'—now a cliche for the therapeutic power of drugs such as penicillin—should be interpreted as often a fairly literal expression. For them, it is not hard to imagine, the main issue would have been to obtain some treatment which might possibly help them or their loved ones. If the scientists weren't able to say that streptomycin would definitely help, at least they couldn't say for sure that it wouldn't. And what some patients knew undeniably was that nothing else had worked for them. If a slim hope was more comfort than no hope at all, the value of streptomycin might be incalculably great. Those members of the public who had great resources at their disposal could go to correspondingly great lengths in an attempt to procure the drug.

Over the period from September 1945 through December 1946, the strength of British public demand for streptomycin greatly increased. This is evident from the MRC's miscellaneous streptomycin enquiries file, specifically the first volume, ending in December 1946. Unless otherwise indicated, archival references in this chapter are to this file, FD1/6760. The enquiries received by the MRC can be taken as representative, because of the government policy, publicly declared, that it would be responsible for allocating supplies. Not all the requests passed through the MRC, and many of them indeed were apparently unrecorded, but what we have provides a clear picture of the MRC's techniques for handling distribution. The vast majority of these enquiries consisted of

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22 Three more volumes were opened by the MRC at the beginning of each succeeding year.

23 The Ministry of Health's file of enquiries about streptomycin, originally labelled 93205/1/234, is not to be found in Class MI355, which contains the Public Health Services Registered Files from the 93000 series. It has almost certainly been destroyed.
unsuccessful requests for streptomycin for use in tuberculosis; with a few exceptions, letters were re-filed if a dormant request was subsequently approved. A few examples are taken also from the file of successful requests for the drug, FD1/6766, which invariably came from accredited scientists. The files of enquiries are a rich source of information on the perceptions of streptomycin (and of medical research) by the members of the general public; my intent here, however, is to focus on the way government officials understood the public demand for the drug, and how they responded to it.

In this chapter and elsewhere in the thesis, I omit information which would identify individual patients to the reader, although all cited documents can be traced using dates and initials. I make three exceptions to the rule of confidentiality, namely Sir Edward Mellanby's nephew (who appears in Chapter 5), Sir Charles Hambro's grandson, and to some degree, the brother-in-law of the Cardiff Medical Officer of Health. In these cases, some identifying information is essential to the story, in that the officials attempted to use their positions of influence for personal advantage.

Section 3.2 presents examples of enquiries to the MRC. Some were primarily related to the treatment of individual patients and some were from researchers or from institutions seeking to participate in clinical trials. The first enquiry the MRC received regarding streptomycin came from a Fellow of the Royal College of Physicians, and was ultimately successful. Most others were not. The volume of enquiries prompted routinization of response, culminating in the preparation of a standard statement to the public, which is reproduced as Appendix B. Section 3.3 follows the case of an extremely wealthy and powerful man who sought streptomycin for a condition in which the medical rationale for its use was dubious. The incident thus highlights the problem of fairness of distribution. Section 3.4 illustrates the way that one hospital took the problem of distribution into its own hands, with the cooperation of the BBC. This solution which ushered in a long series of emergency broadcast appeals which the MRC and MoH attempted to stop, on grounds that they were deleterious to a rational scheme of distribution. The appeal to the need for careful research was not sufficient, on its
own, to limit public demand, and thus here I argue that the toxicity of the drug began to be presented in a deliberately pessimistic fashion. Compared to the research on which the statements were ostensibly based, the picture is shown to be misleading. Section 3.5 provides a recapitulation and conclusions.

3.2 Requests for streptomycin

The first request for streptomycin came to the MRC in September 1945, from a member of the Council's penicillin clinical trials committee. During the first half of 1946, enquiries trickled in at a rate of less than one a month. Following the Ministry of Supply's public announcement in late September 1946 that the Council would control streptomycin supplies, the public pressure mounted: eight written requests arrived in the last week of the month and twenty during October. In order to routinize the work of responding to these letters, which was taking up increasing the time of senior MRC administrators, a stencilled statement was prepared. This was sent to most enquirers, both institutional and individual.

The nature of the requests, as well as the number, changed in September 1946. Until that time, when medical superintendents of sanatoria or general practitioners wrote in to the MRC, they would either discuss individual patients, or else not mention specifically the purpose for which they wanted streptomycin. Patients themselves also wrote in, and all these kinds of applications for the drug continued to arrive over the next years, along with the occasional purely informational enquiry. But after the MoS announced that the MRC would devote streptomycin supplies to clinical trials, not surprisingly, enquirers often framed their requests for supplies in terms of seeking to participate in the MRC's scheme. In many cases, such institutions appeared to the MRC to lack any capacity to conduct worthwhile research, their programmes appearing to be an expedient for the sake of gaining access to the drug, and Council staff wasted little time in turning these away. A few of the larger and more prestigious organizations, however, such as the London County Council, the Welsh National Memorial Association and the Papworth Settlement, already had their own clinical research
programs. These were taken far more seriously by the MRC. The council used the argument that research needed to be restricted to a limited number of centres. By presenting the existence of this list of centres as a fait accompli, the Council was able to resist demands for inclusion of centres which they knew privately would have been low on their list even once supplies expanded. The policy of tight control was an initiative of MRC staff rather than, say, of the pharmaceutical companies. An outward policy of barring exceptions was in fact quietly breached, with a very few individuals obtaining tiny quantities for laboratory experimentation in advance of the clinical trials. While restriction of streptomycin to the MRC’s selected centres served to rebuff demands from institutions, in the case of individual patients, a further tactic was used, the exaggeration of the toxic side effects, and this I will discuss further in section 3.4.

Hand in hand with the strict control of streptomycin supplies went the control of information about the streptomycin situation. Publicity about streptomycin production and clinical trials was generated by the Ministry of Supply’s Chief Information Officer, in an attempt at what we would now call open government. This release of information to the public, with the ensuing increase of public pressure, undermined the MRC’s ability to maintain a monopoly of supplies. The MRC officials thus did not welcome the MoS announcement in the least. Moreover a few highly placed individuals who did not share the administration’s conception of good scientific practice had to be managed carefully, among them Sir Alexander Fleming.

The first enquiry: the typhoid carrier

The first enquiry which the MRC received regarding streptomycin was sent on 10 September 1945. The petitioner in this case was Lawrence P. Garrod, a physician at the venerable voluntary hospital St Bartholomew’s, and also a member of the MRC’s Penicillin Clinical Trials Committee. Garrod had under his care a surgical lieutenant in the Royal Naval Volunteer Reserve, whom he said had become "a profuse and intractable typhoid carrier" in the course of his service in the Far East. The Navy had turned over the surgeon, who was a "Bart’s man", to
the care of the hospital. Sulphonamide treatment had failed, Garrod wrote, and he added that neither the patient nor anyone involved in the case was inclined to a cholecystectomy (i.e., treatment by removal of the gall bladder). In this context he cited a paper which had appeared in the JAMA on 19 May. This study was done during a local epidemic of typhoid fever in Philadelphia beginning in December 1944, in which 8 people died, out of a total of 60 cases. Reimann and colleagues reported a case series of 5 typhoid patients, of whom 3 recovered during treatment with streptomycin. That is, the mortality rate among the streptomycin patients, 40%, was considerably higher than that among the patients treated by other means, 9%. Garrod thus remarked dryly, "The evidence of a curative action in typhoid fever is not wholly convincing". But, he continued, "on theoretical grounds this should certainly be worthy of trial in a carrier."

The trouble, as Garrod put it, was "to get hold of some of the stuff." It is implied by his letter that he had already tried, without success, the "ordinary sources in this country". He reported moreover that the English agents of Merck & Co-- the leading American manufacturer-- knew "nothing whatever" about streptomycin. He suggested contacting the Medical Headquarters of the American Services in London-- with whom it is clear he was not in contact, since he expressed uncertainty as to whether they had already packed up and gone home. He also asked if the MRC's representative in New York might make enquiries. He concluded by saying he was sure Bart's would more likely obtain the material

24 Garrod to Green, 10 Sep 1945.


26 Garrod to Green, 10 Sep 1945.

27 ibid. Undoubtedly he was referring to the susceptibility of E. typhosa reported in the paper on the basis of in vitro tests.

28 ibid.

29 I have found no other reference to such a New York representative in the course of the MRC's attempts to procure the drug, as described in chapter 5, and believe that Garrod was mistaken regarding this office.
if his request had the backing of the MRC than if he were simply to write personally to friends in the USA.  

Garrod's letter illustrates several motifs which would reappear time and time again in the MRC's enquiries file. First is the petitioner's belief that if the MRC were to act as his intermediary, it would be considered authoritative by foreign officials and manufacturers. Second are the signs displayed that he was knowledgeable about scientific medicine—although this hardly seems necessary in his case, where he was well known to the MRC administrators as an experienced and reliable researcher. Garrod could take advantage not only of his position as a Fellow of the RCP with an honorary post in one of the great hospitals, but also of his ability to summarize the pharmacological information in the Reimann paper. As sources of news about streptomycin, professional journals carried greater weight than the newspapers and radio broadcasts to which numerous other enquirers referred. Furthermore it demonstrated his sophistication that he expressed caution in drawing positive conclusions about the potential of the new drug. Third is his invocation of the desirability of medical progress: "You will doubtless realise that should the treatment succeed it may be an important advance in dealing with a very troublesome condition." Fourth, we see in many of these petitions the attempt to establish—with varying degrees of persuasiveness—that all other alternative treatments had failed or been judged unsuitable.

Garrod's letter was received on 11 September 1945, and the following day, Landsborough Thomson, the Second Secretary of the MRC, forwarded it to Hart at National Institute for Medical Research (NIMR) Farm Labs in Mill Hill. Thomson commented in his covering note, "I know that typhoid is not in your ordinary line, but I think that you may be able to tell me something about the chances of our being able to get hold of some streptomycin, and through what channel." In a telephone conversation, Hart then recommended that Thomson contact Harold King, who directed the chemical side of the NIMR's research into

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30ibid.

31ibid.

32Thomson to Hart, 12 Sep 1945.
chemotherapy, and was (like Hart) a member of the MRC's Chemotherapy Committee.33 Thomson next passed the Bart's enquiry to King on the 15th. He recalled, "I understand from Hart that you brought some back from America as a gift to Hopkins".34 He went on, "[B]ut I do not know whether they would be willing to part with some on the ground that a severe case of a typhoid carrier which has resisted all other treatments would be an interesting object of research."35 He asked for an indication of what channel the MRC might use to get hold of the material.36 King replied with a short handwritten note, "Streptomycin is certainly worth trying if Merck or Squibb's will part with the material."37 After this flurry of correspondence, it is somewhat surprising that no reply was made to Garrod until two and a half months later. Following a reminder sent to Green,38 Thomson apologized for the delay, without giving any reason for it. He explained the position thus: "the American makers are at present very reluctant to part with any, except for lines of work in which they are not themselves particularly interested."39 At the end of January 1946, Thomson reported that the BCSO said it was "practically impossible to get even small

33Hart to Thomson, 13 Sep 1945. See FD1/7206.
34Thomson to H. King, 15 Sep 1945. It is not clear whether the streptomycin to which he referred was intended for the treatment of Gowland Hopkins, the doyen of biochemistry, then 85 years old.
35Ibid. Presumably, by "them", Thomson was referring to King's American contacts, but no specifics were stated in the letter.
36Ibid.
37H. King to Thomson, 17 Sep 1945. At a meeting of the Chemotherapy Committee a few weeks later, it was one of the Secretaries—Francis Hawking or J. Walker—rather than King (who was also present), who promised to send another member small amounts of streptomycin and also streptothricin for the stated purpose of testing on spirochaetal infections. 27th meeting, 9 Oct 1945, FD1/7206.
38Garrod to Green, 4 Dec 1945.
39Thomson to Garrod, 8 Dec 1945.
quantities at present". In February, Garrod acknowledged Thomson's two letters and proposed that the patient, who he stressed was "living at the expense of the Admiralty", go to the USA for treatment. Thomson expressed great doubt that it would be worth exploring the possibility of sending the patient to America. Interestingly, Thomson volunteered that he had heard, about British production of streptomycin, that Boots were at present furthest ahead in the matter. There matters remained until November, when Garrod was appointed to the Streptomycin Clinical Trials (Non-Tuberculous Conditions) Committee. At this Committee's first meeting in December, among the miscellany of non-tuberculous conditions to be included in the trials, it was suggested that streptomycin might be tested on typhoid carriers. The earliest shipment of streptomycin for clinical purposes arrived just before the end of 1946, and thus, some twenty months after his initial request, Garrod finally got to try out streptomycin on his patient. Most other enquirers, of course, did not share Garrod's qualifications and status, and their attempts to be involved in the MRC's

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40Thomson to Garrod, 26 Jan 1946. This letter, incidentally, is the earliest evidence of the MRC's creation of a separate file (3157/12) for streptomycin, which previously had been included in a file (3157) dealing more generally with essential drugs and supplies from the USA.

41Garrod to Thomson, 14 Feb 1946.

42Thomson to Garrod, 8 Mar 1946.

43Thomson to Garrod, 8 Mar 1946. The source of this rumour is not recorded.

44Extract from minutes of Council, 22 Nov 1946, FD1/7943.

45Minutes of first meeting of SCT(N-TBC)C, 6 Dec 1946, FD1/7943. By this time, Keefer had reported, on the basis of 51 typhoid patients studied under the auspices of the COC and others described by Reimann et al, that there was no evidence that streptomycin in doses of 4 gm per day shortened the course of the fever. Accordingly, typhoid fever itself was explicitly excluded from the MRC's trials. Chester S. Keefer et al, "Streptomycin in the treatment of infections: A report of one thousand cases", JAMA 132 (7 Sep 1946), 4-11, at p.10. Back in August, G.S.Wilson had attempted unsuccessfully to obtain streptomycin to treat convalescents from an outbreak of typhoid in Aberystwyth, who he predicted would become chronic carriers. Extract from Wilson to Cruickshank, 29 Aug 1946, FD1/6756.
research on streptomycin were rebuffed.

Further requests for treatment of individual patients

By the end of 1946 the MRC received some twenty-odd written requests regarding streptomycin for individual patients. In these letters, just as in Garrod's appeal, we frequently find claims that the patient was suitable for research, that there was no alternative treatment and that the doctor in charge was well versed in scientific medicine. The second enquiry on file about streptomycin was received by the MRC in February 1946, from the Acting Medical Officer of Health of Newcastle. According to this letter, he had heard about the drug from Mr W.E.M. Wardill, a Fellow of the Royal College of Surgeons (FRCS) who was in charge of the genito-urinary department of Newcastle General Hospital. Reportedly, Wardill had just returned from the USA and there been impressed by what he called Streptomycin. Responding to the public health official's request, Thomson wrote that he regretted that there was none of the material available.

Motifs such as pity for children and advancement of research are illustrated by a letter received in April from a medical and surgical practice in Holywell, Flintshire. The enquirer, F.M.E. Davies, had written initially to the British Medical Association (BMA). The Association's Assistant Secretary advised him that they were not concerned with the supply of drugs, and gave him the address of the MRC, not without warning him that it was difficult to obtain streptomycin. Davies' appeal consisted of the following:

Could you put me in the way of obtaining supplies for a little boy with bi-lateral T.B. of kidney who has been given up as a hopeless case. I think he would be a suitable subject for research. I do not

46 A. Leslie Banks to Medical Research Council, Feb 1946.
47 Thomson to A. Leslie Banks, 7 Feb 1946.
48 A.V. Kelynock to Dr F.M.E. Davies, 24 Apr 1946.
think the parents are able to afford much financially.49

But at this point, the MRC had none of the drug to distribute even if it had been
swayed by such entreaties. Thomson responded, "I am sorry to say that
streptomycin is as yet quite unobtainable in this country". He explained, using a
phrase which would be repeated, with slight variations, in numerous letters, "The
Medical Research Council have for some months been trying to get quite small
quantities from America for purposes of test, but without success."50

Several public officials attempted to make use of their positions to gain
access. Local authorities were responsible under the Public Health (Tuberculosis)
Act, 1921 for tuberculosis prevention and treatment in their areas. Late in May,
the Medical Officer of Health and School Medical Officer for Cardiff wrote to
Thomson with a plea that the MRC "fractionate" a bit of the "tiny spot of
streptomycin" he had heard they had. Making what he admitted was an appeal 'ad
misericordiam', he asked for the material for the use of the tuberculous brother of
his pregnant and "very worried" wife.51 He assured Thomson, "any material sent
would be used strictly in the way of research".52 And he promised the
cooperation of officials from the Welsh National Memorial Association (WNMA),
a philanthropic body to which many of the anti-tuberculosis functions in Wales
were officially delegated. Thomson responded however that it was not the case
that the MRC had any streptomycin. He added, for the first time applying an
argument which would eventually become a key element of the Council’s letters of
refusal: "It is perhaps poor consolation, but I may mention that the first reports of
the value of streptomycin in tuberculosis seem to have been rather too optimistic,
and the indications are that its chief uses may be in other conditions."53 The
Medical Officer concurred with the suggestion that it provided some consolation,

49F.M.E. Davies to MRC, 25 Apr 1946.
50Thomson to Dr F.M.E. Davies, 27 Apr 1946.
51J. Greenwood Wilson to Thomson, 23 May 1946.
52ibid.
53Thomson to J. Greenwood Wilson, 29 May 1946.
that there was doubt about the drug’s value. Thomson wrote similarly to a doctor in Guildford in July, "I may add that in spite of some rather optimistic reports, present indications are that streptomycin is not dramatically successful in the treatment of tuberculosis." A feature of replies which became increasingly common from the summer onwards was the framing of "success" of the drug in terms which ensured that the criteria remained unfulfilled. That is, I argue that the MRC consistently used phrases which were intended to convey a negative impression. This was done for the purpose of discouraging demand for the drug. By July 1946, it could no longer be written in all honesty that "present indications are that streptomycin is not successful in the treatment of tuberculosis." It seems likely that the word "dramatically" was inserted by Thomson in order to move the goalposts and make a negative-sounding statement plausible.

A further point is that this Guildford practitioner had written that he would be glad "for any references to recent work on it [streptomycin] in America & this country". This part of his request was ignored altogether in Thomson’s response. I point out that, continually in the enquiries file, the MRC staff invoked the authority of recent research to support their claims that there was greater uncertainty about the drug’s effectiveness (or greater danger of side effects) than had previously been believed. However, citations of American research literature were not provided, even to those who because of their medical qualifications might have been presumed capable of interpreting the findings, and even though several abstracts were readily to hand in file 3157/12b.

54J. Greenwood Wilson to Thomson, 1 Jun 1946.

55Thomson to Dr R.C. Matson, 23 Jul 1946. My emphasis.

56Furthermore, I suggest that the statement is open to being read (misleadingly) as an ironic understatement. That is, some members of the British public might conclude that the drug was very unsuccessful. But it is not clear to what extent irony would be expected to be found in official communications.

57Letter to The Secretary, Medical Research Council, 14 Jul 1946.

58The sole references to journal research papers in the enquiries file are those to Reimann’s typhoid paper and to discussion of a substance named diason, which was one of the sulphones and not in great demand. H. [Harmesson] to MRC, 15
One man told the MRC in late August, "I am writing to ask you whether any experimental subjects are required for this research as I thought that I might be a useful subject." His speculation about his usefulness for research was supported by information which it is hard to imagine the MRC finding the least bit persuasive; the MRC's conferences and committees decided to apply detailed bacteriological and other diagnostic criteria. Thomson thanked him for his letter but advised him that when clinical trials were run in this country— which he said would be several months in the future— "it is probable that certain hospitals rather than individual patients will be selected." Here we see another motif of the refusals, one which became more insistently expressed as the incoming requests increased in frequency: the MRC refused to deal with individual patients. I return to this point shortly.

On Saturday 21 September, *The Times* and *BMJ* carried a press release from the Ministry of Supply; it appeared a week later in the *Lancet*. It announced that pilot-scale streptomycin production was underway in Britain, under the auspices of the Ministry and in collaboration with the MRC among others, and that it was hoped that preliminary clinical trials would begin before the end of the year. Previously the MoS had come under some heavy criticism in the case of penicillin production, for which it was also responsible. It was accused on the one 

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Nov 1946; Green to Resident Medical Superintendent Croydon, 20 Nov 1946. In neither did the MRC supply references not already known to the enquirer.

59S___ B___ to The Secretary, MRC, 28 Aug 1946

60eg, First Conference Minutes, para 3, 29 Jul 1946, FD1/6756. The patient wrote that he had had tuberculosis in both lungs for eight years and also laryngeal tuberculosis since October 1944. He stated his age, 38, and the fact that he had a family history of tuberculosis. That was all. S___ B___ to The Secretary, MRC, 28 Aug 1946.

61Thomson to S___ B___, 2 Sep 1946.

hand of interfering with the enterprise of private firms working under contract and
of wasting money, and on the other hand of not pushing ahead quickly enough
with new and better forms of production methods, e.g. the deep culture method,
which I will discuss further in the following chapter. According to Richard
Williams-Thompson, the Chief Information Officer, the remedy for low morale of
the officials in Penicillin Production Control was a press conference, which he
arranged soon after he took his post in April. Williams-Thomson firmly believed
that frank and authoritative statements would clear up speculation and
misinformation, so it is quite likely that the press release in September on
streptomycin was his initiative. Soon after, a flurry of new enquiries was
received, many referring explicitly to these publications. The Deputy Medical
Superintendent of the Grosvenor Sanatorium Ltd, Ashford, Kent, for example,
asked the MRC the following Monday for "some Streptomycin for experimental
purposes", in connection with a long-term patient for whom he said active surgical
treatment had failed in every respect. This doctor, H. Brodereck, wrote also to
the Ministry of Health on Tuesday, citing the BMJ. Thomson's reply, posted also
on the Tuesday, said that there were no supplies in the country at present. A
patient on a Royal Air Force ward at a hospital in West Lothian wrote, "I was
heartened & pleased to read that this new drug is to be made in Scotland." This
patient wrote, "I have heard conflicting rumours on this drug, is it for-instance

63See Richard Williams-Thompson, Was I Really Necessary? (London: World's
Press News Publishing Co. Ltd., 1951), esp. pp.75-'77; also documents in
AVIA49/44.

64H. Brodereck to the Medical Research Council, 23 Sep 1946.

65Thomson to [Brodereck], 24 Sep 1946. Curiously, it took nearly a month for
the Ministry of Health to forward their copy of Brodereeck's enquiry for the
Council's attention. [illegible] to The Secretary, Medical Research Council, 19 Oct
1946.

66D. G__ to [not stated], 21 Sep 1946. This was clearly a reference to the
planned factory at Ardrossan, which was mentioned in the Ministry of Supply
press release.
true that tuberculosis patients have been cured with it?" It was rather unusual for those who wrote in to be so frank about their uncertainty, although he in particular did not ask for supplies. Thomson answered that the American evidence was "as yet inadequate for any definite opinion" on the tuberculosis question. A similar flurry of requests occurred following the radio publicity which I describe in Section 3.4. For example a man from Leeds explained, "After hearing a recent broadcast on the progress of streptomycin, I decided to write to the people responsible for this talk offering myself as what you might call a human guinea pig in tests and experiments with this drug". He had been referred to the MRC, to whom he stressed, "First of all I'd like to say that I am not a crank." 70

By October, Green's letters to enquirers routinely included the statement, "I regret to have to tell you that the Medical Research Council are unable to entertain requests from individual patients for inclusion in the official trial of streptomycin." 71 The same argument was repeated in a stencilled statement which the MRC began enclosing with its letters of refusal. This stencil, dated 8 Oct 1946, is reproduced as Appendix B. 72 The stencilled statement laid out key lines of argument which the government persistently used. First it was stressed that there was a need for information about streptomycin, information which would be derived through a programme of clinical trials. The resulting knowledge had to be in place before general distribution took place, it was asserted. A second point was that distribution was not safe until laboratory tests had confirmed the quality of the product. This was relatively uncontroversial, although one MRC official is reported

67 ibid.

68 Thomson to D. G, 27 Sep 1946.

69 S. G. P. to [MRC], 5 Nov 1946.

70 ibid. Whether or not this declaration undermined itself, it illustrates that patients too recognized the importance of credibility to the scientific enterprise.

71 Green to W. W, 16 Oct 1946.

72 Stencil MRC.46/248, "Streptomycin". It is unclear why the page was labelled "Restricted", in that it was produced for distribution to members of the public.
to have been begged by parents "not to waste the wonder drug on animals, but to use their children for experiments". 73 Third, the scarcity of the drug was said to make it necessary to select a limited number of centres, thereby precluding any granting of supplies to individual patients or hospitals. I return below to the fourth, the uncertainty surrounding the value of the drug, which was played up in statements to the British public. Hart, having been sent a draft of this document, declared to Thomson, "I think the draft statement about streptomycin is first-rate." 74 Hart suggested only that "perhaps it should be made a little more definite that the decision has been made that, while supplies are very small, they should be restricted to cases of Tuberculosis in our controlled trials, and not used for other conditions (tests on the latter are being carried out in the U.S.A.)." 75 Apparently as a justification of his parenthesized remark, he explained, "I am thinking of the enquirer who feels that it is wrong that trials of other conditions are held up pending the long-term tuberculosis investigation." 76 It is perhaps not surprising, given Hart’s inclination to put himself into the enquirer’s shoes, that he was advised to leave press relations to headquarters. 77 In any event, he requested a copy of the stencil, once it was finalized, to be able to enclose with his replies to "the growing numbers of enquirers". 78 Thomson replied:

I think, and Mellanby agrees, that it would be better not to add anything explicit about excluding conditions other than tuberculosis, because we should leave ourselves free to alter that policy whenever it may seem desirable to do so. In any event it does not seem likely


74 Hart to Thomson, 4 Oct 1946. No early draft survives in the file and it is possible that the final text was the same as what Hart saw near the beginning of the month.

75 ibid.

76 ibid.

77 Thomson to Hart, 30 Sep 1946.

78 Hart to Thomson, 4 Oct 1946.
that we are going to be bothered by inquiries except in respect of tuberculosis.\textsuperscript{79}

Such alteration of the policy did indeed take place. It turned out that just a few days after Thomson wrote the letter quoted here, the U.S. Department of Commerce allocated an initial small shipment of streptomycin to Britain, and this supply was eventually declared unsuitable for the MRC's clinical trials in tuberculosis, so it was made available for research on non-tuberculous conditions, as we will see in Chapter 6. Green told one enquirer about the committee which he said was going to use a small amount of forthcoming American material for trials on conditions other than tuberculosis.\textsuperscript{80} To return to Thomson's letter to Hart, it was recorded in an annotation on it that 25 copies of the stencil were sent on 9 October. The count might have included, for example, the copy forwarded on this date to Dalrymple-Champneys, the Deputy CMO, to whom Thomson explained, "At the moment it does not seem necessary to issue the statement to the press, but we may do so if our hands are forced by further publication from other sources."\textsuperscript{81} Likewise, two copies were sent on 14 Oct to the Privy Council Office, for the use of Herbert Morrison, who as the Lord President was the Minister responsible for the MRC. Morrison's office needed to reply to Herbert Butcher MP, who had passed on a constituent's letter.\textsuperscript{82} This stencilled statement asserted, "requests for supplies, or for the inclusion of particular institutions or

\textsuperscript{79}Thomson to Hart, 7 Oct 1946.

\textsuperscript{80}Green to Everidge, 7 Nov 1946. This was in response to one of the relatively few letters regarding non-tuberculous conditions. John Everidge OBE FRCS, Senior Surgeon and Lecturer in Urology, King's College Hospital, wrote to the MRC regarding a case of chronic cystitis he wished to treat. John Everidge to the Officer-in-Charge, Medical Research Council, 4 Nov 1946. Green promised to send Everidge's letter to the Secretary of the committee once it was set up. The relatively favourable handling of this enquiry I attribute to his high status.

\textsuperscript{81}Thomson to Dalrymple-Champneys, 9 Oct 1946.

\textsuperscript{82}Thomson to J.A.K. Christie, 14 Oct 1946. I suspect that Thomson was expected to read irony in Christie's characterization of Butcher's constituent as "offering his services" to the MRC. J.A.K. Christie to Thomson, 12 Oct 1946.
individual patients in the scheme of trials, cannot be entertained. The structuring of clinical trials around the limited number of hospitals designated by the MRC would be a key element of its control of supplies.

Requests for streptomycin for research at laboratories, hospitals and sanatoria.

A track record in research was crucial to gaining access to streptomycin through official channels. In 1943, London County Council staff led by the Principal Medical Officer, Fred Heaf, ran a clinical trial of Promin, one of the sulphone drugs. They described their results from treating 19 tuberculosis patients at the sanatorium at Colindale for six months as "indefinite". In mid-May 1946, the LCC's Clinical Research Committee resolved to ask Chester Keefer, the American COC official, for a supply of streptomycin, in accordance with the procedure described in the Pharmaceutical Journal of 6 April. However Allen Daley, the Medical Officer of Health for the London County Council, was asked at the meeting to seek the MRC's advice first. Accordingly, a fortnight later he informed Mellanby of the LCC's intention to run clinical trials in tuberculous meningitis. Thomson's reply informed Daley of the discouraging supply position. Daley soon wrote to Thomson, hoping that "in the event of a supply becoming available in this country, the Medical Research Council will consider the advisability of utilising the Council's hospital service as a field in which trials might be carried out." According to the most recent figures available, the LCC's medical staff likely had access to the majority of cases of tuberculous

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83 Appendix B, para 5.
85 Daley to The Secretary, Medical Research Council, 29 May 1946.
86 Thomson to Medical Officer of Health, LCC, 3 Jun 1946.
87 Daley to Thomson, 13 Jun 1946.
meningitis in London.\textsuperscript{88} The MRC's First Streptomycin Conference at the end of July selected the British Postgraduate Medical School (which operated out of the LCC's Hammersmith Hospital) as one of the centre for trials in tuberculous meningitis.\textsuperscript{89} Though Heaf was out of town at that time, he attended the subsequent conference and was invited to join the MRC Committee, which finally ratified the decision to involve the LCC facilities when it first met in November.\textsuperscript{90}

Like the LCC, the Welsh National Memorial Association had a tradition of carrying out research into tuberculosis. Its research director, Dr W.H. Tytler, was one of two Professors of Tuberculosis in the UK and had carried out a major review of the sulphone drugs as well as original research on promin.\textsuperscript{91} When he and the Principal MO of the WNMA wrote to Wilson Jameson asking for 50 to 100 grams of streptomycin, they clearly demonstrated their familiarity with issues involved in planning a clinical trial: "we understand that supplies of the drug will for some time be insufficient for more than a very small total of pulmonary cases, and that, at the outset, non-pulmonary conditions will be favored as requiring less material, and giving, perhaps, a more rapid indication of activity."\textsuperscript{92} By the time they wrote, in fact, the MRC administrators had agreed to invite Tytler onto the new streptomycin committee.\textsuperscript{93} A Welsh hospital was added several months into the pulmonary trial.

After the \textit{BMJ} and \textit{Times} articles appeared on Saturday 21 September,

\textsuperscript{88}In 1938, when 145 deaths were attributed to tuberculous meningitis in the county of London, more than two thirds had been treated in LCC hospitals. \textit{Ibid.} This ratio is probably explained partly by the voluntary hospitals' preference for admitting patients who were considered curable.

\textsuperscript{89}First Conference Minutes, para 4, FD1/6756.

\textsuperscript{90}FD1/6756.


\textsuperscript{92}Tattersall and Tytler to Jameson, 17 Oct 1946

\textsuperscript{93}Mellanby note, 14 Oct 1946, FD1/6764.
announcing that the MRC was planning to run clinical trials, there was a new influx of enquiries regarding research, as well as the enquiries about individual treatment which I have discussed above. Lady Florey wrote to Mellanby that same day requesting the opportunity to study streptomycin in urinary infections caused by gram-negative organisms, which were not susceptible to penicillin or sulphonamides.94 She told him she had already used on wounds "a very small amount kindly given me for trial by Cairns and Duthie, and have prepared a paper on these results in comparison with various other agents."95 As she pointed out, she had more experience with antibiotics than most people.96 Mellanby replied on the following Monday, "The notice in the British Medical Journal about streptomycin was there without my knowledge or approval. We have received no streptomycin yet and I do not think we shall get any for some months."97 Likewise he wrote a few days later to a friend who had remarked on the BMJ statement, "I had no previous knowledge of the statement appearing in the medical press about streptomycin, nor should I have approved of it if I had known it was going to be inserted."98 The editor of the Pharmaceutical Journal asked Hart on 25 September for a statement on the proposed line of investigation.99 Hart passed the request to Thomson, who advised him, "I think that it will be better if we deal with the Press from here".100 The MoS, Thomson remarked, had omitted to

94See e.g., "Effect of streptomycin on bacteria in urinary infections," JAMA 129.12 (17 Nov 1945), 807.

95Dr E.S. Duthie, a member of the Oxford team that had developed penicillin, obtained a small quantity of impure streptomycin from the USA in 1945, and made it available to Dr Peter Medawar and to the leading neurosurgeon Hugh Cairns.

96M. Ethel Florey to Mellanby, 21 Sep 1946.

97Mellanby to Lady Florey, 23 Sep 1946.

98Mellanby to C. Lee Pattison, 26 Sep 1946.

99Editor, Pharmaceutical Journal to Hart, 25 Sep 1946.

100Thomson to Hart, 30 Sep 1946.
consult the MRC about the terms of its statement mentioning the Council.  

Thomson responded to the *Pharmaceutical Journal* that nothing could yet be added to what had already been announced by the Ministry of Supply.

The wave of new enquiries stiffened the MRC's resolve to maintain strict limits on access. Eight written enquiries were received between 21 September and the end of that month; for comparison, three had come in during the previous three weeks, in addition to the eight which had accumulated by the end of August. The Medical Superintendent of the Westmorland Sanatorium at Grange-over-Sands told the MRC he was interested in streptomycin as a result of hearing Feldman's talk in Oxford in July. Now, having read in the *BMJ* that streptomycin was to be produced in this country, and that the supplies for clinical trial were under the auspices of the MRC, he asked if his institution could have a supply. Likewise the Medical Superintendent of the Wooley Sanatorium of Northumberland County Council, who referred on 26 September to unspecified newspaper reports and to information from the commercial traveller of Glaxo, offered his cooperation in "any kind of special enquiry and investigation" that the MRC was conducting. Thomson sent identical letters to the two men, telling them the MRC had no supplies and referring to the forthcoming clinical trials as a "limited series". Thus we see the routinization of responses, which had been taking up increasing amounts of the time of Thomson and Green. Since the MRC Streptomycin conference in August resolved that individual enquiries should be deflected from the Secretary, it is fair to assume that there were a considerable number of telephone calls of which no record survives. Such pressure next led to the

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101 ibid.


103 Campbell to The Medical Research Council, 26 Sep 1946.

104 F.L. Woolaston to The Secretary, Medical Research Council, 26 Sep 1946.

105 Thomson to The Medical Superintendent, Westmorland Sanatorium, 27 Sep 1946.


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production of the stencilled statement in early October.

The strategy of the MRC was to restrict the supplies of streptomycin to a small number of clinical centres under the control of personnel sympathetic to their aims, as I will discuss further in Chapter 6. This list was kept secret, possibly so that new centres could be added as the need arose without undermining the claim made to the public that the list was fixed.\textsuperscript{107} By presenting the list as a fait accompli, the MRC was able to resist the demands for the inclusion of sanatoria it considered backward. This had been the MRC's strategy with penicillin clinical trials: those trials had expanded from an initial four centres to fourteen, as the supplies had increased. Enquirers seeking streptomycin were told that in the first instance, the supply was "likely to be sufficient for only a very small number of patients, possibly in a single institution."\textsuperscript{108} This statement was written before the release of any substantial American supplies was made known to the MRC, and thus was based on the Second Conference's plans to run a pilot trial using the initial British production on a small-scale. The statement went on: "Even the larger scale trials which it is hoped to undertake at some date in 1947 will necessarily be limited to a few institutions."\textsuperscript{109} One of the members of the MRC staff, G.S. Wilson, responded in October to an enquiry from the Chelmsford County Public Health Department, which had asked whether its hospitals might be included in the trials. He told the Medical Officer, "The centres at which the trials are to be conducted have already been fixed, and I doubt if it will be possible to include any fresh ones;"\textsuperscript{110} he promised, however, to bring the letter up at the next meeting of the Committee, and to ask the Chairman whether anything could be done about it.\textsuperscript{111} According to the minutes of the first meeting of the

\textsuperscript{107}The list of meningitis centres was eventually made public in the spring of 1947. "Streptomycin and T.B. meningitis," \textit{BMJ} 1 (7 Jun 1947), 814; "Distribution of streptomycin," \textit{Lancet} 1 (14 Jun 1947), 833.

\textsuperscript{108}Appendix B, para 3.

\textsuperscript{109}Appendix B, para 4.

\textsuperscript{110}G.S. Wilson to W.A. Bullough, 22 Oct 1946.

\textsuperscript{111}ibid.
Streptomycin in Tuberculosis Clinical Trials Committee, a month later, agreement to cooperate had been obtained from the six institutions which had been proposed at the Second Conference in August. But while the list might have been fixed at the time, surely Wilson expected that it was likely to expand in due course. Indeed the Great Ormond Street Hospital for Children, and the Radcliffe Infirmary where Cairns was carrying out his research, were both formally added in February 1947 although Cairns had already been sent 20 grams of streptomycin on 6 December 1946 (see below). Centres such as Chelmsford, however, had no chance of being added.

The MRC officials had a broader overview of the streptomycin situation than even the fairly well-informed pharmaceutical manufacturers. Imagining how contentious a public scramble for supplies might become, it was the MRC rather than industry which tried to maintain a public policy of strict control without exception. The Boots Pure Drug Company in Nottingham, one of the British firms which was attempting to develop streptomycin manufacture, announced its plans at a press conference early in October. Sir Alexander Fleming, reading this news in The Times, therefore wrote to Sir Jack Drummond, the Scientific Director at Boots. He requested streptomycin for research on treatment of infections due to gram-negative organisms, especially in the chest, and also for a

112 FD1/6756.
113 The penicillin precedent was described in the stencilled minutes of the August meeting at Marshall’s house. These certainly would have been circulated to Wilson. MRC.46/212, FD1/6756.
114 Hart to Thomson, 18 Feb 1947, FD1/6756; [Thomson] to Harington, 6 Dec 1946, FD1/6766.
115 This situation is comparable to Pfizer’s provision of penicillin for treatment of subacute bacterial endocarditis, against the wishes of the COC. Contrast Hobby, Penicillin, pp.165-170 and Adams, “Greatest Good”, pp.78-81.
colleague who he said had a \textit{B. coli} urinary infection.\cite{117} Drummond replied the next day, asking how much streptomycin Fleming wanted. But he noted the company's undertaking to supply all its material through the MRC's new Committee and the Ministry of Health.\cite{118} Fleming explained his project and asked, "Would it be possible to sacrifice something like 10 million units for this?"\cite{119} Drummond passed the request to Hart, declaring, "My colleagues and I would like to be able to let Fleming have what he wants, but as you will see from the enclosed correspondence, I do not feel justified in sending it without some sort of backing from you and the M.R.C. committee. I hope you will share my view that Fleming is rather an exceptional case, and that we could spare [sic] him the 10 grammes when we have some material of good potency available."\cite{120} Hart responded, "You are raising a most important and difficult matter... Doubtless in the framing of this, Fleming's views as a Council member can be put. Meantime I feel we should adhere to the present interim policy which is to keep all produced material for the impending trials in tuberculosis and to resist reduction of this accumulation by expending for trials in other conditions or in individual cases of disease."\cite{121} Hart noted that the matter was to be discussed at the upcoming meeting of Council; it was agreed then to consider forming a committee to look into the use of streptomycin in non-tuberculous conditions, at such time when supplies became available.\cite{122} As we shall see in Chapter 6, Fleming was invited in November to become this committee's chairman, and got his supplies in December. Drummond, meanwhile, continued to refer enquirers to the MRC; at the start of November, he sent a Dr Wroughton who was asking for streptomycin for what he called a special case. This was the context for Thomson's remark,

\begin{itemize}
  \item [117]Fleming to Drummond, 2 Oct 1946.
  \item [118]Drummond to Fleming, 3 Oct 1946.
  \item [119]Fleming to Drummond, 6 Oct 1946.
  \item [120]Drummond to Hart, 9 Oct 1946.
  \item [121]Hart to Drummond, 11 Oct 1946.
  \item [122]Extract from Minutes of Council, 18 Oct 1946, FD1/7943.
\end{itemize}
quoted at the beginning of this chapter, "As you can imagine, we are receiving many applications of this kind. For the time being we are able to say that we have no streptomycin. Later on we shall have to take the line that the limited supplies as yet available are all ear-marked for cases within the scheme of clinical trials." He complained to Drummond, "When Wroughton spoke to me on the telephone he said that his information was that Boots could supply if only the M.R.C. could be induced to authorise." This interpretation had been expressed by other enquirers, and was causing embarrassment to the MRC; Thomson suggested that Boots instead tell people that such small quantities as the company held were already pledged. Hart explained to Thomson, "Drummond does not seem to realize that he cannot supply streptomycin which is already bought, nor does he seem convinced that the milking of material ear-marked for important trials, to provide for individual cases, would be disastrous in the long run."

A particularly delicate situation for the MRC arose out of an enquiry from Sir Arthur S. MacNalty, who had been the chairman of the MRC Tuberculosis Committee throughout the 1920s. Writing on the letterhead of the Ministry of Health, where he had been Chief Medical Officer until his retirement in 1940, MacNalty asked Thomson if the Council might consider including the Papworth Settlement. This was a well known community near Cambridge, where long-term and former tuberculosis patients lived together in accordance with the idea that social rehabilitation was the key to the broader problem of tuberculosis.

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123 Thomson to Drummond, 4 Nov 1946.
124 Ibid.
125 Ibid.
126 Hart to Thomson, 6 Nov 1946. It is perhaps somewhat curious that Drummond had such an attitude to what was essentially a rationing argument, in that he had worked as a special adviser to the Ministry of Food during the war.
127 MacNalty to Thomson, 10 Dec 1946.
128 For the general history of the settlement, see Linda Bryder, "Papworth Village Settlement: A unique experiment in the treatment and care of the
MacNalty pledged that the Papworth Medical Research Committee, of which he was Chairman, would of course co-operate fully on the lines suggested by the Council. Green forwarded this letter to Hart, asking, "Could you send me some ammunition for a reply. I would like, if possible, to give MacNalty a reasoned and informative answer, rather than the somewhat curt type of 'turn-down' which we have to send to so many enquirers for streptomycin." Hart suggested on 13 December that Green reply along the following lines:

The supplies available for our use are likely to be extremely small in the first instance and we are therefore limiting our activities to a very few centres so that we may be able to provide at least provisional information on the effect of the drug in well defined types of the disease, rather than spreading activities over more varied types in a rather larger number of centres. I am happy to say that we are having the advice of two members of your Committee, namely Professor G.S. Wilson and Professor Tytler, both of whom are members of our tuberculosis Committee. Should the rate of supplies increase we will certainly give consideration to availing ourselves of your willingness to cooperate.

He added that this might be blended with the content of the editorial in the latest issue of the *BMJ*; as I will elaborate in Section 3.4, this said that recent results in tuberculous meningitis were far less encouraging than had been originally hoped. Green's letter to Sir Arthur stated that trials were to be limited to a very few centres, but, interestingly, omitted Hart's suggested explanation of the Committee’s reasoning. In the end, Papworth had no involvement in the tuberculous?", *Medical History* 28.4 (1984), 372-390.

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129 MacNalty to Thomson, 10 Dec 1946.

130 Green to Hart, 12 Dec 1946.

131 Hart to Green, 13 Dec 1946.


133 Green to MacNalty, 16 Dec 1946.
MRC’s clinical trials of streptomycin, probably because it tended to accommodate chronic tuberculosis patients whose medical condition was considered unlikely to show clearly the effects of the drug.

Although the MRC took the stand that supplies were to be kept together for the clinical trials run by its Committees, in fact a few exceptions were made. Robert Cruickshank from the Public Health Laboratory Service in Colindale originally asked in August 1946 for streptomycin for investigation of intestinal infections, though it was only in the following March that he got 120 grams. The Microbiological Research Experimental Station run by the MoS at Porton had to go through the MRC to get 5 grams of streptomycin as a stock to hold in case of accidents with the virulent bacteria it handled. Its request in October was satisfied two months later, once the American shipment had arrived. In November, Marjorie Stephenson, from the Biochemical Laboratory at Cambridge University asked for streptomycin for the tissue culture work of Mrs Simon-Reuss from the Department of Radio Therapeutics and for her own research, which was similar. She asked for 10,000 units but declared, "I have no idea whether this is an outrageous request." In fact, this amounted to only one hundredth of the contents of the smallest available vial, so rather than attempt to divide the material, Green arranged to post to them an intact 1-gram vial early in December. Also in November 1946, Mrs H. Schwabacher from the Central Pathological Laboratory in Watford applied to the American authorities.

135C. Wilson to Thomson, 7 Mar 1947, FD1/6766.
136Stone to Thomson, 1 Oct 1946, FD1/6766; Thomson to Stone, 6 Dec 1946, FD1/6766.
137Stephenson to Duncan, 16 Nov 1946, FD1/6766; Stephenson to Green, 28 Nov 1946, FD1/6766.
138Green to Stephenson, 20 Nov 1946, FD1/6766; Green to Stephenson, 2 Dec 1946, FD1/6766.
139Foster to Stephan S. Rosenak, 19 Nov 1946, FD1/6766.
in the new year, Ashley Miles at the NIMR endorsed her application: "She is more than capable of making a reasonable bacteriological survey of cases under treatment and, from our conversation, I think she has got good clinical collaborators and understands the necessity for some control cases and for a proper clinical and bacteriological follow up, especially of the patients with bronchiectasis, that she proposes to treat." She was given 50 grams in March 1947.141

The most interesting exception, however, in light of the public statements which would soon be made about the danger of streptomycin (see Section 3.4), is the arrangement for treatment of an individual case at the Radcliffe Infirmary in Oxford. Sir Hugh Cairns telephoned Thomson on 27 November to ask for 20 grams of streptomycin to continue the treatment of a particular female patient who had tuberculosis with meningitis. The MRC made no written record of her identity, but it is implied that she was somehow personally connected with the Infirmary. Perhaps she was a relative of Cairns, who had personally brought back from the USA a quantity of the drug. (Rumour of Cairns's supply quickly reached Drummond, who immediately relayed the news in confidence to Thomson.) Cairns said it would be sufficient for intrathecal treatment of about 12 cases of tuberculous meningitis; he had obtained pure streptomycin because severe reactions could result if impure material were injected directly into the spinal column, as his own research paper in August had noted. But he needed a corresponding quantity of streptomycin for systemic treatment of the patient via intramuscular injection, and since the latter route was much less sensitive to the presence of impurities, ordinary streptomycin would suffice. Thomson told him, "I may say that in general we shall not be able to make any allocations outside the particular series of clinical trials which the Committee on the subject are now planning, but there seem to us to be special circumstances in this case."142 Early

140 Miles to Mellanby, 22 Jan 1947, FD1/6766.

141 C. Wilson to Thomson, 7 Mar 1947, FD1/6766.

142 Quotation from Thomson to Cairns, 28 Nov 1946; see also Cairns to Thomson, 28 Nov 1946, FD1/6766; Drummond to Thomson, 28 Nov 1946;
in January the MRC agreed to provide Cairns with another 40 grams of
streptomycin so he could continue treatment of the patient for another eight
weeks.143

3.3 The Hambro incident

One revealing incident in October 1946 revolves around an immensely
powerful industrialist and banker, Sir Charles Hambro. He was the head of
Hambros Bank Limited, and had been the Ministry of Supply’s top advisor on
procurement of uranium from the Congo during the war, as Director General of
the British Raw Materials Mission in Washington. It appears that his political
power failed to help him; however, in the end, his wealth enable him to obtain the
drug. The effects his intervention had on British or American policy and procedure
are difficult to determine, but it seems unlikely that he obtained the medical
outcome he desired.

It is recorded that on the morning of Saturday 12 October 1946, Sir
Charles telephoned MRC headquarters and spoke to a Miss Couzens.144
Following this call, his Private Secretary, Daphne Sears, wrote a letter to
Couzens, which covered an enclosed set of typed copies of three telegrams
between Hambro’s office and his contacts in the USA; according to her letter, he
had referred in his phone call to these telegrams.145 That afternoon, at 1:45 pm,
Couzens typed a memo to Frank Green, which began, "Sir Charles Hambro
telephoned, regarding Streptomycin, a small supply of which he is anxious to
obtain for the treatment of his grandson who is suffering from leukaemia."146

Thomson to Hart, 4 Dec 1946, all filed in FD1/6766.

143 Thomson to Cairns, 3 Jan 1947.

144 Daphne Sears to Couzens, 12 Oct 1946.

145 Sears to Couzens, 12 Oct 1946.

146 [Couzens] memo to Green, 12 Oct 1946.

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The events as I reconstruct them from the copies of the three cables are as follows.\footnote{In the following, for the sake of avoiding further convolution in the telling of an already complicated story, I assume that the copies in MRC files were faithful to the original. They were evidently not exact facsimiles, in that some information about transmission was omitted.}

Hambro cabled his business associate H.S. Morgan, of Morgan Stanley, New York, on or before Friday 11 October 1946. This original cable most likely stated that for his grandson’s treatment, Hambro needed a particular quantity of streptomycin, which he asked the American banker to procure. Morgan replied with a cable to Hambro, which is recorded as received at 4:17 pm on 11 October.\footnote{Cable, Morgan to Hambro, 11 Oct 1946.}

As I will describe in Chapter 5, Keith Macrae of the British Supply Office in Washington was told on Thursday 10 October that the UK was to be allocated a quota of 600 grams of streptomycin for the month of October.\footnote{Macrae to [Warburton] Director of Medical Supplies, MoS, 11 Oct 1946, FD1/6751.}

Morgan reported to Hambro that Macrae had advised that on the 10th, various countries were allocated a "small allotment" of streptomycin. Morgan reported also that Macrae had cabled London to say how much this amount was, and, in the telegraphic idiom, "Macrae thinks no difficulty obtain dosage needed".\footnote{Cable, Morgan to Hambro, 11 Oct 1946. We may infer from this that the 600 gram quota itself was kept secret from Morgan. According to a later cable, the original request was for 10 grams. Cable to H.M. Representative, 12 Oct 1946.}

Macrae suggested that Hambro apply for the "needed dosage" to H. Wilkinson, of the Directorate of Medical Supplies, at Portland House. This was one of the branches of the Ministry of Supply. Morgan wrote that Wilkinson would advise Hambro as soon as the allotment for England was flown over, and that this would happen as soon as the export licence was obtained.\footnote{Cable, Morgan to Hambro, 11 Oct 1946. This allotment and those that followed it were actually intended for the whole of the UK, but were frequently referred to as being for England.}
Later on the Friday afternoon, Hambro’s office cabled the British Ambassador in Washington.\textsuperscript{152} This cable reported that Hambro had been in touch with Morgan, and repeated the information Morgan had provided (aside from the location of the Directorate). The cable stated, “Hambro will to-morrow approach the Ministry of Supply as suggested but has asked that in view of extreme urgency of this case you will use your best endeavours to accelerate shipment at the earliest possible moment.”\textsuperscript{153} It was explained to the Ambassador that the drug was for the “grand-son of Charles Hambro whom you know aged three”.\textsuperscript{154} The opening paragraph reported that the illness of the grandson commenced three weeks previously and that he was critically ill. His diagnosis, acute leukaemia, had reportedly been confirmed by Dr. Windeyer of the Middlesex Hospital and Dr. Wilfrid Sheldon of Great Ormond Street Hospital.\textsuperscript{155} Brian W. Windeyer had been appointed Radium Officer of the Middlesex in 1931, and was Professor of Radiology (Therapeutics);\textsuperscript{156} it is very likely that he had some connection to Hambro’s uranium work.\textsuperscript{157} The Ambassador was told that specialists, presumably Windeyer and Sheldon, had written a letter to Dr Saster of the Medical Section, International Trade Department [sic], U.S. Department of Commerce.\textsuperscript{158} In their letter, the specialists “confirm”-- the cabled summary recorded-- “that only cure worthy of trial is streptomycin otherwise chance

\textsuperscript{152}Cable to H.M. Representative, 11 Oct 1946.

\textsuperscript{153}ibid. It is not recorded whether Hambro made an unsuccessful attempt to phone on the Friday.

\textsuperscript{154}ibid.

\textsuperscript{155}ibid.


\textsuperscript{157}The omission of his first name from the cable suggests that he might also have been known to the Ambassador.

\textsuperscript{158}Cable to H.M. Representative, 11 Oct 1946. There is no record of any reply being sent by Saster, nor any indication why this was sent as a letter, which would take a minimum of 5 days, rather than a cable. The proper title, incidentally, was the Office of International Trade.
recovery hopeless".\textsuperscript{59} The Ambassador was reminded, "You will appreciate also that time factor is of maximum importance".\textsuperscript{60} It was suggested that he intervene on two specific points. First, if Macrae foresaw any delay in obtaining the export permit, "longer than say 2 or 3 days", to attempt to persuade Saster to allow a "small amount" to be flown over in advance of the permit.\textsuperscript{61} And, in any event, to ask that "full instructions for use" be cabled to Hambro via Morgan Stanley, on the grounds that "this will be first time this drug will be used in this country for treatment of leukaemia".\textsuperscript{62}

It is likely that the Embassy cabled back to Hambro's office, but if so, we may infer that the content did not strengthen Hambro's case, or else the cable would have been included in the dossier sent to the MRC. On Saturday a second cable was sent to the Ambassador.\textsuperscript{63} It reported that Hambro had spoken with Everett of the Ministry of Supply, who was dealing with the matter in place of Wilkinson. Everett, it was recorded, needed the authority of the Medical Research Council to initiate an Import Licence, and this he was said to hope to get early the following week. The Ambassador was told, "Hambro is in touch with Medical Research Council to obtain authority to use this consignment for this case."\textsuperscript{64} The suggestion made in conversation with Couzens was that a small quantity of the material be flown over.\textsuperscript{65} Hambro asked Couzens to ask Green to ring Everett on Monday morning. Meanwhile, Everett had suggested that the Ambassador ask Saster "for a special allotment for this specific case which according to experts should require not more than a total of 10 million units administered at three hour

\textsuperscript{59}ibid.

\textsuperscript{60}ibid.

\textsuperscript{61}ibid. The exact quantity, 10 g, was not stated in this first cable.

\textsuperscript{62}ibid.

\textsuperscript{63}Cable to H.M. Representative, 12 Oct 1946.

\textsuperscript{64}ibid.

\textsuperscript{65}[Couzens] memo to Green, 12 Oct 1946.

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intervals for period of about 10 days." While Hambro was undoubtedly sincere in his belief that streptomycin was worth trying, the argument which his office recommended to the Ambassador is notable for its self-interested framing of the situation:

You could point out that as leukaemia very rare disease incurable by existing methods and as medical profession on both sides of Atlantic feel that treatment with Streptomycin holds out greatest hope of success could be treated specially as of great interest to the profession as a whole and therefore an extra supply for this case might be considered of equal interest to the American public as the British.167

In the first place, we may notice Hambro’s extrapolation to the medical profession as a whole from his contact with two London physicians; for a lay person of the time, a "second opinion" from Windeyer or Sheldon might have constituted adequate evidence of a consensus in the profession. The line taken by Hambro in conversation with Couzens may be inferred from her memo, where she suggested, extrapolating beyond the documentation provided in the telegrams, "An American doctor (I think closely connected with the supply of Streptomycin) is very interested in this patient, from the experimental viewpoint." And while Hambro surely had faith in the expert status of the medical men he consulted, the MRC administrators would have had cause to doubt whether an eminent paediatrician and a radiologist had any more claim to special knowledge about streptomycin than did the medical superintendents of provincial sanatoria. Fairly strong and nearly contemporary evidence as to the specialist authority of Hambro’s experts comes from the 5550-item bibliography on streptomycin research, to which

166Cable to H.M. Representative, 12 Oct 1946. There is no indication of how the figure of 10 million units, equivalent to 10 grams, was derived.

167ibid.

168[Couzens] memo to Green, 12 Oct 1946. It is not clear to which doctor on the western side of the Atlantic he was alluding, as later in the paragraph I have quoted it is recorded only that Windeyer had "agreed" to consult Dr Retznikoff of New York Hospital, not that he had already consulted him.
I referred in Section 2.1. Neither Windeyer, Retznikoff nor Wilfrid Sheldon were indexed as an author of any publication on streptomycin. The bibliography indexed only a single paper on leukaemia, which did not appear until 1951. Hambro's claim that streptomycin in leukaemia would be of "great interest to the profession as a whole" cannot have been taken very seriously by the MRC. The corresponding authorities in the USA were aware of a demand for streptomycin for treatment of leukaemia and other cancers, but had specifically forbidden these applications of the drug.

It is reasonable to assume that Green did phone Everett as suggested, although there is no record of a conversation. In fact, no action by the MRC is recorded. Thomson wrote on 21 October, at the bottom of Couzens' memo, "I was told some days ago that Sir C Hambro had obtained 10 gms of streptomycin from U.S.A. personally." This implies that the official channels were unforthcoming, and that the material was arranged through the black market. Ten grams of streptomycin at that time would have cost anywhere up to $150 on the legal market, but even allowing for an exorbitant mark-up on the black market, one cannot imagine this being a barrier to a man of Hambro's means. As well, we

169 Selman A. Waksman, *The Literature on Streptomycin 1944-1952*, (New Brunswick NJ: Rutgers UP, 1st ed 1948, rev ed 1952). This source cannot be considered exhaustive, and it contains more than a few errors of text and indexing, but it is very suggestive of the weight of research opinion.

170 Robert D. Barnard, "Streptomyces fermentation derivatives in acute leukaemia", *Lancet* 1 (26 May 1951), 1157-1159. Early in 1949, the author reported, he began giving acute leukaemic patients a crude by-product of the fermentation of *Streptomyces griseus*. It appears from his paper that the original purpose of this approach had been to provide the patients with vitamin-B12, and that remission of leukaemia was only later attributed to an antibiotic component of this by-product. Interestingly, the tissue culture research undertaken by Medawar and the two women at Cambridge University, Simon-Reuss and Stephenson, which the MRC apparently first heard about in November 1946, was on human carcinoma tissue; they found that such cells appeared to be prone to infection with gram-negative organisms. But there was no hint from any of them that this project was close to clinical application. See Stephenson to Green, 28 Nov 1946, FD1/6766.

may wonder what position Everett took on this attempted import, in which I doubt he found much medical merit. On occasion he went against his scientific judgment for the sake of political expediency. My guess is that he and Green simply waited for the U.S. Department of Commerce to throw up enough delays that action in London became irrelevant. But we shall probably never know the full story.

Very few people in Britain had personal and institutional connections as powerful as Sir Charles Hambro’s, but the rest could and did appeal to ordinary sympathy for the sick and suffering. In the next section we see another threat to rationalist distribution: humanitarian appeals in emergency cases.

3.4 Emergency broadcast appeals and the toxicity scare

Since the vast majority of ordinary citizens were unable to obtain streptomycin through official channels, and the demand was great, it is not surprising that some of them found alternative means of procuring the substance. The BBC broadcast numerous emergency appeals for streptomycin. A particular focus was the treatment of young children with tuberculous meningitis, for whom the drug represented the only hope for survival. These appeals increased the public’s perceptions that there were stocks of the drug to be had in Britain, and thus interfered with central administrative attempts to maintain a rule-bound system of distribution. If appealing to rationalist principles of distribution could not dampen the demand for the drug as much as the MRC and MoH wished, there was a more plainly intelligible argument at their disposal: that the drug was

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172 Copy of J. Cairncross memo, 13 May 1946, original on S.46518, T225/25. Here Everett recommended continuation of a grant to research at Imperial College on synthesis of penicillin, largely on the grounds that Sir Robert Robinson, the President of the Royal Society, was backing the project and it would be "a little awkward, to say the least" for the government to pull out.

173 The PRO retains a file labelled "Sir Charles Hambro’s papers", AB1/504, but this consists only of the volume (formerly BT 1-2-1/02) which ends at June 1946.
dangerous. The government thus deliberately created a toxicity scare in order to stem the tide of public requests which it could not meet.

Supplies of streptomycin that were sent more or less clandestinely from the USA to Britain must have ranged from smuggling rackets, at one end of the spectrum, to donations to hospitals and gifts to family members, at the other end. There is no way to determine the scale of such activities, because of their underground nature. It is impossible to say how much streptomycin—outside the official export allocation that was purchased wholly by the government—reached the UK. We know for example that small quantities of streptomycin, amounting to a few grams, were sent to scientists at Mill Hill, carried in the pockets of returning British travellers. We also know that the Board of Trade decided late in 1946 to issue licenses for imports of streptomycin for personal use certified by the patient's doctor, in keeping with the general policy derived during the war. Where profiteering was the motive of covert imports, it is possible that buyer and seller made contact through networks not dissimilar to those for other black-market goods. But of course black market drugs were extremely expensive and might well be adulterated, as illustrated in Graham Greene's film and novella, *The Third Man*, written in 1948. The plot was based on reports from *The Times*’s correspondent in Vienna. In the story, black-market penicillin

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174 Hart to Thomson, 15 Jul 1946, FD1/6751.

175 Marchbank to Marre, 30 Nov 1946, MH58/636. This matter will be discussed further in Chapter 4.


heavily diluted with filler was given to children with meningitis (of an unspecified type). The children ended up "off their heads" and could not even be saved with full-strength penicillin because the infections had become drug-resistant. Fake penicillin in Berlin, made from dextrose or yellow face powder, was reportedly selling for £375 an ampoule in 1946.\textsuperscript{178} In the famous ferris wheel scene of the movie, the villain Harry Lime told his school friend Martins that for the life of each of the human 'dots' moving far below them, he could earn £20,000-- "free of income tax, old man".\textsuperscript{179}

So how might a patient in need bypass the system of controls and designated hospitals, and locate a supply of genuine streptomycin that had been imported privately? The solution which emerged rather anarchically was a series of emergency broadcast appeals, and interestingly it was the BBC News Service which took on the coordinating role. The BBC evening news on Friday 1 November carried a broadcast appeal for streptomycin for what it called an urgent case. A young boy was critically ill with tuberculous meningitis in the Royal Surrey Hospital in Guildford. It was later reported to Landsborough Thomson that a small quantity of the drug was supplied within a couple of hours by a firm in Tottenham. Further information, he wrote, was that the child had died immediately after receiving an injection-- although, he noted, not necessarily as a result of it.\textsuperscript{180} Hart reported to Thomson on Wednesday, "The response to the B.B.C. broadcast appears to have been much ado about almost nothing. My latest information is that the material sent consisted of one bottle containing $\frac{1}{2}$ gramme of streptomycin, this being material that the firm had had from America as a standard in case they started making any (which they have not done)! Well, well."\textsuperscript{181} On the Friday following the broadcast, Drummond wrote that Boots

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\textsuperscript{178}"Imitation penicillin in Berlin: Black Market Arrests", \textit{The Times} (22 Apr 1946).


\textsuperscript{180}Thomson memo on phone conversation with Dalrymple-Champneys, 5 Nov 1946, FD1/6764.

\textsuperscript{181}Hart to Thomson, 6 Nov 1946.
\end{flushleft}
had suspected that the firm in question had been the British end of John Wyeth and Company, which was based in Philadelphia.

Many individuals close to the MRC and Ministry of Health reacted indignantly to such broadcasts, of which there were many more over the following months. On the following Monday, for example, one doctor wrote to Hart, "Surely the Medical Research Council should stop this sort of thing at once by a reasoned pronouncement in all the papers; otherwise the public is being seriously and cruelly misled." The tone of such correspondence is strikingly illustrated by a letter from the microbiologist C.H. Andrewes, who then worked at NIMR:

One expects ill-informed and sensational items from the less responsible elements of the Press, but something rather better from the B.B.C. They go to a lot of trouble to get scientific advice for some of their feature programmes... but are apparently [sic] quite lacking in guidance where news bulletins are concerned... I do not venture to suggest the best remedy but feel that the mystery disease affecting the B.B.C. news department cannot be incurable.

Thomson recorded, from his conversation with the Deputy CMO on the following Tuesday, "Sir Weldon agreed that it was improper of the B.B.C. to broadcast appeals for a substance which was not available, and he promised to look into that aspect of the matter." If fact, if the substance had genuinely been completely unavailable, then the radio appeal would of course have failed. One of the authorities' objections was that the appeal, and its many successors, would create the impression in the public's mind that there was enough of the drug around that one could obtain it by asking long and loud enough. This of course was unacceptable to the MoH officials. As one of them explained to the news editor of

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182Drummond to Thomson, 8 Nov 1946.
183Clayton to Hart, 4 Nov 1946.
184C.H. Andrewes to Mellanby, 18 Dec 1946, FD1/1378. He later directed the MRC Common Cold Research Unit.
185Thomson memo on phone conversation with Dalrymple-Champneys, 5 Nov 1946, FD1/6764.
the BBC, "The broadcast 'S.O.S.' may however have the unfortunate effect of giving the impression that supplies are already available over here and can be obtained for treating specific diseases. This is far from being the case."\(^{186}\) The officials' predictions that the appeals would stir up demand turned out to be well-founded. The incident was widely reported, for example in the *Express* story, "Car races rare drug to boy",\(^{187}\) It even reached journals in Belgium, whereupon a doctor, F. Droogmans, wrote to the Royal Surrey Hospital.\(^{188}\) The Secretary-Superintendent of the hospital asked the MRC to explain the position to the Belgian doctor, whose letter he enclosed.\(^{189}\) In any event, Green replied to Droogmans that it was "quite impossible" to meet the request.\(^{190}\) He explained, "The chemical firm in Tottenham, to which you saw reference in the newspaper, had only a minute sample in hand, and this was insufficient for the treatment even of one patient."\(^{191}\) The public enquiries continued. On the Tuesday following the first broadcast, Green sent a memo to Thomson, saying, "Balfour Kirk of the Medical Intelligence Department, Ministry of Health, telephoned to say that the Ministry are daily being pestered with requests."\(^{192}\) He suggested that a joint statement from the MRC and the Ministry be published in the *Lancet* and

\(^{186}\) Harding annotation on Ryan to Harding, 12 Nov 1946, MH58/636.

\(^{187}\) Circa 2 Nov 1946, filed in FD1/6760.

\(^{188}\) Droogmans to Monsieur le Directeur de Royal Surrey Hospital, 16 Nov 1946.

\(^{189}\) R.S. Regan to The Secretary, MRC, 18 Nov 1946. Given that during the previous fortnight, the House of Lords had debated the protection of voluntary hospitals under the coming nationalization, it is worth recalling this small cooperative act; for a hospital to become involved in streptomycin distribution by radio appeal did not necessarily imply that it was trying to attack the government over its distribution scheme for the drug.

\(^{190}\) Green to F. Droogmans, 20 Nov 1946.

\(^{191}\) Ibid.

\(^{192}\) Green to Thomson, 5 Nov 1946.

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A statement was indeed produced, but before they were able to take action, a new piece of American research added fuel to the fire.

Back in August, a highly unfavourably report on the use of streptomycin in several types of meningitis was rushed into print by authors from the Radcliffe Infirmary in Oxford. They declared: "At a time when urgent appeals are being made in this and other countries for supplies of streptomycin for treatment of individual cases of meningitis we think that our preliminary results should be made known even though they are not conclusive." Their two patients with tuberculous meningitis died, one within 8 hours of treatment with streptomycin. An authoritative report from the Mayo Clinic declared at the end of November that four of their nine patients with tuberculous meningitis had survived for several months. Among the patients whose tuberculous meningitis was arrested, blindness of one patient was attributed to the disease itself, while in the case of a deaf patient, they wrote, "there is a question whether the deafness is due to the streptomycin." A third patient was reported to have "profound disturbances of cerebellar function", but the fourth was described as "clinically well, ambulatory and free of all symptoms,” five months after

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193 ibid.


195 ibid

196 H.C. Hinshaw, William H. Feldman, and Karl H. Pfuetze, “Treatment of tuberculosis with streptomycin: a summary of observations on one hundred cases”, *JAMA* 132.13 (30 Nov 1946), 778-782, at p.779. A fifth meningitis patient was still alive but had been under treatment for only a month so he was excluded from the analysis.

197 ibid.

198 ibid.

199 ibid.
having been admitted with "severe symptoms of early tuberculous meningitis". The Oxford group had stressed that there was little point in instituting treatment of meningitis unless it was begun promptly. There was thus an incentive to get treatment whenever a child was suspected of having tuberculous meningitis, since bacteriological confirmation of a presumptive diagnosis of the condition would take weeks, by which time it would be too late. The public's search for emergency supplies thus became more frantic.

Pessimistic framing by the MRC of American research findings has been described above in Section 3.2. This approach is illustrated particularly by the October stencilled statement, which concluded, "The evidence from such trials as have already been made in America leaves it at present quite uncertain whether streptomycin is likely to prove of great value in tuberculosis, and it may eventually prove that its chief uses lie in the treatment of certain other conditions." Around the end of October, again through framing that was pessimistic to the point of being deliberately misleading, the MRC began to use the argument that streptomycin was positively dangerous. At that time, Green told an enquirer that one of the MRC's fellows, who had just returned from the USA, had reported that streptomycin "works ill" in some clinical forms of the disease. There is no indication of the identity of the travelling fellow, but it is possible that Green was resurrecting the warning which Raistrick and Keep had heard in May: "Streptomycin appears to be very promising in the treatment of tubercular meningitis but he [Chester Keefer] stressed the fact that because of the brain lesions in this disease even if the patient recovers he is liable to be a permanent invalid." It is of course highly likely that Keefer's warning had

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202Green to Shore, 24 Oct 1946.

203We can rule out the 1946-47 Dorothy Temple Cross Travelling Fellow, Dr T.F Jarman, who had only just arrived in the USA. See Herrald to Jarman, 4 Nov 1946, FD1/3052.

204[Raistrick and Keep] memo, Streptomycin, FD1/6759.
also been tailored to discourage requests for the drug. Green elaborated:

Thus this travelling fellow told me that, while a few children with miliary tuberculosis and meningitis appeared to have been saved in America by prolonged treatment with the drug, they were almost all left hopelessly mentally deficient and permanently deaf, the latter, at least, being a side effect of the drug’s action.\textsuperscript{205}

Likewise Green told an enquirer from the Warneford General Hospital that “recent results in America with Streptomycin in tuberculous meningitis have been very discouraging.”\textsuperscript{206} Late in November, he wrote, introducing a theme which would be commonly expressed by the Council, “The American work has, however, shown that Streptomycin is potentially a considerably more dangerous drug than penicillin”.\textsuperscript{207} Around this time, as a result of the BBC emergency appeals, the Medical Sub-Editor of the \textit{BMJ}, Dr Grahame E. Murphy, wrote to Hart.\textsuperscript{208} Hart passed the request to headquarters, where Green provided a draft statement for use as an annotation in the \textit{Journal}. He informed Murphy, “We would prefer it to be used in that way, rather than as an official statement emanating from this office”.\textsuperscript{209} Upon receiving the proofs, he insisted again, “We should really like it to be regarded as emanating from your office, rather than from ourselves”.\textsuperscript{210}

Regarding the tuberculous meningitis patient treated with streptomycin, a leading article that appeared in the issue dated 14 December declared, “there seems to be a very real risk that, even if the infection is controlled (as has only very rarely happened), the patient will usually be left mentally deficient, deaf, blind or

\begin{itemize}
\item \textsuperscript{205} ibid.
\item \textsuperscript{206} Green to Warneford General Hospital, 30 Oct 1946.
\item \textsuperscript{207} Green to Mrs J. D\textsuperscript{,} 26 Nov 1946.
\item \textsuperscript{208} Grahame E. Murphy to D’Arcy Hart, 28 Nov 1946, FD1/6756. Hart had taught Murphy at University College Hospital before the war.
\item \textsuperscript{209} Green to Murphy, 4 Dec 1946, FD1/6756.
\item \textsuperscript{210} Green to Murphy, 10 Dec 1946, FD1/6756.
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otherwise a hopeless invalid." The _Lancet_, on the other hand, did not publish any statement of this kind. Instead, early in January, it published a report which had been prepared in the autumn by a team led by Dr D.G. Madigan, the Tuberculosis Officer of Kent County Council, whom we shall meet again in Chapter 6. This report said their experiences were free of the perils reported in previous trials such as that by the Radcliffe Infirmary group. Moreover, they presented evidence that toxicity was inversely proportional to purity, and, noting that the purity of preparations had been steadily improving over time, they declared themselves convinced that streptomycin could be used in safety at the dose levels they had adopted.

The allegation of danger from the use of streptomycin in tuberculous meningitis would be repeated to the public frequently in the coming months. In January, Russell-Smith from the Ministry of Health consulted the MRC about the draft statement. Thomson wrote, "We should welcome its issue in any event, as we are being bothered almost hourly with requests for the drug from people who know nothing of its dangers." The statement, made in Bevan's name, appeared in _The Times_ on 23 January. It warned, "in the very small number of patients with tubercular meningitis whose life has been prolonged by the treatment there has nearly always been permanent serious mental derangement, blindness or deafness." This provoked a much sharper response than the similar statement in the _BMJ_ had done in mid-December. Waksman cabled Drummond to find the background to the statement. Although American officials advised Waksman to ignore the matter, Waksman contacted Alexander King at the BCSO in

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212D.G. Madigan, P.N. Swift and George Brownlee, "Clinical and pharmacological aspects of the toxicity of streptomycin", _Lancet_ 1 (4 Jan 1947), 9-11, at p.11.

213Thomson to Russell-Smith, 17 Jan 1947, FD1/6769.

214"Streptomycin" _Times_ (23 Jan 1947).

215"Henry Welsch [sic]", 28 Jan 1947. This document and ones that follow are filed in "Streptomycin (British corres.)", Box 2 Main Series, Waksman
Washington. King soon cabled his superiors that the American authorities were "seriously concerned" about the statement on toxicity. 216 A testy response was cabled back to Washington: "In view of scarcity of streptomycin in this country great embarrassment has been caused by exaggerated press claims for its value which go beyond evidence as yet available especially for tuberculosis. It has accordingly been necessary to inform British public that treatment is still in experimental stage and not free from danger. Facts regarding the latter are drawn from American medical reports." 217 Green later explained the MoH statement to the Foreign Office, "It was intended to discourage broadcast appeals for the drug, by indicating that these cannot be met from British sources at the present time." 218 Thomson, in response to pressure from Russell-Smith, declared, "The Americans are apparently disturbed by our attempts to play down the publicity about streptomycin. We do not feel repentant as the trouble is due to their playing it up." 219 Drummond related his own version of events, saying he thought the Minister's statement was fair even if it erred on the side of being over-cautious. 220 Hinshaw, when asked by the British United Press for the American reaction, referred to the Mayo Clinic's *JAMA* paper of 30 November 1946, which he said "fully describes present viewpoints concerning streptomycin in tuberculosis". 221 Meanwhile, continuing to take an independent line after the *Times* warning appeared, the *Lancet* published a leading article at the end of January, which summarized the positive Mayo findings in tuberculous meningitis.

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216 telegram, King BCSO to Verry DSIR, 30 Jan 1947, FD1/6769.
217 outward telegram, Verry to King, 8 Feb 1947, FD1/6769.
218 Green to Under-Secretary of State, Foreign Office, 16 Apr 1947, FD1/6769.
219 Thomson to Russell-Smith, 5 Feb 1947, FD1/6769.
220 Drummond to Waksman, 4 Feb 1947, Waksman Papers.
221 Hinshaw to Waksman, 12 Feb 1947, Waksman Papers.
Though it denied that chemotherapy was a "shortcut to cure," the journal asserted, "In spite of transient and permanent toxic effects, uncertainty regarding the development of drug-resistance by tubercle bacilli, and difficulty of purification and production of streptomycin, these early reports give great hope for the future.""222

The Ministry's continued interventions failed to prevent a succession of similar broadcasts for many more months. Interestingly, the BMA's Charles Hill acted as a mediator between the MoH and the BBC, chairing a conference—which the MRC boycotted.225 It is difficult to tell what effect the toxicity scare of the winter of 1946-1947 had on actual usage of streptomycin during the following few years. As Waksman and Bryder have noted, in 1950, once there were ample supplies of the drug in Britain, the Ministry of Health published a report that noted, with some concern, "There appears to be a belief prevalent amongst many medical practitioners that streptomycin treatment does no more than prolong life or produce 'recovery' as a physical and mental wreck. This is not true."226 If general practitioners were indeed confused on this point, responsibility can be laid squarely back at the door of the MoH itself, for this was the interpretation that the Ministry had previously inculcated. While there was some improvement over these years in the prognosis for tuberculous meningitis treated with chemotherapy, this incident can mainly be attributed to the Ministry's earlier biased presentation of reports, in which it had had the full cooperation of the MRC.

3.5 Conclusion


223 ibid.


225 C. Hill to Greene [sic], 16 May 1947, FD1/6769.

During the period from September 1945 to January 1947, the demand for streptomycin greatly increased. The supply of the drug in Britain also increased markedly, from a few grams to tens of kilograms. But demand remained far in excess of supply for several more years. The British government tackled this shortage in three ways. First it attempted to increase supplies, both by stepping up production, as we will see in the next chapter, and by buying considerable amounts of the drug from the USA, as I will show in Chapter 7. Second it implemented a system that applied fixed criteria in many decisions over distribution, and attempted to persuade the public that the system was indeed fair. Third it attempted to decelerate the rising demand, through propaganda implying that the drug was dangerous and possibly ineffective. This chapter has covered the latter two strategies.

Let us recapitulate our story of demand and distribution. The first request for streptomycin on file was made in September 1945, and, exhibiting greater persistence than most, the eminent enquirer eventually got a small supply of the drug, some fifteen months later. A handful of enquiries were received by the MRC in the spring of 1946. Six more letters appeared in the interval between Feldman’s public lecture in July and the announcement in *The Times* and *BMJ* in late September of forthcoming MRC clinical trials. The ten days at the end of the month saw eight new enquiries arrive, and the pace continued to accelerate. Early in October the MRC produced a stencilled statement, which was sent to those seeking streptomycin for tuberculosis. Despite the government’s attempt to have all supplies channelled into the MRC’s clinical trials, some quantities—probably small though we will never know for sure—were present in Britain as a result of leaks in the system. One such leak occurred through the efforts of Sir Charles Hambro to procure streptomycin for his critically ill young grandson. Independently controlled supplies of streptomycin became the object of a succession of emergency appeals, the first of which was broadcast at the start of November. The Ministry of Health attempted unsuccessfully to put a halt to the broadcasts. It then issued several widely publicized statements warning that streptomycin was of unproven value in tuberculosis, and in particular that streptomycin treatment of tuberculous meningitis was likely to leave the patient
with severe mental or physical damage.

The basic pattern of distribution that was set in the early winter of 1946-47 remained stable despite widening availability over the next three years. Namely, the government channelled its own supplies into research. Initially it did this through the MRC's clinical trials. Then, once the MRC committee reported privately to the Ministry of Health that efficacy of streptomycin in tuberculous meningitis had been established, wider distribution became imperative. The Ministry created in September 1947 its own 'clinical trials' scheme under which children could be treated in some twenty hospitals around the country. That project is beyond the scope of this thesis, but it illustrates that officials recognized the effectiveness of medical research as a rationing mechanism. This argument will be developed further in Chapter 6.

This distribution pattern was conditioned by two factors. First, the government departments did indeed need information about the properties of the drug. As we will see in Chapter 6, there is some question as to whether the government could have simply waited for American findings to appear, rather than running its own research programme. But the basic point stands, that there could be no fairness in allocating streptomycin in the absence of some degree of agreement about how useful the drug was in treating specific conditions. Various scientific criteria were applied, initially to decide which cases would be more useful for the research programme, and eventually, which cases most needed the drug for treatment. A second factor was that officials wanted the public to perceive that the system was fair. Thus the government's publicity argued that the shortage created a need for rational control over distribution. In particular, an absolutely central element of the public relations strategy was the assertion that supplies had to be allocated to experimental use within clinical trials. Restriction of distribution of the drug to a small number of centres was justified on the grounds of the need for knowledge. By channelling the drug to cases selected on scientific criteria, the government could avoid both waste and the public perception that distribution of this substance was determined by economic and political influence. In fact, as the example of Cairns's patient shows, it was possible for scientists to get preferential treatment, but this was apparently not widely known.
The government’s ability to meet its objectives depended in part on its exclusive control over its own supplies, in other words, on its ability to resist the demands of petitioners. It was relatively easier to turn people away if the government could plausibly maintain the impression that no other member of the public was able to get the drug either. This claim was then blatantly contradicted when particular individuals were able to get supplies by making appeals over the airwaves. Instead of having a central authority assign allocations according to rationalist principles, the radio appeals provided a method by which control over distribution was exercised voluntarily by cooperating institutions, reacting to explicitly humanitarian entreaties.

I have established in the current chapter a further point which is separate from, but complementary to, my claim about the government’s use of clinical trials as a rationing mechanism. Namely, I have shown that the government continually attempted during 1946 to slow the growth in demand for the drug. This strategy can be understood partly as an effort to avoid the political embarrassment which a shortage entailed. The two-pronged method of discouraging public requests for the drug consisted of highlighting the uncertainty over the efficacy of streptomycin, and exaggerating the risk of harmful side effects. If anyone attempted—relying solely on government correspondence to the British public—to discern the status of research into streptomycin’s effectiveness and toxicity, they could be forgiven for concluding that the observed outcomes of streptomycin treatment were getting continuously worse. Repeatedly, the MRC staff compared what they referred to as early optimistic reports versus the present position; repeatedly, the latter position was said to be less promising. In particular, one would never guess from these letters to the public that the purity of the streptomycin available to researchers in the USA had increased markedly since the first clinical test was done. Facing a flood of enquiries, the Ministry concocted a toxicity scare which, although it never contained outright untruths, used misleading half-truths in an effort to discourage appeals.

In the attempt to manage distribution of (and demand for) the drug, the scientific expertise of the MRC was a key resource. Certainly it appears to have been effective in persuading members of the public that the government’s position
was sound. There is a paucity of repeat enquiries in the Council’s files in which, say, patients or doctors disputed the rationale which had been provided, or pressed the MRC to back up its claims by providing specific evidence.

One unfortunate consequence of the concentration of expertise within the MRC and MoH was that there was weak accountability for the publicity and distribution policy. Parliamentary scrutiny of the distribution system proved ineffectual, in that questions which would have revealed the fabrication of the toxicity scare were not asked. Few people in Britain, outside the government itself, had the expertise to challenge the MRC’s overly pessimistic framing of American research. In this effort the *BMJ* cooperated fully with the Ministry, while the *Lancet* provided a more balanced view but did not openly criticize the government’s handling of streptomycin. Drummond at Boots took the Ministry of Health’s side when queried by American scientists.

Looking ahead, Chapter 5 on imports will illustrate the resemblance between the responses that the American authorities issued to the government of the UK (and to the governments of other nations) during a period of American export control, and the MRC’s responses to public requests for streptomycin. As well, I will look at the issue of government control of small-scale private imports which provoked the controversy regarding emergency appeals, described above. Chapter 6 will describe the scheme of approved institutions where research took place; here we have seen how useful this arrangement was in placating the public, under the circumstance that distribution was unavoidably limited for the time being. We shall see in Chapter 7 how the MRC took advantage of the risk of political controversy over distribution of streptomycin. It argued to the Treasury that the acceptance of a large shipment of imported streptomycin would absorb American-made supplies of the drug into its programme of clinical trials, thereby making the allocation of such material somewhat less contentious.

Turning now to the links with chapter 4, we have seen that official attempts to undo the toxicity scare would not appear until streptomycin was abundant in the UK. And an end to the streptomycin shortage hinged upon the development of domestic production of the drug. As well, we have seen the public demand for
streptomycin growing over the course of 1946 from a trickle of requests to a heavy flow. Such strong demand was predicted early in the year—although without certainty because of the unclear clinical picture of streptomycin at the time. Several pharmaceutical firms thus became interested in manufacturing the drug for sale in the British (and eventually export) market. In the highly controlled postwar economy, these production endeavours were a matter for central government sponsorship.
Chapter 4. Production Policy

I daresay you know that I have been trying to hustle up the Ministry of Supply to erect a pilot plant for the manufacture of antibiotics. I think they have more or less agreed in principle to do this, but they are frightfully slow about everything. I have given up the pharmaceutical manufacturing firms of this country as hopeless.

Sir Edward Mellanby to Howard Florey, 12 Mar 1946

4.1 Introduction

By the end of 1946, the British government made a major financial commitment in the course of its introduction of the drug into the nation. In this chapter I look at the origins of that commitment—which as of June of that year still explicitly excluded any financial aid. I identify the government’s key initial interest in streptomycin as the question of commercial pharmaceutical manufacture in Britain. Here I explain the government’s reasons for approving attempts at streptomycin production. In particular I make it clear that it was the Ministry of Supply (MoS) that played the Government’s leading role in the beginning of the British streptomycin story. But while the Medical Research Council (MRC) can

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1 FD1/6751.

2 The Ministry was created on the eve of the Second World War to manage the procurement of supplies for the Armed Services. The Department had since grown to become Britain’s single largest employer, controlling a vast array of munitions factories. Among its many responsibilities was to act as Production Authority for medical supplies including penicillin, the first antibiotic to be widely used. As the relevant Production Authority, the MoS was accountable for ensuring that sufficient penicillin was available to meet the projected requirements of the Services in wartime. To achieve this end, the Ministry held broad emergency powers, which remained in force after the end of hostilities. Plans to produce a number of other antibiotics, which will be described below, were being touted by various parties, and decisions about possible government sponsorship of production of these substances also came under the Ministry’s jurisdiction. See Edgerton, "Whatever happened to the Ministry of Supply?".
be seen as primarily responding to the demands of other, larger institutions, the way its senior administrative staff conducted external negotiations reflects a high degree of autonomy— not to mention skill— in the accomplishment of the Council’s advisory role. As with the enquiries previously described, in this chapter on streptomycin production policy we will see illustrations of a theme running throughout this study, namely the MRC’s careful use of its scientific expertise and credibility in order to achieve its institutional goals in the scramble for resources that accompanied the period of reconstruction and reorganization.3

Interest in the potential of the antibiotic approach to the treatment of disease can be attributed to commercial competitiveness, military preparedness and scientific advance. In particular, the streptomycin discussions took place against a backdrop of British bitterness over 'losing' penicillin to the Americans, and protracted efforts to maintain national self-sufficiency in vital medicines. And though the greatest impact of penicillin on public health was yet to be experienced, there was already a great deal of enthusiasm for the "miracles" that had been wrought. One sign of this prestige is the awarding of the Nobel Prize in December 1945 to the three men who had been instrumental in the discovery and development of penicillin, namely Fleming, Florey, and Chain. What the next great antibiotic would be was somewhat of an open question after the war, although already streptomycin had a head start which would not be surpassed. When the MRC pushed for the enhancement of microbiological production, it is possible to see it as appealing to much more than a scientific project: it was promoting the modernization of Britain.4

Planning for supplies was largely concentrated in the hands of a few officials. The most senior man within the MoH dealing with drug supplies was Sir Weldon Dalrymple-Champneys, who was not held in high regard by his colleagues. A strong-minded Principal in the Ministry of Health, by the name of Frank Marchbank, was preoccupied with the protection of the British

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4 On antibiotics and modernization, see Robert Bud, "Penicillin and the New Elizabethans".
pharmaceutical industry. Time and time again he argued for policies which would result in the establishment of a special status for domestic industry and would result in keeping out imports from American firms, which, in the wake of the destruction in mainland Europe, constituted the primary competitive threat to British industry.

One of the key economic issues which was at stake, according to the MoH files, was the allocation of skilled manpower. A limited number of workers knew enough about industrial scale fermentation that they could have contributed to the production of penicillin or streptomycin. An exemption from military service was in place, for any workers who had been declared essential for the production of penicillin. A question remained to be settled, presumably between the MoH, the MoS and the Ministry of Labour & National Service, over whether this exemption might be extended to workers involved in the production of other antibiotics. Clearly such a decision would have major ramifications for the allocation of labour within the pharmaceutical industry, and the availability of workers in general. Without this approval of labour resources, any new plant would not be of much use.\(^5\) With important economic issues at stake, some assessment of the potential return on investment was clearly of interest to the Ministry’s planners.

A final point worth stressing is that the decision to let industry go ahead with streptomycin production was made without evident input from politicians.\(^6\) It was only later, beginning in the autumn of 1946, that Members of Parliament became involved to any degree in the issue of streptomycin production. In November, one Colonel Crosthwaite-Eyre MP (Cons, New Forest and Christchurch) asked Herbert Morrison, the Lord President, among other points, whether moneys were allocated for streptomycin research and production.\(^7\)

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\(^5\) The MoH files are consistent with the possibility that responsibility for the decision was either shared between MoH and MoS or had recently been transferred. This might have been a reason for the MoH to become involved in certain of the industrial decisions.

\(^6\) Nor did it require rubber-stamping by Franks or even by either of the Ministry’s Second Secretaries.

\(^7\) *HC Debates* vol 430, no 5, (18 Nov 1946), filed in FD1/6765.
Likewise Bevan was asked questions but there is no sign that any of the interventions had any direct effect on the production policy that was followed. The route of influence can be traced rather through the civil servants’ perception, evident in many government records of the time, that the public was demanding access to the drug and that the substance would be commercially viable.

I provide an overview of production policy in the USA and UK, and then put into context one of the MRC’s main arguments to the MoS, on the enhancement of Britain’s capacity for micro-biological production, including the inter-departmental negotiations over a pilot plant for antibiotic substances. I describe the MRC’s arguments for having clinical trials conducted in Britain and for maintaining its own status as the foremost organizer of such clinical research. I look at the actual decision by the MoS, and attempt to reconstruct some of the reasons that production was approved. Then the links between production and the MRC’s changing plans for clinical trials are presented.

4.2 Streptomycin production in the USA

The world’s most advanced manufacturer of streptomycin was Merck & Co, a family firm based in New Brunswick, New Jersey, not far from Rutgers University, with which Merck had a contract for industrial development of substances discovered by Waksman’s lab. The Journal of the American Medical Association carried, in September 1945, Merck’s announcement that it was to spend approximately $3.5 million on new plant for the production of streptomycin. At an exchange rate of $4.03 to the pound, this was about £750,000, a cost on the same order of magnitude as that of either of the large new British plants for penicillin, located at Barnard Castle in Durham and Speke near Liverpool. The notice in JAMA said that production of streptomycin would take place at the firm’s Stonewall Plant at Elkton, Virginia, and that there would also

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8 "Expanded facilities approved to produce streptomycin," JAMA 129.3 (15 Sep 1945), 224.
be a unit for drying and packaging the drug at Merck’s main plant at Rahway, New Jersey. The September 1945 announcement also stated that Merck’s plans had received approval, at the beginning of the previous month, by the War Production Board (WPB), which was analogous in function to Britain’s Ministry of Supply. There remained in the USA after the end of the war a system whereby federal government permission was required for major industrial developments. As in the case of penicillin, streptomycin was produced by fermentation. Culturing of Actinomyces griseus was beset with technical difficulties. Most notably, the broth could easily become contaminated with unwanted organisms which could either inhibit the growth of the desired strain, or yield toxic chemicals.

4.3 The consultation in March 1946

On 19 March 1946, senior officials of the Ministry of Supply and the Medical Research Council met to discuss the Government’s programme for research and development of new antibiotic substances, one of which was streptomycin. One of the decisions which now lay before the Ministry was whether priorities should be granted to two British pharmaceutical firms, the Boots Pure Drug Company and Glaxo Laboratories, which were planning to manufacture streptomycin. Glaxo’s board of directors had decided on 29 January 1946 to

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9 Within a few months ten other American companies undertook to manufacture streptomycin. Almost all of them had wartime experience making penicillin, were still at a fairly early stage of development. See Minutes of the Streptomycin Producers Industry Advisory Committee (SPIAC), WPB policy documentation files, USNA.

10 The organism was added to a broth containing various nutrients— in the original experiments, glucose, peptone (a substance derived from protein), corn steep, meat extract and salt— left to grow, and then the extract was purified and dried.

11 See Porter, "Streptomycin".

12 On the priorities system, see M.M. Postan, British War Production, WWII UK Civil Series, (London: HMSO, 1952); J.D. Scott and Richard B. Hughes, The
invest £250,000 in a new factory to produce streptomycin. This was agreed on the basis of the projected importance of streptomycin in treatment of not only tuberculosis, but interestingly, also whooping cough and typhoid—about which we have seen the rather unconvincing clinical evidence. The proposals regarding streptomycin had come to the Penicillin Production Control (PPC), a relatively small MoS unit with which the two firms had already been dealing since the start of 1945 in connection with their role as penicillin producers.

Sir John Edward Lennard-Jones, the Chief Scientific Officer of the Ministry of Supply, raised the question of the streptomycin proposals at the meeting in March 1946. Sir Charles Harington, the Director of the National Institute for Medical Research (NIMR), the MRC’s main research establishment, represented the Medical Research Council. He was prepared to discuss the possibility that the Ministry might construct a pilot plant to produce antibiotics, but not, we shall see, the issue of streptomycin production. On issues related to this pilot plant, there survives a letter of agreement between the MRC and MoS, which was apparently signed at the meeting. But there is no sign that minutes were taken at the meeting, nor a formal agenda. What we know about the streptomycin discussions at the meeting, therefore, is drawn from a note which Harington wrote the next day to his chief, Sir Edward Mellanby, the Secretary of the MRC, and Harington’s follow-up letter to Lennard-Jones, which exists in draft and final


14 The Ministry of Supply attempted to divest itself of its medical supply functions. The civilian side of these functions was finally transferred in December 1947 to the Ministry of Health. One consequence of this transfer is that the surviving MoS files on antibiotic production are found at the Public Record Office within a class of records pertaining to the Ministry of Health, MH136. See files AVIA49/53 and AVIA49/75. Similarly, MoS transferred responsibility for housing supplies to the Ministry of Works. Richard Williams-Thompson, Was I Really Necessary?, pp.77-84.
versions. Harington’s letter records that he was asked at the meeting for “the view of the Medical Research Council on the projects for the large-scale production of streptomycin which are now under consideration by the Ministry of Supply”. It was understood, Harington wrote, that two pharmaceutical firms were “anxious to obtain facilities” for large-scale production of streptomycin. Glaxo and Boots were not named in any of the correspondence regarding the meeting, though it is possible that they were identified orally to Harington. Harington also noted in his letter that one of these companies had requested “priorities for new buildings”.

Permission from MoS, in the form of the granting of priorities, was required for any major industrial venture, by virtue of the Ministry’s control over a variety of resources. Specifically in the case of pharmaceuticals, these included building materials, steel tanks, industrial solvents and skilled labour, all of which were in short supply. An official of the Ministry of Health (MoH), Frank Marchbank, declared soon after the MoS-MRC meeting that hitherto, practically all such newly qualified personnel had been directed to penicillin production as a condition of deferment from call-up to military service. He asked the MoH Deputy Chief Medical Officer, Dalrymple-Champneys, whether the exemption from military service should be extended to workers producing other antibiotic substances. The opinion Marchbank stated internally, in preparation for a discussion with MoS, was that any such exemption for industrial workers should be made conditional on government agreement that the substance in question was of medical importance. Examples of substances on whose production he asserted,
"we do not particularly wish to waste qualified personnel", included two
antibiotics named hypholin and vivicillin.\textsuperscript{21}

Harington had no authorization from Council to make a recommendation
regarding the two firms' streptomycin proposals, it appears from the careful
phrasing of the letter which he sent to Lennard-Jones a week later. A draft of that
letter, dated the day after the meeting, declared, "I am now authorised to confirm
that the views of the Council would be those which I expressed at our meeting on
the 19th March as follows."\textsuperscript{22} But this wording was amended, following a
consultation over the telephone between Harington in Hampstead and Mellanby at
the MRC headquarters in Old Queen Street in Whitehall. Harington sent the draft
letter to Mellanby for vetting. In the margin of that draft, an annotation apparently
by Mellanby, was amended several times. It is plausible to reconstruct, as the first
version of this marginal annotation, the statement, "I have discussed the matter
with Mellanby & he agrees that the following represents their [i.e. the Council's]
general views, views which I expressed at the meeting".\textsuperscript{23} This version is more
cautious than the original, in that Harington this time did not suggest that he knew
the views of Council. But Mellanby would have been in no better position to know
what actually represented the Council's general views, and thus the next version of
the amendment states, "that the following can be taken to represent the Council's
general views".\textsuperscript{24} In the version of the letter which is recorded as sent to
Lennard-Jones on the 26th, Harington stated, "I have discussed the matter with
Mellanby and he agrees that the general views of the Council can be taken to be
those which I expressed at our meeting on the 19th March as follows."\textsuperscript{25} This
series of progressively more non-committal phrasings suggests that the Medical

\textsuperscript{21} Marchbank to DCMO, 11 Apr 1946, MH58/636.

\textsuperscript{22} Harington to Lennard-Jones (draft), 20 Mar 1946, FD1/6751.

\textsuperscript{23} Undated annotation on Harington to Lennard-Jones (draft), 20 Mar 1946,
FD1/6751.

\textsuperscript{24} Harington to Lennard-Jones (draft), 20 Mar 1946, FD1/6751. My emphasis.

\textsuperscript{25} Harington to Lennard-Jones, 26 Mar 1946, FD1/6751.
Research Council's administrators considered it important indeed to avoid making any unauthorized policy declarations in the name of the Council.

Harington expressed several main points about streptomycin to the MoS's Chief Scientific Officer. First he declared, "On the evidence hitherto available concerning the therapeutic effects of streptomycin the Council could not advise that the large scale production of this substance itself is a matter of immediate urgency." The most important argument, he wrote, centred on enhancement of Britain's "micro-biological production" capabilities. Harington acknowledged that streptomycin itself might in the end turn out to be of "limited use". But he argued that if this transpired, most of the buildings and plant which had been used in the production of streptomycin could be turned with relative ease to the production of penicillin or other substances. Around this time several penicillin plants were being phased out, as the major new deep fermentation plant at Barnard Castle was producing penicillin more cheaply and in much greater quantity than the existing surface culture plants could do. The issue of surface culture versus deep culture is important, and I shall return to it below. Harington predicted that the development of streptomycin production would necessarily involve the training of skilled personnel. He asserted that the MRC considered such training crucial to the prospects of a "modern chemical industry".

It appears that Harington was trying to discourage the MoS from approving large scale production, which evidently had been the companies' hope. He wrote, "The fact that large scale production is planned in the United States may be significant, but in this connection it has to be remembered that one of the proved uses of streptomycin is in the treatment of tularemia, a disease which is prevalent in parts of North America but not in this country." Of all the comparisons Harington could have made between the potential demand for streptomycin in the two countries, this was the one that would leave the most pessimistic impression of the drug's prospects. In announcements about streptomycin published in American journals, we find that tularaemia was mentioned far less frequently than several

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26 Harington to Lennard-Jones, 26 Mar 1946, FD1/6751.
other conditions, such as tuberculosis, typhoid fever, plague, and certain urinary tract infections which were not susceptible to treatment with penicillin or sulphonamides. He mentioned by name only one disease. By this time the American pressure for the drug in cases of tuberculosis was clear, as the MRC's discussions with the Royal Institute of Public Health and Hygiene have shown. As mentioned in Chapter 2, throughout the war years, England and Wales suffered about 25,000 reported deaths annually from tuberculosis. In light of the fact that the Mayo researchers had published some clinical results already by the time of the meeting between Lennard-Jones and Harington, and that this research had been disseminated to the British medical profession via a *Lancet* leader January 1946, it is implausible that Harington would not have foreseen the tuberculosis demand. The key distinction, one might well infer from his letter, was the difference in the potential demand for streptomycin in the two countries. Recall that tularemia was one of several conditions in which streptomycin had been used with reported success. In the annual compilation of British vital statistics, one would not find tularemia given its own entry in the table of causes of death—whereas diseases as rare as relapsing fever (with two reported deaths during the decade) were listed. We may get some idea of the public health significance of tularemia in the USA from the paper by Heilman and colleagues, the Mayo researchers who conducted the first experiments with streptomycin in treatment of tularemia (experiments which were done on animals). The researchers wrote that tularemia had been reported in all of the states in the United States and in many other countries. According to the *U.S. Public Health Reports* which they cited, 1,641 cases were reported in the USA in 1940. They wrote that the mortality rate from the disease was reported to be from 3 to 5 per cent. If we assume that the notifications were reliable, the stated mortality rate would imply that there were roughly 50 to 80 deaths from tularemia in a year in the USA. However, the disease in humans was "associated with a high morbidity", Heilman and colleagues

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27 *Registrar General's Statistical Review*, various years.

noted, and symptoms ranging from four weeks in mild cases to several months in severe cases were common.\textsuperscript{29} It is reasonable to suppose that the two British firms had argued in submissions to MoS that the decision by WPB, in favour of large-scale production of streptomycin by industry in the USA, should be taken as a precedent for allowing their own plans to proceed, in Nottingham and Ulverston. Harington argued that the British case was significantly different from the American case. It is reasonable to read into Harington's statement, quoted above, an intent to suggest that the potential demand for streptomycin as a treatment for tularemia had been a significant factor in the American decision to approve large scale production. But the surviving Merck and WPB files do not support the suggestion, and it is hard to see how Harington could have known this in any case. The focus on tularemia is puzzling, unless, as I imagine, Harington's intent was to persuade MoS to grant priorities for streptomycin production only conditionally. That is, I suggest that Harington was angling for imposition of a condition that the MRC be guaranteed supplies for clinical trials.

Harington made two major points to Lennard-Jones regarding clinical trials of streptomycin. First was a justification for conducting research in Britain, on the grounds that British workers needed to have firsthand experience with the substance. Second, that the MRC ought to be the organization to conduct the said British clinical trials. Harington told Lennard-Jones in his letter that the Medical Research Council considered it important, "that clinical trials of streptomycin should be carried out in this country so that first-hand knowledge of its therapeutic uses may be obtained." That is to say, the subjectivity of first-hand knowledge was portrayed here not as a problem but as a desirable feature. British scientific and medical men, Harington implied, could not gain the kind of knowledge they needed simply by reading the reports published in America. They needed to work with the material themselves.

The running of clinical trials had been a traditional responsibility of the MRC, whose committees had tested insulin in the 1920s, several sulphonamide

drugs since the late 1930s and penicillin during the war. It is clear from internal MRC documents that the organization was keen on keeping responsibility for this to itself. This we can see that the MRC successfully accomplished, first in that the agreement with MoS in March acknowledged that the MRC would hold responsibility for clinical trials. Second, a document produced some time before the end of September 1946 explained that the MRC would have authority for allocation of all supplies of streptomycin in Britain, and would by implication be able to control who was able to run clinical trials. The reasons for this are not hard to infer from the experience with penicillin, and the discord which appears to have been rampant between the MRC and the Royal Army Medical Corps, under whose auspices some medical research went on during the war. So the methods of conducting clinical trials were certainly not unknown outside the confines of the MRC, and the question at stake was who would be considered competent to perform them. Even at the early stage of March 1946, there had been a few enquiries, some of which we can infer were considered vexatious by the MRC headquarters staff. And so it would be predictable for the MRC to seek to monopolize the control of the material commodity which was an essential element of the conduct of clinical trials. That concern is evident in the MRC’s correspondence during the summer of 1946, but it was also set out by Thomson in February in an internal memo:

Sir Mr. O.S. Franks's letter of 20.2.46 contains a suggestion that because the Ministry of Supply is the production authority, it might be regarded as responsible for research on substances of possible  

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30 I have been unable to locate the latter document, which is alluded to in, eg, J.F.S. Stone to Thomson, 1 Oct 1946, FD1/6766.

31 The RAMC for example was where Guy Scadding acquired his experience of clinical trials, at a station in the Middle East, where he compared several treatments for dysentery. J.G. Scadding, "Comparative effects of sulphonamide drugs in mild bacillary dysentery", Lancet 1 (17 Jun 1944), 784-786; and J.G. Scadding, "Sulphonamides in bacillary dysentery: Further observations on their effects", Lancet 2 (3 Nov 1945), 549-553. He stated in a recent interview that he had not had contact with the MRC prior to being invited on to the Streptomycin Committee.
pharmaceutical value. It might be well therefore to make it clear that the Medical Research Council regard fundamental work in this field as being their affair. On the other hand, there might be advantage in encouraging the Ministry to take responsibility for developmental work. This would put on them the onus of financing medium-scale production, which they might otherwise undertake only on a repayment basis; and this would be satisfactory, provided that the clinical trial of the substances so produced was left to the M.R.C.\textsuperscript{32}

One could hardly ask for a more forceful or clear statement of the MRC’s intentions.\textsuperscript{33} In the context of the MRC’s advisory role towards the MoS industrial priorities question, the Council was able to get its own way. In the agreement of 19 March, it was clearly stated, "The Medical Research Council will be responsible for fundamental research up to the stage which suggests that a new substance is likely to be of therapeutical value and also for conducting extended clinical trials."\textsuperscript{34}

4.4 Approval of Priorities, June 1946.

The activities of this Ministry [of Supply] in the production of Penicillin, Streptomycin and other Antibiotics will be the assumption of the same general overall responsibility and sponsorship of the industry as is exercised by U.S./E. [Under Secretary, Engineering] in respect of the Engineering Industry—giving general help and encouragement to the industry, assistance in obtaining labour and

\textsuperscript{32} Thomson memo, 1 Mar 1946, FD1/7009, emphasis added.

\textsuperscript{33} What in fact is slightly puzzling, is why Thomson should have found it necessary in the first place to spell this view out, if indeed as I suspect it was widely shared at MRC headquarters.

\textsuperscript{34} FD1/7009.
materials, sponsoring building scheme etc. There will be no question of financial help.35

Prof Harold Raistrick, the MoS Senior Scientific Adviser on Penicillin Production, and T.B. Keep, the Controller of Penicillin Production went to the USA in May, to gather information about antibiotic production and testing facilities there. Slightly different copies of their 4-page report survive in MRC and MoH files.36 The report said that current monthly American production was then about 35 kilograms. Intriguingly, the report revealed that construction of at least one large scale plant—probably Merck's—had been slowed down pending the results of certain clinical trials. A "general pronounced attitude of caution" was noted regarding the projected commercial production of penicillin by the American manufacturers interviewed by Raistrick and Keep.37 Chas Pfizer Company had by this point managed to produce what was described as a "large supply of pure crystalline streptomycin", which was made available to Dr Walsh McDermott of the New York City Hospital. His team was said to be investigating whether the previously observed side effects of streptomycin, such as "[t]emporary deafness and dizziness" and "distrubing [sic] renal troubles" were attributable to "impurities contained in the commercial product". Raistrick and Keep wrote, "The same toxic effects had been observed with pure crystalline streptomycin as had previously been observed with a clinical material of 50% purity." The price of a gram of streptomycin was $15 at this time. The MoS officials found it "startling" that one drug company president, apparently George Merck, predicted that this price would not fall below $5/gram, even once the drug was being made on a large scale. The

35 U.S./M.S. [Under Secretary, Munitions Supplies] to D.E.S. [Director of Equipment and Stores], 11 Jun 1946, MH136/70.

36 FD1/6759 and MH58/636.

37 Most curiously, Raistrick and Keep declared, in a paragraph they attributed to Chester Keefer, the view that there were about a thousand cases of tularemia annually and "up to the present it has been almost uniformly fatal"; this mortality rate is completely at odds with research published in American journals, which as mentioned above gave a figure of 5-10% of cases.
cost of a full course of streptomycin in treatment of tuberculosis was estimated at a minimum of £900. This was obviously very expensive, and yet Raistrick and Keep pointed out that if the result were a "complete cure", this would compare favourably with the cost of prolonged hospital treatment.

Two months after Harington’s meeting with Lennard-Jones, his letter was forwarded to the Ministry’s Under Secretary, Munitions Supplies, named A.R. McBain. McBain received a note from the Director of Equipment and Stores (DES), F.H. Harrison, that covered Harington’s letter and several other documents. The DES asked for guidance as to how far the Ministry of Supply’s support should extend in the case of streptomycin and other antibiotics. McBain’s reply is quoted above at the beginning of this section. There is in fact some question as to whether McBain’s decision had been made informally long before he replied in writing to the DES, as an inter-Departmental meeting on streptomycin production targets was held the very next day, and it is hard to believe that it could have been called by the DES unless streptomycin production had been given at least provisional approval.

We have limited information as to what the Under Secretary actually considered in making his decision, in that the DES’s covering letter to him survives, but the eight enclosures cited in that letter are not in the file. It is also

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38 This figure corresponds exactly to 4g/day over 180 days, at a cost of $5/g and at an exchange rate of 4 dollars to the pound. The exact rate remained $4.03 to the pound until September 1949, when it was changed to $2.80.

39 This official, one of ten third-ranked permanent civil servants in the MoS, was despite his title also responsible for Non-Munitions Supplies, which included medical supplies such as penicillin.

40 D.E.S to U.S./M.S., 23 May 1946, MH136/70.

41 Circumstances strongly suggest that Harington’s letter to Lennard-Jones, retained in another file, was one of those enclosures. We can gather also that two of the enclosures forwarded were the proposals from Glaxo and Boots; the originals of these industry documents are not found in government files but we can infer a little information from the discussion of them in other documents. As I argued previously, it is likely that the companies’ proposals invoked as a precedent the WPB’s approval of Merck’s factory in Virginia. By April the first major institution to seek streptomycin at an institutional level, the Fazakerley Sanatorium
highly likely that prior to making his decision, the Under Secretary saw the report
on streptomycin by Raistrick and Keep.

4.5 Domestic production of streptomycin for clinical trials

Until the M.R.C. have indicated minimum requirements it cannot be
determined whether surface culture production will provide
sufficient for clinical trials or whether [d]eep culture capacity will
have to be developed.

Note of inter-Departmental meeting,
12 Jun 1946

This section establishes that the demand for streptomycin supplies for use
in clinical trials constituted a major factor determining the plans for domestic
production of the drug. In particular, the dependence of production targets on the
estimated needs for clinical trials was set out at an inter-Departmental meeting in
mid-June. There it was decided that the Ministry of Health was to obtain this
estimate from the MRC. It is clear that only extreme frustration at the Ministry of
Supply, over the MoH's delay in execution of this seemingly simple commitment,
could account for an eventual departure from this agreed division of responsibility.
This shows how important it was to the MoS that clinical trials be conducted. This
in turn implies that the MRC's arguments, detailed in the previous chapter, had
been decisive.

Furthermore, it was accepted that there were technological limits on the
scale of production which could be achieved using different methods of
fermentation. Consequently, the MRC's clinical trial plans also ended up
determining that deep fermentation would be used in British manufacture. A clear

had made an enquiry, which interestingly was sent in the first instance to the
Ministry of Supply rather than the MoH or the MRC. See Everett to Marshbanks
[sic], 1 Apr 1946, MH58/636; and attached correspondence.

42 MH58/636.
causal relationship is demonstrated by the changes in production policy which followed the various changes in clinical trial design which were agreed during the second half of 1946.

The Under Secretary of the Ministry of Supply, A.R. McBain, allowed Boots and Glaxo to proceed with development of plant for production of streptomycin. Once 'priorities' were approved, the next step was for the Ministry to set targets so that resources could be allocated to production, under the government's system of direct controls over British manufacturing industry. McBain thus chaired an interdepartmental meeting on streptomycin, on Wednesday 12 June 1946, the day after sending his note on streptomycin priorities to the Director of Equipment and Stores (DES), F.H. Harrison. The Ministry of Health was represented at this meeting by Frank Marchbank and Sir Weldon Dalrymple-Champneys. The main purpose of the MoS-MoH meeting, judging by Harrison's recorded introductory remarks, was for the MoS to obtain guidance on its policy for the development of streptomycin production in Britain. The passage quoted at the beginning of this section shows that the production targets and methods were to be determined by the MRC's requirements of streptomycin for clinical trials. At a minimum, it was declared, British industry had to produce enough streptomycin for the MRC's clinical trials. The first stage in implementing this plan was to find out how much was expected from the two firms concerned. Interestingly, Marchbank's record of the meeting was fairly specific as to estimated figures: "There are two firms in this country (Glaxo and Boots) preparing to make Streptomycin, but it is unlikely that their combined output will exceed 4 kgs. per month—enough for only 32 patients." In contrast, the minutes were less precise about British production figures:

In so far as British industry is concerned at the moment it is known

43 Notes of meeting at Shell Mex House, Wed 12 Jun 1946, MH58/636.

44 Two others present from the MoH were Miss C. Mozley-Stark and Dr J. Balfour Kirk, whose roles I have been unable to determine. Neither is listed in the Imperial Calendar and Civil List, 1946.

45 Marchbank memo, Streptomycin, [12 or 13] June 1946, MH58/636. He did not specify the date this output was expected.
that Glaxo and Boots are in production but on what scale and with what results is not clear. It is thought that "substantial" quantities may be available in 3 to 4 months, but as few people realise the measure of production which may be required for adequate clinical [trial] these "substantial" expectations may be completely insufficient.46

In the streptomycin files, it went virtually without saying that government scepticism on this point arose from previous disappointment with what British firms considered adequate quantities of penicillin.47 Since sponsorship of streptomycin production had just been approved the previous day, it is not particularly surprising that the Departments should meet privately before bringing industry into the planning process.48 It is rather remarkable, however, that the meeting had no representation from the MRC, despite the Council's stake in these issues, as was evident in the discussion.49 In any event, it ought to have been clear to Dalrymple-Champneys, who was designated to approach the MRC, that getting an estimate of the quantities the Council required for clinical trial was a matter of some urgency, in that a host of industrial plans depended on it.50 But swift action was not forthcoming. At the end of the week following the Wednesday meeting, Dalrymple-Champneys sent a letter to Thomson, seeking to ascertain "whether clinical trials of this antibiotic could be arranged and, if so, the total quantity of Streptomycin which would be required to carry out satisfactory clinical

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46 The document is damaged, and the partially obliterated word could as easily be "trials".

47 For some rare examples of explicit remarks, see FD1/7009.

48 Industry representatives did attend the October 1946 meeting on the setting of a British standard for streptomycin.

49 It appears also that the MRC was not provided minutes of this meeting, judging by Dalrymple-Champneys's subsequent letter to Thomson.

50 It is not recorded why Dalrymple-Champneys was chosen to carry out this task.
He ended his letter with the remark, "I should be very grateful if you would let me have your views on this proposal as soon as possible." After more than a week had elapsed, still no answer had been received from the MRC, by either of the Ministries of Supply or Health. On 2 July, Everett told Marchbank that the MoS had nearly completed its preliminary survey of the activities of British firms in research, development and production of streptomycin. Thus the MoS, Everett wrote, was "most anxious" to get information regarding the quantities of streptomycin which the MRC would require for clinical trial. He reminded Marchbank, "In our discussion this morning you kindly agreed to do everything possible to expedite the supply of this information." This prompted Marchbank to ask Dalrymple-Champneys, "Can a reminder be sent to Dr Landsborough Thomson?" Dalrymple-Champneys replied to Marchbank that he had written to Thomson on 21 June 1946. He added, "& I now understand that he had put up the case to Sir E. Mellanby & hopes to let me have a reply v. shortly."

It was indeed Mellanby who replied, in a letter to Dalrymple-Champneys dated 8 July, three and a half weeks after the MoS-MoH meeting. He declared, "I have no doubt that the Medical Research Council would be glad to make some co-ordinated effort to add to knowledge on the therapeutic value of streptomycin, if substantial quantities were available. I can hear you say-- what do you mean by substantial quantities-- here again, I am in a difficulty because it depends greatly

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51 Dalrymple-Champneys to Landsborough-Thomson, 21 Jun 1946, FD1/6751; also filed in MH58/636.
52 ibid.
53 Everett to Marshbanks [sic], 2 Jul 1946, MH58/636.
54 ibid.
55 ibid.
56 Marchbank annotation to DCMO, MH58/636.
57 Dalrymple-Champneys annotation to Marchbank, MH58/636.
on the purity of the preparation supplied. Writing upon Mellanby’s letter in the file, Marchbank complained to his colleagues, "This is not very helpful". What Marchbank wanted to know from the MRC, according to his annotation, was simply: "How many patients will be required for a thorough test? For how long?" This information, he wrote, would allow the MoH to "estimate how much penic streptomycin would be needed for the treatment of that number of patients (using American experience as a guide)". At an unspecified later date, he recorded having mentioned this point to Mr H.T. Lester at PPC, whom he described as "most anxious to get something more concrete urgently". However, Marchbank’s evident sense of urgency appears not to have been shared by certain other members of his Department. It is, for example, recorded that in the middle of August, long after events had proceeded along other paths, one Ministry of Health official was still arranging for the signature of a reply to Everett’s letter of 2 July. There is no sign that Dalrymple-Champneys wrote again to the MRC to press for more definite information. Rather, he planned a streptomycin conference at the MoH, to which Mellanby promised to go. It is recorded that Raistrick persuaded Dalrymple-Champneys to abandon this tack, which presumably the MoS considered unnecessarily cumbersome. Instead, Raistrick took the more direct approach of visiting Mellanby in person.

58 Mellanby to Dalrymple-Champneys, 8 Jul 1946, MH58/636. Mellanby declared himself responsible for the delay in responding, though without giving grounds more specific than the information, which was hardly new, that the Americans had not allowed any of the substance to come to Britain.

59 Marchbank annotation to DCMO on Mellanby to Dalrymple-Champneys, 8 Jul 1946, MH58/636.

60 ibid.

61 ibid.

62 Marchbank annotation, undated, on Mellanby to Dalrymple-Champneys, 8 Jul 1946, MH58/636.


64 Mellanby memo, Jul [1946], FD1/6756.
Raistrick showed up at the MRC headquarters on Wednesday 24 Jul 1946, exactly six weeks after the MoS-MoH consultation. His purpose was "to discuss the question of streptomycin", according to note taken by Mellanby, which is our only record of their conversation.\(^6\) The pressure put upon Mellanby is suggested by his recorded response, "I promised that I would move at once and give him an answer by the end of the week".\(^6\) It is not actually clear what was the question to which he promised this answer shortly. The most important answer, for which the MoS had been waiting so long, was generated on the spot at the meeting, it appears, namely that 75 kilograms of streptomycin would be needed for clinical trials. The derivation of this figure is interesting, and significant in light of different estimates which would be produced in November. Mellanby wrote:

Apparently the parenteral daily dose is of the order of 4 gms. so that to treat a case for six months would require 3/4 kg. I said that it seemed to me, although I was not wedded to the idea, that it might be well to concentrate on tuberculosis and if we had one hundred cases of tuberculosis treated for six months, that would require 75 kg. of streptomycin. He [ie, Raistrick] said that he could arrange for this amount to be supplied.\(^6\)

First of all, observe that Mellanby appears not to have been familiar enough with current American research to have known, prior to the meeting, that the standard injected dosage was 4 grams per day.\(^6\) It was "generally agreed" by American researchers that 4 grams was a minimum daily dose in treatment of tuberculosis, according to the report written by Raistrick and Keep on their visit to North America in May. The report also said, apparently on the basis of discussions with the Mayo Clinic researchers, that six months was regarded as probably the

\(^6\) Mellanby memo, Jul [1946], FD1/6756.

\(^6\) ibid.

\(^6\) ibid.

\(^6\) Surely it was at Mellanby’s request that the following day Geoffrey Marshall brought to MRC headquarters a summary, from the Medical Intelligence group of the Ministry of Health, of recent research papers on streptomycin.

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minimum length of treatment for tuberculosis.\textsuperscript{69} It is fair to assume that Raistrick informed Mellanby on these points, though it is peculiar that there is no sign that anyone from the MoS provided the MRC with a copy of the report.\textsuperscript{70} As for the choice of tuberculosis, it had been suggested in the letter from Dalrymple-Champneys. The choice of 100 as the number of cases of tuberculosis is perhaps curious. There is no indication anywhere in the files as to how Mellanby came up with this figure, which I suspect was simply a fairly large 'round' number.\textsuperscript{71} If so, the scope and direction of the British streptomycin production programme hinged on an arbitrary number chosen under pressure.\textsuperscript{72} The resulting estimate of 75 kg was consequential, in that it entailed a shift in the MoS's views on production, namely to encourage industry to aim directly towards deep fermentation, as I will explain below. Later documents show the production approach being tailored to the 75 kg as a minimum target.\textsuperscript{73}

Mellanby protected his plans from challenge or renegotiation. The immediate result of the visit from Raistrick was that Mellanby called, on short notice, a Conference of clinicians, which will be discussed in greater detail in Section 6.2. At this Conference, on Monday 29 July, he announced that "on

\textsuperscript{69} MH58/636.

\textsuperscript{70} As we will see below, an extract of the Raistrick-Keep report was sent to the MRC by Dalrymple-Champneys in August. FD1/6759.

\textsuperscript{71} Such round numbers were not uncommon in clinical reports. For example, H.C. Hinshaw, William H. Feldman, and Karl H. Pfuetze, "Treatment of tuberculosis with streptomycin: a summary of observations on one hundred cases", \textit{JAMA} 132.13 (30 Nov 1946), 778-782; and Chester S. Keef er et al, "Streptomycin in the treatment of infections: A report of one thousand cases", \textit{JAMA} 132 (7 Sep 1946), 4-11 and (14 Sep 1946), 70-77.

\textsuperscript{72} The figure of 3/4 kg likely came from 4 grams per day for six 30-day months, then rounded up from 720 grams to 750. It is not surprising that there is no mention in Mellanby's note of the complicating factor of potency with which he had put off giving an answer to Dalrymple-Champneys early in the month.

\textsuperscript{73} It is not exactly clear when Raistrick himself expected this quantity to be produced, although it was soon stated (in the First Conference Minutes) that this would be "a few months". In May 1946, the total output of 10 or 12 American firms was approximately 35 kg per month, according to the Raistrick-Keep report.
apparent current dosage in the U.S.A., the English supplies would allow for the
treatment for six months of some 100 cases of tuberculosis." This clever piece
of rhetoric thus suggested that the choice to involve 100 patients, far from being
the basis of the 75 kg figure (which itself was not recorded in the Minutes), was
rather a consequence of supply limitations. The arbitrariness of the 100-patient
estimate was thus concealed, from the clinicians at least. Then when Mellanby
wrote to Dalrymple-Champneys the day after the Conference, he implied that it
was "after discussing the matter with some clinicians" that he suggested that the
trial start with 100 cases of tuberculosis, and that this would therefore require 75
kg of streptomycin. That is, Mellanby's choice of 100 patients was framed as a
decision by the MRC's clinical experts, to whom the DCMO had said he would
defer, even though the clinicians themselves had been presented with a fait
accompli.

The MRC's plans were in fact challenged. Dalrymple-Champneys himself
remarked, upon receiving Mellanby's letter, on Thursday 1 August 1946, "No
further action appears necessary at the moment." But Marchbank, to whom he
had passed the letter, had several objections. Marchbank's reckoning, written in
the margin, was that the quantity was "12 kg per month". He replied to the
DCMO the same day, asking him:

a/ Should not the M.R.C. envisage a considerably more extended
trial than 6 months?

b/ Do we definitely want M/S [the Ministry of Supply] to press
manufacturers for a larger production than 12 kg per month?

I should have thought the answers to both these questions is

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74 First Conference Minutes, para 1. Emphasis added.

75 Raistrick was absent from the Conference; however, he would have received
the minutes.

76 Mellanby to Dalrymple-Champneys, 30 Jul 1946, MH58/636; copy filed in
FD1/6756.

77 annotation on ibid.

78 ie 75/6, rounded down from 12.5.
I attribute Marchbank's first recommendation to the Raistrick-Keep report, which had been presented at the inter-Departmental meeting he had attended in June. Chester Keefer, of the Committee on Chemotherapeutics, was quoted in the report as having expressed the opinion that it would take "at least two years and more probably five years to get the final answer" to the question of the clinical future of streptomycin in the treatment of tuberculosis. On the second point, Marchbank was advocating that the MRC's requirements be treated by MoS as only a minimum for production, and that the actual target be set in excess of the stated needs for clinical trials. This is not surprising in light of his earlier comments on British streptomycin production, for example, in April, "As with penicillin we seem in danger of falling behind the U.S.A. in the opening stages of production." On 12 August, a week and a half after this latest salvo, Dalrymple-Champneys wrote back:

As regards your (a) a full trial would probably occupy many years, indeed the remaining life of the patients, but short of this 6 mths. would probably be sufficient to tell us the two things we want to know before encouraging production[:] 1. does it give immediate benefit? 2. can it be used without undue danger? (b) I think until we have the answer to 1. & 2. above it would be unwise to encourage M/S. [Ministry of Supply] to build up a higher rate of production.

Dalrymple-Champneys, the Ministry of Health's most senior official responsible for pharmaceuticals, was clearly advocating a conservative policy on production. He placed the burden of proof on those, such as Marchbank, who wished to see

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79 Annotation, Marchbank to DCMO, 1 Aug 1946, on Mellanby to Dalrymple-Champneys, 30 Jul 1946, MH58/636.

80 MH58/636.

81 Marchbank to DCMO, 11 Apr 1946, MH58/636.

production increased. Admissible evidence would, according to the DCMO, not arise until completion of the six-month clinical trial. A few days later, it was his view, rather than Marchbank's, which was conveyed to Everett at MoS: "Our Medical Advisers think it would be unwise to press manufacturers to build up a higher rate of production than is required for the trials at present envisaged until the results of those trials are known." There is no sign that the MoS adjusted the production target at this point. But very soon, the production scheme was disrupted, when the clinicians selected by the MRC elaborated their plans for clinical trials, which would include a small pilot trial.

The key question of production policy which was at stake in the estimation of supplies of streptomycin needed for clinical trials was this: should streptomycin be produced by surface fermentation or deep fermentation? A similar choice had been faced regarding production of penicillin during the war. In that instance, deep fermentation was not achieved in Britain on a large scale until the end of 1945. For both antibiotics, the choice was symbolic as well as practical. First, to get deep fermentation functioning at all required greater technical skill and greater investment in plant, but the running costs were much lower. But also, deep fermentation represented modernization and efficiency in pharmaceutical manufacturing, as discussions between the MoS and MRC over the pilot plant show.

The initial position of the MoS on the methods of fermentation for streptomycin production is found in the report by Raistrick and Keep. In May, these two officials from PPC recommended "that consideration be given to the modification of one or more of the bottle plants in this country to enable them to produce Streptomycin by the surface culture method which has in fact already

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83 A.R. Thompson, MoH, to Everett, 19 Aug 1946, MH58/636. It is conceivable that this was a coded statement that the administrative staff were not united behind the DCMO on this point. After all, it was not, but surely could have been, identified as the Departmental view, by writing instead, "We think it would be unwise...".
been done in the U.S.A.\textsuperscript{84} There were at that time several plants still making penicillin by the surface method. The MoS had decided, however, on the grounds that the Barnard Castle and Speke plants were producing by deep culture enough penicillin to meet the country’s needs, that these small plants with high running costs were to be phased out.\textsuperscript{85} Interestingly, at the 12 June meeting it was declared, "The use of any part of the present Penicillin Deep Culture capacity for Streptomycin production is out of the question, the requirements of Penicillin are too large."\textsuperscript{86} In contrast, "Production [of streptomycin] by surface culture could be undertaken on the Penicillin surface culture plants[,] the conversion of which would be comparatively inexpensive and it was agreed that negotiations for the disposal of the surface culture plants should not be pressed forward too quickly.\textsuperscript{87}" But there remained in June the question of whether surface production of streptomycin would be large enough to satisfy the needs of the MRC for clinical trial. To repeat the quotation which opened this section, the meeting considered, "Until the M.R.C. have indicated minimum requirements it cannot be determined whether surface culture production will provide sufficient for clinical trials or whether Deep [sic] culture capacity will have to be developed."\textsuperscript{88} Based on Mellanby’s declaration that 75 kilograms would be required for adequate clinical trial, the MoS decided that the firms should develop deep fermentation of streptomycin instead. It appears that Glaxo had already been inclined in this direction, as it was, by the start of 1946, one of the two firms making penicillin by deep fermentation (at Barnard Castle), using a process under licence from Merck. Distillers, which ran the Speke penicillin plant as the agent of MoS, become involved in streptomycin production at some time prior to the Conference

\textsuperscript{84} MH58/636.

\textsuperscript{85} MH136/70.

\textsuperscript{86} Minutes, MH58/636.

\textsuperscript{87} ibid. This was a reference to the sale to private firms of assets which had been developed under the government’s wartime Capital Assistance Schemes.

\textsuperscript{88} Note of inter-Departmental meeting, 12 Jun 1946, MH58/636.
in late August. A Mr Coulthard from Boots told an MoH official, W.P. Kennedy, in July it was then producing streptomycin solution amounting to somewhere between 9 and 20 million Units per week at its Daleside plant, the equivalent of 9 to 20 grams.\(^9\) It is rather remarkable that Kennedy concluded, "It would appear, taking into consideration the running production, that it should be possible to provide sufficient for at least a preliminary clinical trial."\(^10\) By early August, the firm was in a quandary over a production problem, which Hart explained to Mellanby as follows.\(^91\) The director of Boots' Research Department, Sir Jack Drummond, whom we met in Section 3.2, had said when Hart was visiting Nottingham on 7 August, that his company's production of streptomycin was on a development basis. It had one small bottle plant for surface fermentation, and two small experimental tanks for deep fermentation. To increase production, it was reported, the company could either turn over one of 6 large deep-culture tanks currently producing high-quality penicillin, or use a large bottle plant which was then idle. But it was accepted at Boots that the latter plan would inevitably expose workers to spores of *Actinomyces griseus*. The hitch was that the Works Doctor at Boots, Dr Lloyd-Davis, reportedly was not convinced that the organism which yielded the antibiotic substance was itself not pathogenic; he was said to be unimpressed by American assurances on this issue. Hart wrote about the latter option, the use of the surface plant, "If the doctor maintains that there is a pathogenic risk, his requirements are a radical change in ventilation which Boots estimate will hold up the start of production for 6 to 9 months!"\(^92\) Hart at this time evidently favoured Boots going ahead with surface production, on the grounds that it would produce "quite adequate S. for trials."\(^93\) But the officials at

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\(^90\) ibid. An amusing error in taking dictation shows that one member of the MoH's secretarial staff was rather new to medical terminology: Kennedy's letter was initially typed with the phrase "pinnacle trial".

\(^91\) Hart to Mellanby, 9 Aug 1946, FD1/6756.

\(^92\) ibid.

\(^93\) ibid.
Penicillin Production Control in MoS were not convinced. On 27 August, in response to A.R. Thompson’s letter quoted above, which had advocated no increase in the production target, Everett wrote as follows:

Large scale production of Streptomycin will inevitably be by deep culture methods, and it would seem unwise for early clinical work to be done in terms of surface culture material which may not be representative of material which would later be available from deep culture. The surface culture method would be very costly and the quantity would be so small that we do not feel it is worth complicating the situation by consideration of this method of production. There is also the point that we do not wish the firm concerned [i.e., Boots] to divide their technical resources, and feel that it is better that they should concentrate all their efforts on deep culture production.

This MoS policy, recall, was declared following Mellanby’s demand for 75 kilograms of streptomycin. Such a quantity, Everett predicted in August, having consulted further with the firms, was not likely to be available until the spring of 1947. But though the MoS position against development of Boots’ surface fermentation capability appears quite firm on the evidence of Everett’s statement quoted here, this policy was to be reversed. The impetus for the change came from the clinical experts who had been selected by the MRC.

A Second Streptomycin Conference was held at MRC headquarters on Tuesday 27 August, the same day Everett sent to the MoH his letter justifying the policy against use of surface culture. Significantly, and similarly to the First Streptomycin Conference in July, no one from the MoH was invited. Everett himself attended, in the absence of Raistrick, and explained the prospects for British streptomycin production by three or four firms. These were not named in the minutes, but we know from the MoS’s announcement in September that they

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94 Everett to A.R. Thompson, 27 Aug 1946.

95 Everett was accompanied by his colleague, H.T. Lester.
were Glaxo, Boots, Distillers, and the Heyden Chemical Company. He reportedly told the Conference that the firms' combined output, using deep fermentation methods, of 15 kilograms of pure streptomycin base per month "would be achieved by spring 1947". The minutes are remarkably bland on the important point which followed:

> This supply can be anticipated by surface-culture (bottle plant) from one firm (Boots), starting in the autumn, at the rate of 0.4 kg. (streptomycin base) in the first month and 0.8 kg. per month subsequently (sufficient for, say, half a dozen and a dozen patients respectively).  

What is absent from the minutes is any suggestion that the MoS was opposed to using surface culture. Everett explained to Marchbank a fortnight later:

> At that meeting [the Second Conference] I referred to the small output by surface culture referred to also in my letter of the 27th August to [the MoH's A.R.] Thompson but stated that we did not recommend this particular production. The M.R.C. were, however, so anxious to obtain a supply, however small, as early as possible that under pressure from them we agreed to arrange for Boots of Nottingham to undertake production at the rate of about 2 kilograms per month. We believe that this should yield about one kilogram in November and 2 kilograms per month afterwards.

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96 The latter was then proposing to build a factory to produce penicillin and streptomycin at Ardrossan, Scotland. "Four British Firms to Make Streptomycin", *The Times* (21 Sep 1946).

97 This was, of course, in excess of the 12.5 kg per month which Mellanby had estimated in July as the requirement for clinical trials.

98 Second Conference Minutes, para 3C.

99 Everett to Marchbank, 12 Sep 1946, MH58/636. The estimated production figures appear to be different in the minutes and Everett's letter, but this is most likely explained by the potency factor, which Mellanby had said in early July was so important: the gross quantity would consist of 40% of the active ingredient, the streptomycin base, and the remainder would be the combining ion in the salt, such as sulphate or chloride, plus various impurities.
The purpose of turning to surface production, as the quote above from the minutes states, was so that a pilot trial could be run, with a small number of patients. It is clear that the MRC staff were not expecting the clinicians to come up with this pilot trial scheme; there certainly had been no proposal for it on the agenda. Hart wrote the next day, in advance of the production of formal minutes, to Mellanby, who was about to go on holiday,100 and a similar letter to Thomson.101 He described as the "main result" of the meeting that in all likelihood there would be a pilot trial in the autumn, to be followed by the main trials in the spring.102 Everett's arguments, for example that the results from tests on material produced by surface fermentation might not be extrapolable to the eventual deep production,103 were evidently not sufficient to sway the group. Hart himself appears to have been fairly sanguine about the plan: "This procedure is dictated by the supply position but may have advantages in that we shall learn a lot of lessons from the pilot trial."104 And a week later, his appraisal of the scheme of pilot trials to begin in November carried on in a similarly positive vein: this, he wrote to Thomson, "seems quite a good programme", on the grounds that the schedule fitted in with when he and others would be back in the office following holidays.105 No concern by the clinicians regarding representativity was recorded; the minutes state that the Second Conference considered that the preliminary supply would be "most valuable", provided that the quality, potency and safety of the material from surface-culture turned out to be satisfactory.106

Following the Conference, there was a rather convoluted exchange of correspondence. The confusion resulted from the fact that the Ministry of Health

100 Hart to Mellanby, 28 Aug 1946, FD1/6756.
101 Extract of Hart to Thomson, 28 Aug 1946, FD1/6756.
103 Everett to A.R. Thompson, 27 Aug 1946, M15 578/6 36.
105 Hart to Thomson, 4 Sep 1946, FD1/6756.
106 Second Conference Minutes,para 3c.
had not been represented at the Conference, and, for a while at least, operated on the basis of the old MoS policy, which had opposed the use of surface production. Recall that Mellanby wrote to Dalrymple-Champneys on 30 July, immediately after the First Conference, to say that the MRC's clinical trials would require 75 kg of streptomycin over six months,\(^{107}\) and that Thompson from the MoH wrote on 19 August to the MoS regarding Mellanby's request.\(^{108}\) The reply from Everett was sent to the MoH on 27 August, and began, "I am afraid we can hold out no hope of useful quantities of Streptomycin being available for clinical trials to start in about ten weeks, and it is unlikely that Streptomycin could be available for use at the rate of 75 kilogrammes per six months until the spring of 1947."\(^{109}\) This much of Everett's letter was in accord with what he had stated at the Second Conference. But Marchbank, apparently unaware that this information was being conveyed to the MRC directly by Everett, wrote to Mellanby on 29 August.\(^{110}\) Thomson forwarded to Hart on 4 September, for his information, the letter from Marchbank and the enclosure from PPC.\(^{111}\) There Thomson remarked, "You will see from this that the prospects of early delivery of the material on the scale we require are less good than we had hoped."\(^{112}\) This is rather puzzling, in that Thomson had already been told by Hart, a week earlier in fact, that the main trials would not begin until the next year.\(^{113}\) In light of the

\(^{107}\) MH58/636; copy filed in FD1/6756.

\(^{108}\) MH58/636.

\(^{109}\) Everett to A.R Thompson, 27 Aug 1946, MH58/636.

\(^{110}\) FD1/6756; copy filed in MH58/636. It is in fact not clear whether Marchbank was even aware of the occurrence of the Second Conference.

\(^{111}\) Thomson to Hart, 4 Sep 1946, FD1/6756. The typed extract Marchbank had enclosed, from Everett's letter, identified the source only as Penicillin Production Control, and omitted the date.

\(^{112}\) ibid.

\(^{113}\) extract of Hart to Landsborough-Thomson [sic], 28 Aug 1946, FD1/6756. As well, it is likely that by this time, the Second Conference minutes, which explained the supply prospects, had been prepared and circulated.
conflicting information it is not surprising that Hart established, for the first time, direct contact between his office and Penicillin Production Control. He informed Thomson when he wrote back the same day, 4 September, that the situation was "not so black" as the enclosed PPC document suggested. He went on, "As a result of our last meeting the Ministry of Supply are now asking Boots to start on surface-culture in October so that we should have small supplies for half a dozen or a dozen patients for pilot trials in about November." No further developments in production policy took place until October, when the MRC attempted to place an actual order for the material for its clinical trials. I will take up that thread in Section 7.1. And at the end of that month, a meeting was held with the manufacturers to settle on a provisional British standard for streptomycin. Finally, I note that in November the pilot trial scheme was abandoned after the large American import was approved. No impediment then remained against the Ministry of Supply reverting to its policy of sponsoring Boots' use of deep fermentation.

4.6 Conclusion

Let us recapitulate the story so far. Streptomycin was isolated in the autumn of 1943 at Rutgers University, and in 1944 Merck & Co began commercial production. A body of scientific research on streptomycin began to accumulate. This research was interpreted to suggest that streptomycin might be a solution to problems including the previously intractable one of drug therapy of tuberculosis, a disease which remained a major killer in both the USA and UK. The MoS and MRC negotiated about the scope of a pilot plant for medium-scale production of therapeutic substances under investigation, particularly antibiotics.

114 Hart to Thomson, 4 Sep 1946, FD1/6756.
115 ibid.
116 ibid.
117 See FD1/6755.
which were considered an exciting new field of research. Meanwhile, two British companies submitted plans to the government in the winter of 1946, arguing that the MoS ought to follow the 1945 example of the War Production Board in the USA, in approving large-scale production of streptomycin. The MoS had experience with penicillin production, but for these streptomycin proposals turned to the MRC for advice on the new drug’s clinical potential. The MRC was eager to maintain its elite status in the field of clinical trials, which were one of their main sources of institutional credit. And in order to run trials, the MRC needed access to supplies of the drug. What would have been most in the MRC’s interest was for commercial production to be approved, under the condition that supplies be made available to the MRC. Negotiations on streptomycin were conducted at a high-level meeting between the MoS and MRC in March 1946, which had been arranged in order to lay the administrative groundwork for the antibiotics pilot plant. Three months later, a senior civil servant in the Ministry of Supply granted approval of streptomycin production. A further outcome of the MRC’s lobbying was that it was later granted control over supplies in Britain.

Section 4.5 explained how clinical trials were planned in relation to domestic production. The interdepartmental meeting in mid-June decided that the MRC’s needs for clinical trials would determine what production technique industry should be encouraged to use, surface or deep fermentation. Dalrymple-Champneys was designated to approach the MRC, but did not get the necessary information quickly. Therefore Raistrick bypassed the MoH and went directly to Mellanby, who came up with a figure of 100 patients, apparently out of thin air. This implied a quantity of streptomycin large enough that the MoS decided that deep fermentation was necessary. However, these plans were waylaid at the Second Streptomycin Conference in August, when the MRC’s clinicians decided that they would like to run a pilot trial, using the product of surface fermentation. However, in a final reversal, the pilot trial scheme was scrapped in November, at the first meeting of the Committee, partly because it was by then possible to proceed straightaway with large-scale clinical trials using the major American import which had just been approved by Treasury.

I have focused on the arguments put forward by the Medical Research
Council in order to persuade the Ministry of Supply to allow industry to manufacture the new substance. I argue that a key feature of the MRC's advisory role was its framing of scientific information in such a way as to accomplish certain institutional goals. As Thomson's internal memo of February 1946 makes clear, one such goal of the MRC was to maintain its control over clinical trials. The MRC would have preferred not to see large scale production approved immediately as this might be wasteful and would weaken its own role in conducting clinical trials. Small scale production would not have been acceptable either, as this would not provide sufficient material for clinical use— and indeed this would in later months and years turn out to be the problem with the British industry's halting attempts at production. So medium-scale production would be the ideal outcome in the eyes of MRC headquarters, and the organization's external correspondence was therefore tailored toward this objective. As the clinicians changed their plans for clinical trials, the Ministry's production policy continued to be adjusted to fit them.
Chapter 5. Imports

There is clearly a determined policy on the part of the United States authorities to refuse to send this drug to this country.

Sir Edward Mellanby to The Under-Secretary of State for Foreign Affairs, 25 Apr 1946

Introduction

This chapter establishes how dependent the British government was on decisions taken in the United States with regard to streptomycin. I draw attention to the contrast between the information available to individuals in different institutional settings in Washington and London, as well as to the more obvious matter of access to the drug itself. I note also the range of arguments which the MRC and its allies used in appealing to the US medical authorities for the release of streptomycin—arguments which will have appeared already in Chapter 3 regarding appeals which were made to the MRC itself by members of the British public. And likewise the justifications which the Americans gave for denial of requests were similar to the words of their British counterparts.

The first section describes different types of attempts by officials of the MRC and other British Government Departments to procure streptomycin. The stated purposes of these requests were clinical trials (in the first instance in the treatment of plague), clinical observation of an individual patient with tuberculosis, and laboratory experiments. The first two attempts were unsuccessful during 1946, and the third yielded results only after the intervention of a sympathetic American.

In the next section I discuss the loosening of restrictions on American exports of streptomycin. It might be tempting to assume that the government's more open policy could be attributed solely to technologically-determined increases in American production. Although there arose a surplus of production over domestic

\[1 \text{FD1/6751.}\]
American consumption, I suggest, using the example of Merck, that this situation should be seen also in relation to the commercial policy of the manufacturers themselves. Finally I describe this process of approval in the case of an allocation of 600 grams of streptomycin for the month of October; this case will serve as a benchmark for comparison with that of the later large shipment to be discussed in Chapter 7.

4.1 Attempts to procure small amounts of streptomycin from the USA, 1945-Sep 1946.

Supplies requested for clinical trials

The first attempt by the MRC to procure streptomycin from the USA was made in December 1945, according to an explanation which Mellanby later gave to the Foreign Office. This initial request for streptomycin was sent by Landsborough Thomson to the British Commonwealth Scientific Office (BCSO) in Washington DC. Thomson’s letter was addressed to Alexander King, the director of the UK Scientific Mission, which was the largest constituent of the BCSO. He began, "We are very anxious to get some of the new mould product, streptomycin, for purposes of clinical trial, particularly on cases of plague in India. We should therefore be very grateful if you could make some enquiries on

2 Mellanby to The Under-Secretary of State for Foreign Affairs, 25 Apr 1946, FD1/6751.

3 This liaison organization had been established as the British Central Scientific Office (BCSO), in March 1941, at the recommendation of the Scientific Advisory Committee to the Cabinet, chaired by Lord Hankey. The acronym BCSO came to designate the British Commonwealth Scientific Office in the summer of 1944, when the mission from the UK was merged with missions from Canada, South Africa, Australia and New Zealand.

4 Thomson to A. King, 21 Dec 1945, FD1/6751.

5 As of shortly after V-E Day, the BCSO consisted of 27 technical staff. BCSO Organization Guide, circa Jun 1945, File "BCSO", Box 16, E-165, RG227, USNA.
our behalf.\textsuperscript{6} The MRC’s stated interest in the potential use of streptomycin in treatment of plague, we may recall from Chapter 3, may be traced back to October of that year, when Fildes called Thomson’s attention to animal experiments which had been done at Porton on that question.\textsuperscript{7} In April 1945, R. St.John-Brooks, the curator of the National Collection of Type Cultures at the Lister Institute, Elstree, Hertfordshire, had requested cultures of \textit{Actinomyces lavendulae} and \textit{Actinomyces griseus} on behalf of Harold Raistrick. Workers at the Station undoubtedly produced a crude preparation starting from this culture of \textit{Actinomyces griseus}.\textsuperscript{8} It is likely that the quantity and quality of streptomycin which could be produced in such a fashion was rather limited, and if so, this might partly explain the MRC’s request for a commercial preparation of the substance. Thomson’s remarks to King suggest that the MRC was not in direct contact with the American manufacturers: “We understand that several firms in America are beginning to produce streptomycin. Of these Merck has probably got furthest, but we gather that they are not very willing to part with the material, and that Dr. Geoffrey Rake of Squibb’s might perhaps be more cooperative.”\textsuperscript{9} King himself must surely have had direct links with Merck & Co; I infer this on grounds that he was personally responsible at BCSO for “control of insect vectors of disease, use of agricultural products as chemical raw materials, emulsions, and miscellaneous chemical and general enquiries”,\textsuperscript{10} and that the firm was a major manufacturer of the new insecticide DDT. I have found no reference to any such connections, however, with regard to King’s enquiries to the firm about streptomycin. Thomson continued, “The quantity we have in mind is 500

\begin{itemize}
  \item[6] Thomson to A. King, 21 Dec 1945, FD1/6751.
  \item[7] Fildes to Thomson, 2 Oct 1945, FD1/6751.
  \item[8] St.John-Brooks to Waksman, 9 Apr 1945, File "Streptomycin (British Corres.)", Box 2, Waksman Papers, Rutgers University.
  \item[9] Thomson to A. King, 21 Dec 1945, FD1/6751. It is not recorded on what basis Thomson made these conjectures about the American firms.
  \item[10] \textit{BCSO Organization Guide}, circa Jun 1945, File "BCSO", Box 16, E-165, RG227, USNA.
\end{itemize}
grammes, but this may be in excess of what is likely to be spared at this stage." There is no indication in the MRC streptomycin files how they arrived at the figure of 500 grams, but most likely it was based on estimates found in the Porton report, which I have not located. In any event, Thomson’s stated pessimism about the availability of streptomycin proved to be well founded. King replied to him in the new year, "No one can forecast when quantities of the order of 500 grams will be available; probably not within six months." He recounted, "I thought that I would in the first case approach the Committee on Medical Research, who have a fairly wide knowledge of progress towards production of chemotherapeutic substances." At the CMR, which we may recall was a branch of the governmental Office of Scientific Research and Development and had had extensive dealings with the MRC over penicillin, Dr E. Cowles Andrus took up King’s enquiry. King reported to Thomson that Andrus had said he had "consulted a number of his people as well as some of the firms". It was, King wrote, "apparently quite impossible to let us have anything like the quantity mentioned in the near future." This situation he attributed, possibly echoing Andrus, to the control of "the whole project" by the US Army. Furthermore King stated, "the firms are all experiencing extreme difficulty in establishing large scale production by direct translation from their laboratory experiments." He promised to keep in touch with the MRC about the streptomycin situation, and before receiving Thomson’s letter of acknowledgement, despatched an update, along with what he called "a full list of firms in the United States now attempting to produce this

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11 Thomson to A. King, 21 Dec 1945, FD1/6751.

12 A. King to Thomson, 17 Jan 1946, FD1/6751.

13 A. King to Thomson, 17 Jan 1946, FD1/6751.

14 A. King to Thomson, 17 Jan 1946, FD1/6751. King’s phrasing. There were substantial links between the CMR and industry.

15 A. King to Thomson, 17 Jan 1946, FD1/6751.

16 A. King to Thomson, 17 Jan 1946, FD1/6751.

17 Thomson to A. King, 26 Jan 1946, FD1/6751.
substance". King reported that Dr McCormack at the CMR confirmed the
estimate which King had already attributed to Andrus, that quantities of the order
of 500 grams would not be available within six months. Interestingly, the
picture King presented of streptomycin distribution in the USA suggests a
discrepancy between public and private information. He wrote to Thomson, "Most
of the present output is consumed by the Services although a portion is supposed
to be available for public use. Actually I understand that it is unobtainable for
public allocation." King gave no explanation of where streptomycin might be
going, outside the Armed Services.

In the absence of supplies of streptomycin on the open market, its price
might seem a somewhat moot point, but this question was investigated too. In
Thomson's initial enquiry, he asked King for clarification of the cost of
streptomycin. He advised, "We also do not know whether the material would be
offered free for experiment purposes, or if not, at what price it would be sold." In
closing he explained to King, "We therefore cannot do anything about Treasury
authority or allocating part of a dollar credit which the Rockefeller Foundation
have just put at our disposal, until you are able to let us have some

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18 A. King to Thomson, 21 Jan 1946, FD1/6751. His list was: Abbott
Laboratories, Chicago, Illinois; Eli Lilly & Co., Indianapolis, Indiana; Upjohn
Company, Kalamazoo, Michigan; Charles Pfizer & Co., Brooklyn, New York;
Parke-Davis and Co., Detroit, Michigan; Squibb Institute for Medical Research,
New Brunswick, N.J.; and Commercial Solvents Corp., 17 East 42nd Street, New
York 17, New York. Bizarrely, King's list did not mention Merck, which had
been producing streptomycin since the summer of 1944.

19 A. King to Thomson, 21 Jan 1946, FD1/6751. Dr James E. McCormack
was a Technical Aide in the CMR's Division of Medicine.

20 A. King to Thomson, 21 Jan 1946, FD1/6751. Nor did he indicate his other
sources of information.

21 Thomson to A. King, 21 Dec 1945, FD1/6751. Thomson's apparent
uncertainty about cost might be related to the sources of his information on
streptomycin-- which I suspect to have been medical journals, wherein little
commercial information was published.
information. In King's second letter on streptomycin, he provided the financial aspect of the information requested: "The cost is approximately $20.00 per million units. On the assumption that one milligram of the material contains about eight hundred units then the cost of five hundred grams would be about $8,000.00." The cost of streptomycin, as we will see, declined over time (as the cost of penicillin had done), from this figure of $16/g in January to a range of $10-$15/g in May and continuing downwards. The MRC's next step in attempted procurement of streptomycin turned to private channels of influence.

Supplies requested for trial in an individual case.

In February, Mellanby began to make enquiries regarding the procurement of streptomycin and advice on its use in tuberculosis. First, in a letter to Howard Florey, he explained that he and his wife May Mellanby (who were childless) had been "largely responsible" for the upbringing of his sister's son, George Little, whom he identified as a medical man. As Mellanby put it, the nephew had "developed another attack of phthisis", that is, tuberculosis of the lung. Insisting that his information be used with discretion, he explained to Florey, "I expect that, if I gave the Americans the reason for wanting streptomycin, I should not get any, but I am telling you the reason why I want it in this particular instance. I believe the Americans have been very sticky about supplying any to this country, but I should think it would be very difficult for them to refuse you some." He undoubtedly was referring to the international scientific prestige enjoyed by Florey, who was knighted in the summer of 1944, and awarded the

22 Thomson to A. King, 21 Dec 1945, FD1/6751. This issue of financial approval turned out to be of considerable importance by the autumn of 1946 as we shall see below.

23 A. King to Thomson, 21 Jan 1946, FD1/6751.

24 Mellanby to Florey, 13 Feb 1946, FD1/6751.

25 ibid.

26 ibid.
Nobel Prize in December 1945, for his role in the development of penicillin. Florey replied:

With regard to streptomycin the position is this: My wife wrote at my suggestion to the Head of the Research Division at Merks [sic], and asked him for 100,000,000 units to make certain clinical observations. A few days ago she had an answer that they were sending 25,000,000 units and they would send 75,000,000 units at an unspecified date, but they were unable to do better at the moment. He reminded Mellanby, "As you know, the amounts of this stuff measured in units look very large, but in fact 100,000,000 units does not go very far unless used for local application, which was my wife's intention." It is not clear how much either of them knew about dosages being used in tuberculosis— to the extent that there was any uniformity in the first place— but it would not be unreasonable to extrapolate from other figures that Lady Florey's expected 25 million units (roughly 25 grams) might be sufficient for a single patient for at most a few weeks if it were used for this purpose. Howard Florey volunteered to write for information to Herrell or Hinshaw at the Mayo. In conclusion, he proposed either trying to get enough for a "prolonged course", or alternatively, trying to send Little to the Mayo Clinic, "where", he wrote, "the only experienced people exist". Mellanby's investigations during the following few weeks into the
availability of streptomycin are not recorded.\textsuperscript{32} Then, in mid-March, he explained to Florey, "After I had discovered that procuring streptomycin was a very difficult matter, I decided to write to A.N. Richards and see whether he, as a scientific director of Mercks [sic], could do anything in the matter. I shall be interested to see what happens now. Probably nothing."\textsuperscript{33} This was four days after he wrote a letter marked "Personal" to Richards, who was, recall, also the chairman of the CMR.\textsuperscript{34} Mellanby began, "I wonder if you would kindly give me some personal help in a matter in which you can be quite sure that I should not trouble you if I knew any other way of procuring what I need."\textsuperscript{35} He then described his nephew’s case to Richards, suggesting on technical grounds that "any such active form of treatment as thoracoplasty" was not possible.\textsuperscript{36} In any event, the nephew was said to have "persuaded himself that his only chance of recovery would be through the use of streptomycin."\textsuperscript{37} Mellanby thus asked Richards whether he could help "to obtain some for him, together with any information as to the best method of administration".\textsuperscript{38} Richards responded on the 20th, "I have just received your letter of March 8 and can assure you that I shall do everything in my power to find a way of getting the streptomycin to you that is needed."\textsuperscript{39} He explained,

\textsuperscript{32} In particular it is not quite clear how aware the other senior staff at MRC headquarters were of his personal interest in the matter.

\textsuperscript{33} Mellanby to Florey, 12 Mar 1946, FD1/6751.

\textsuperscript{34} Mellanby to A.N. Richards, 8 Mar 1946, FD1/6751.

\textsuperscript{35} ibid.

\textsuperscript{36} Ibid. Mellanby’s explanation was that the patient had a diaphragmatic hernia, and that his alimentary canal was close to the affected lung. I do not know whether this condition would have been believed to preclude less radical forms of surgical treatment such as phrenic crush.

\textsuperscript{37} ibid.

\textsuperscript{38} ibid.

\textsuperscript{39} A.N. Richards to Mellanby, 20 Mar 1946. This letter, in which Richards made no explicit mention of the nephew, was stamped as received at the MRC on the 25th and was at an indeterminable date put with other correspondence on streptomycin supplies in file 3157/12, now PRO:FD1/6751.
"An arrangement has been put in force whereby the streptomycin manufacturers will supply the funds and the drug necessary for an investigation of the uses or limitations of streptomycin analogous to that which was undertaken in connection with penicillin. Dr. Keefer has been put in charge." 40 Richards promised that he would put Mellanby’s letter before Keefer, whom he was scheduled to see the following day, the 21st. 41 Keefer, however, informed Mellanby in a letter on the 26th, "I wish most sincerely that there was something that we could do about obtaining enough for investigation at once, but at the moment it is not possible." 42 He stated that the supplies of streptomycin which were being provided for study were "small", and alongside this he declared the opinion of the Committee to be that it could not undertake the investigation of tuberculosis until a later date. 43 The only exception, he wrote, was to be the completion of treatment of "a few" tuberculosis patients on whom streptomycin was used before the drug was placed under governmental allocation. 44 Richards wrote again to Mellanby, on 13 April, to explain his progress in relation to the second pledge in his earlier letter, which had been, "if necessary, [to] use any influence that I may have with

40 A.N. Richards to Mellanby, 20 Mar 1946, FD1/6751. During the war, Chester S. Keefer of the Evans Memorial Hospital of Boston, chaired the Committee on Chemotherapeutic and Other Agents, which controlled civilian distribution of penicillin in the USA. This committee, widely known as the COC, was an organ of the National Research Council (NRC), the research arm of the National Academy of Sciences (NAS). Although the NAS was an independent organization, it carried out considerable work for the government, and there was substantial overlap of membership between its committees and those of the governmental OSRD, one of which, of course, was the CMR. Richards explained to Mellanby that the CMR was to be wound up by July 1946. The work of the COC has been described in detail by the historian of medicine David P. Adams, "The greatest good to the greatest number": Penicillin rationing on the American home front, 1940-1945 (New York: Peter Lang, 1991).


42 Keefer to Mellanby, 26 Mar 1946, FD1/6751.

43 ibid.

44 ibid. The allocation order took effect on 1 Mar, and it is not clear whether (and if so, why) Richards had been unaware of the policy.
the manufacturers to have your request granted." Richards reported to Mellanby having transmitted his request on 12 April to "the head of one of the most important firms here". This industrialist, not identified in the letter, we may safely infer to be George W. Merck, President of Merck & Co, where, as noted above, Richards was a scientific director. This man's decision, Richards wrote, "was that at the present time the granting of such a request would put the manufacturer who did it in an extremely embarrassing position". Richards gave this as the reason "that the answer, for the present at least, must be no." He declared, in closing, "It gives me the greatest distress to find that we are unable now to provide you with the material. I hope you will understand that were we to do so, a door would be opened to a flood of requests, the answers to which would be embarrassing to us and difficult to explain to those who made them." Similar lines of reasoning were commonly used by the COC in refusing requests for penicillin which appealed to personal connections, as Adams has documented. Mellanby was likely not surprised by this refusal of the firm to provide streptomycin, as he had just written to Sir Henry Dale (who had suggested appealing to George Merck) that Lady Florey had not yet succeeded in getting any streptomycin from that source. We shall see in the following section how the COC's strict policy affected other requests by the BCSO on behalf of the MRC.

Supplies requested for the purpose of standardization.

On the same day Mellanby wrote to Richards, 8 March, a further appeal was sent by Thomson to King at BCSO. This time, Thomson told King he


ibid.

47 A.N. Richards to Mellanby, 13 Apr 1946, FD1/6751.

ibid.

ibid.

ibid.

mellanby to Dale, 9 Apr 1946, FD1/6751.
recognized that there was no immediate prospect of sufficient quantity of streptomycin for clinical trials, saying that this would run to hundreds of grams.\(^{52}\) He asked, however, if King might obtain 5 or 10 grams for the MRC. This, he stated, would be "[f]or purely experimental purposes",\(^{53}\) that is, not for use in human patients. The experiment he told King that the MRC had in mind, we can see from an earlier letter, was to be run by Philip Hart at NIMR Farm Labs. Hart described it as based on R.A. Glover's techniques using mice.\(^{54}\) Thomson added-- twice in this short letter in fact-- that even a single gram would be useful, as Hart had indicated.\(^{55}\) His letter was dealt with by Mrs V. Connell, the technical assistant to King (who at the time was reportedly visiting Australia).\(^{56}\) She responded to Thomson on 26 April, saying that she had just received a letter from Keefer dated four days earlier.\(^{57}\) According to Keefer's letter as quoted, she had written on 3 April to the NRC's Division of Medicine-- which would imply that she was unaware that the COC (which operated within the Division of Medicine) was handling all requests. Keefer wrote, "It would be very helpful to know the nature of the experimental work which Dr. Landsborough Thomson plans and for which he requests streptomycin." He promised only that he would refer the request to the Committee if this information were provided, not that the appeal would be approved.\(^{58}\) Connell told Keefer she believed Thomson's request had arisen from the earlier enquiry relating to clinical trials in plague in India, she reported to Thomson, but she asked him for confirmation and amplification.\(^{59}\)

\(^{52}\) Thomson to A. King, 8 Mar 1946, FD1/6751.

\(^{53}\) ibid.

\(^{54}\) Hart to Thomson, 25 Feb 1946, FD1/6751.

\(^{55}\) Thomson to A. King, 8 Mar 1946, FD1/6751.

\(^{56}\) Connell's area of responsibility was flax. BCSO Organization Guide, circa Jun 1945, File "BCSO", Box 16, E-165, RG227, USNA.

\(^{57}\) Connell to Thomson, 26 Apr 1946, FD1/6751.

\(^{58}\) quoted in Connell to Thomson, 26 Apr 1946, FD1/6751.

\(^{59}\) Connell to Thomson, 26 Apr 1946, FD1/6751.
fact, Thomson explained to her on 1 May, "The small quantity asked for in my letter of the 8th March would not go anywhere in a practical test of the value of the substance in the treatment of plague, and is, in fact, wanted for purely experimental purposes of quite a different nature." He elaborated, "The point is that we are testing various other substances which may possibly have an antibiotic value, and for this purpose we wish to make a comparison with the known effects of streptomycin against infection with tuberculosis, as described from America. In other words, we wish to standardise our own particular test method." He suggested that "American workers in the subject should have sympathy" with this objective. Also on 1 May, King himself wrote to Thomson, "It appears that the real trouble," King wrote, "is a commercial one." Namely, he explained, the NRC research money for streptomycin had been contributed by eleven American pharmaceutical manufacturers who constituted what he called the Streptomycin Producers Advisory Committee. King reported that Keefer "finds it difficult to allocate samples outside the immediate American circle." This, he told the MRC, was why the COC was demanding "really full details... from you in connection with any requests for Streptomycin no matter how small." Hart wrote again to Thomson in July, asking him to ask the NRC for two 1-gram bottles of the purified product. He stated that he had one gram of streptomycin, and explaining, "all ours [streptomycin at the Farm Labs] has been obtained by individuals bringing back a little in their pockets." He suggested in fact that it

60 Thomson to Connell, 1 May 1946, FD1/6751.

61 Ibid.

62 Ibid. This argument did not however persuade the COC.

63 A. King to Thomson, 1 May 1946, FD1/6751.

64 Ibid. Its proper title was the Streptomycin Producers Industry Advisory Committee. The SPIAC was advisory to the War Production Board and to the WPB’s successor, the Civilian Production Administration.

65 Ibid. He did not state the source of his information.

66 Ibid.
might be easier to write to any MRC people who were visiting the USA, to get them to continue this practice.\textsuperscript{67} Thomson replied a week later that he had written once again to BCSO "to press the matter" of the 5-10 grams (or even 1 gram) for the stated purpose of standardization. He added, "This is of course, apart from the attempts which we have made to get larger quantities for clinical trial and which must now be regarded as hopeless."\textsuperscript{68} BCSO was informed that so far streptomycin had been shipped overseas in only three cases, one of these being the Maharajah of Indore.\textsuperscript{69} Thomson declared the situation "rather extraordinary, because we know that people from here who have been visiting America have informally been able to obtain and bring back small amounts of the order of a gram or so. We accordingly assumed that there was no objection to the release of such quantities which could obviously be used only for experimental and not for clinical purposes."\textsuperscript{70} Then in August, a gram of crystalline streptomycin was finally sent to NIMR for Hart's experiments. This may be attributed to the intervention of the Royal Navy's Medical Liaison Officer in Washington, and to a National Research Council officer who had criticized the COC's zero-export policy as "singularly unfriendly".\textsuperscript{71}

Following the discussions in July between the MRC and the MoS regarding clinical trials, as described in Chapter 4, Mellanby advised Ashley Miles at NIMR to contact Raistrick on the subject of standardization of streptomycin.\textsuperscript{72} Miles

\textsuperscript{67} Hart to Thomson, 15 Jul 1946, FD1/6751.

\textsuperscript{68} Thomson to Hart, 22 Jul 1946, FD1/6751.

\textsuperscript{69} J.E.C. [Chadwick] to Connell, 12 Aug 1946, FD1/6751.

\textsuperscript{70} Thomson to Connell, 27 Aug 1946, FD1/6751.

\textsuperscript{71} Philip S. Owen to Keefer, 13 Aug 1946 and 19 Aug 1946, folder "Coms on Military Medicine: Chemotherapeutic and Other Agents: Streptomycin: 1945-1946", NAS-NRC.

\textsuperscript{72} Mellanby to Miles, 24 July 1946, FD1/6755. He also advised Hart, "you had better let Miles do this work". Mellanby to Hart, 30 Jul 1946, FD1/6755.
informed Mellanby that Bruce White had consulted Raistrick. "They agree", Miles reported, "that the most important and urgent step is to negotiate with the American Control Committee for Streptomycin for a sufficient sample of the pure substance. They suggest between 2-5 gm., which will serve as a Provisional British Standard. The Streptomycin HCl-Calcium Chloride Complex is preferred. Raistrick insists that the Americans will not take any notice of a request like this unless it goes through the highest channels. Hence my reason for asking you to negotiate with the Committee." Mellanby appealed to the American Control Committee for Streptomycin, invoking his authority as Secretary of the Medical Research Council. He wrote that the MRC had control over international standards, and assured the American committee that any sample would be handled "with the greatest care". Keefer forwarded Mellanby's letter to the FDA, whereupon Henry Welch replied to Mellanby that the FDA was sending, under separate cover, 5 grams of the working standard of streptomycin. He enclosed the FDA's revised standard, which was a 15-page document detailing the characteristics of streptomycin. He added that he hoped to send the calcium chloride double salt eventually. Mellanby told Welch that this letter and the 5g reached him on the morning of 1 Oct 1946. On that same day he wrote also to Keefer, likely insincerely, "I want to thank you most warmly for having forwarded my request to Dr. Welch, and to assure you also how grateful we are to both of

73 Miles to Mellanby, 7 Aug 1946, FD1/6755. White, a Fellow of the Royal Society, worked in the NIMR department of experimental pathology and bacteriology.

74 Miles to Mellanby, 7 Aug 1946, FD1/6755.

75 Mellanby to Keefer, 9 Aug 1946, FD1/6755. It is not clear from British documents what the relationship was between this committee and the COC.

76 Welch to Mellanby, 11 Sep 1946, FD1/6755.

77 This specification, dated effective 15 Jul 1946, is filed in FD1/6752.

78 Welch to Mellanby, 11 Sep 1946, FD1/6755.

79 Mellanby to Welch, 1 Oct 1946, FD1/6755.
you for having assisted us in this way." Back in June, Mellanby had written, to someone who had told him with enthusiasm that Keefer—incorrectly, that is, rather than Feldman—was coming to Britain to lecture on streptomycin, "I think it is only fair to tell you, however, that I am not overflowing with affection for Dr. Keefer at the moment as he point blank refused to allow streptomycin to come into this country, an action which I regard as most unfortunate in view of the generosity with which we treated the Americans in the case of penicillin." But Mellanby's other statement to Keefer may have been more straightforward: "It will be of enormous advantage to us in our early clinical work to be able to use the same measure of strength of streptomycin as has been used in the U.S.A." Finally, Mellanby forwarded all this correspondence and the sample of streptomycin sulphate to Miles.

Canadian streptomycin.

Finally, I turn to the MRC's attempts to procure Canadian streptomycin for the stated purpose of standardization. The Montreal firm of Ayerst, McKenna and Harrison imported production equipment from the USA at a probable cost of US$250,000, some time after June 1946. Connell was informed during August 1946 that production was underway in very small quantities under the auspices of the National Research Council of Canada. This news she forwarded to

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80 Mellanby to Keefer, 1 Oct 1946, FD1/6755.

81 Mellanby to Dick, 26 Jun 1946, FD1/3258. The chastened Dr Dick described this as "a stupid error" and concluded, "I thoroughly agree with you about the shabbiness of the Americans & their poor grace". Dick to Mellanby, 1 Jul 1946, FD1/3258.

82 Mellanby to Keefer, 1 Oct 1946, FD1/6755.

83 Mellanby to Miles, 1 Oct 1946, FD1/6755.


85 JEC [Chadwick] to Connell, 12 Aug 1946, FD1/6751.
Thompson.\textsuperscript{86} According to King, the Canadian Streptomycin Committee was reserving the drug for "severe infections" (which he did not further identify).\textsuperscript{87} Then in October, he passed on the promise from NRC Canada, that 5 grams of streptomycin would be sent to the MRC for use in standardization. He had been told this by J.B. Collip, the Director of the Division of Medical Research, of the National Research Council of Canada, who was a professor at McGill University.\textsuperscript{88} Thomson replied that the MRC were grateful for this allocation from Canadian production, and added, "Collip is a good friend of ours".\textsuperscript{89} Collip wrote directly to Mellanby in December 1946, saying that 5 million units of Canadian-produced streptomycin were "at last" being sent under separate cover to the MRC. He declared, "As you probably know production of this material has increased to an enormous degree, so much so that it should be possible in a few weeks time to remove all restrictions on its use. Our Special sub-Committee on this subject has just recommended this together with its own dissolution."\textsuperscript{90}

Other attempts to procure streptomycin.

As Hart told Thomson, some streptomycin was being transported from the USA to Britain by individual travellers. There is only fragmentary evidence as to how large this traffic was, whether for humanitarian or black-marketeering motives. A few instances which are not necessarily representative, may suggest the nature of the situation. Dale informed Mellanby that the Middlesex Hospital had

\begin{itemize}
  \item Connell to Thomson, 14 Aug 1946, FD1/6751.
  \item A. King to Thomson, 31 Aug 1946, FD1/6751.
  \item A. King to Thomson, 21 Oct 1946, FD1/6751.
  \item Thomson to A. King, 29 Oct 1946, FD1/6751.
  \item Collip to Mellanby, 17 Dec 1946, FD1/6751. Collip did not identify the manufacturer. This shipment, which amounted to 5 grams of the drug, was received around the end of the year. Mellanby wrote, in his letter of acknowledgement that he did not think removal of restrictions would soon occur in Britain. Mellanby to Collip, 8 Jan 1947, FD1/6752.
\end{itemize}
"some Streptomycin for trial". Hart's investigation of this situation revealed that a 5-gram bottle of streptomycin, obtained by means unknown to him, had been used to treat a secretary from UNRRA for a form of miliary tuberculosis. However, he reported, this supply was exhausted and the patient was said to be relapsing. The Senior Tuberculosis Officer of Kent County Council, Dr D.G. Madigan, was invited to the MRC's Second Streptomycin Conference, where he explained his experiences with administering streptomycin to his patients. He too had what were described as only small supplies.

We also know of a few attempts to procure streptomycin through the Foreign Office. A telegram was sent in January to the British Embassy in Washington, and another in February apparently regarding a separate enquiry. The Ambassador, Lord Halifax, advised the Minister, "I would therefore suggest that the time has perhaps come to persuade the British Medical Research Council to take the question of future procurement of this drug up directly with the United States medical authorities. It would appear that the procedure used previously by His Majesty's Government in order to obtain Penicillin, when it originally became available in this country, might now also be adopted in the case of Streptomycin." This letter, posted in February, appears in MRC files covered by a slip from the Under-Secretary of State for Foreign Office dated 23 April, although Halifax had suggested "that the whole matter is one to be discussed at an early date between members of the medical profession who have the necessary qualifications to speak authoritatively". Mellanby responded at once in a formal letter:

I am to say to you that the Medical Research Council have endeavoured to

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93 Second Conference Minutes.
94 cited in Halifax to Bevin, 16 Feb 1946, FD1/6751.
95 ibid.
96 FD1/6751. No explanation was given for this delay.
obtain streptomycin from the United States on a number of occasions since
December 1945, and have completely failed in their efforts. Two types of
approach have been made by the Council—(1) through the British
Commonwealth Scientific Office in Washington and, (2) by seeking the
help of the highest medical research authorities, such as Dr. A.N.
Richards, Chairman of the Committee on Medical Research of the Office
of Scientific Research and Development, who, as a Director of Merck’s,
was in a position to seek their direct help, and who also approached Dr.
Keefer who is in charge of the supplies of streptomycin now being
distributed for clinical trials.97

We might interpret this letter as having been intended to suggest that his personal
enquiry to Richards and Keefer had been an act on behalf of the Council. In any
event, we can see that communication between the Embassy and the MRC was not
close. And in light of Keefer’s actions, one could hardly challenge Mellanby’s
concluding assertion, “There is clearly a determined policy on the part of the
United States authorities to refuse to send this drug to this country. “98

4.2 Relaxation of American export restrictions. Autumn 1946

As of August, control of Streptomycin distribution in the USA lay in the
hands of a joint committee including representatives of the Civilian Production
Administration and the Department of Commerce’s Office of International
Trade.99 In September the joint committee instituted a system of allocating quotas
of streptomycin to about 1,600 depot hospitals across the nation; from these

97 Mellanby to The Under-Secretary of State for Foreign Affairs, 25 Apr 1946,
FD1/6751.

98 ibid. He added, in mitigation perhaps, “No doubt, this policy will change
when supplies become abundant.”

99 See Policy Documentation File, RG179, USNA; J.E.C. [Chadwick] to
Connell, 12 Aug 1946, FD1/6751.
designated sites other hospitals were permitted to obtain streptomycin. This was explicitly modelled after the system used for penicillin at a similar stage of its diffusion. Government agencies, notably the Navy and Army, were reportedly taking their full allotment, but in September, the depot hospitals drew only about one third of their allotted amount. The American quota system was suspended, at first temporarily, as of 1 November. At this time streptomycin became available without impediment to any American hospital or sanatorium—though not to individual physicians or others. This government decision was made in consultation with the Streptomycin Producers Industry Advisory Committee, one of several dozen IACs which liaised with the various sub-committees of the Joint Committee, on decisions including the setting of export quotas. Merck & Co was one of ten US firms making streptomycin in October 1946, Macrae reported to London.

In September, Merck planned a nationwide advertising campaign for streptomycin, on the reasoning, stated in internal Board minutes, that American doctors were unaware that the drug was now actually available, and were not prescribing it as frequently as had been hoped. Strikingly, in November, Merck reduced its streptomycin production, to one half of capacity, until such time

100 See Administrative Committee minutes, 21 Aug 1946, Folder "Streptomycin-- Dept of Justice Investigation-- Legal-- August 26, 1947", Row 12 Box 5.6.1, Merck archives. The company archives have apparently preserved only brief excerpts from these minutes. These extracts were generated under compulsion in the course of an investigation, under the federal anti-trust laws, of alleged price-fixing. This investigation was dropped in March 1949. File hereafter cited as "Admin [or other] Committee minutes, DOJI, Merck archives."

101 Adams, Greatest Good.

102 Admin Committee minutes, 25 Sep 1946, DOJI, Merck archives.

103 Civilian Production Administration bulletin, 30 Oct 1946, FD1/6751.


105 Admin Committee minutes, 18 Sep 1946, DOJI, Merck archives; See also Advertisements bound volumes, Merck archives.
as the domestic American sales picture improved.\textsuperscript{106} Perhaps it could have lobbied the joint committee for permission to export its surplus, and indeed perhaps it was already in touch with the British Supply Office to arrange an outlet for its excess capacity. On the other hand, the company had traditionally been much more active in the domestic market, and had little infrastructure for overseas marketing.\textsuperscript{107} The distribution picture is rather confusing. I suggest that Merck's executives reasoned that it would be preferable for export levels to remain stable or to increase, rather than be forced into a sudden reduction in the event of a surge in domestic American demand for the drug.\textsuperscript{108}

Available documentation does not indicate the extent of MoS’s negotiations with the joint committee and American industry.\textsuperscript{109} In any event, the Joint Committee decided in October that it would permit limited exports.

\textsuperscript{106} Admin Committee minutes, 13 Nov 1946, DOJ, Merck archives. The excerpt did not state at what proportion of capacity the company had previously been operating. It is not clear what balance between domestic and export sales the company was aiming for.

\textsuperscript{107} Connell, however, identified Merck as one of the US firms "who have associated firms in England". Connell to Thomson, 19 Nov 1946, FD1/6751. I speculate that she was referring to its existing licence with Glaxo, but that she overestimated the closeness of the links between the two companies. A campaign in 1952 by Merck to recruit a few well-placed physicians in the UK suggests that its marketing position in the country was not well developed.

\textsuperscript{108} Merck board minutes indicate that the American market was nowhere near saturation, and thus might pick up quite rapidly. In such an eventuality, the company would be forced to reduce its export levels if there were no slack. Although there was then an opportunity presented by the wartime devastation of the continental European pharmaceutical industry, it was not clear how long this situation would last. According to Merck's relatively cautious corporate strategy, as illustrated in various internal documents, it was considered inadvisable to attempt to take advantage of market opportunities unless they were believed likely to be viable in the long term.

\textsuperscript{109} It is conceivable but in my view unlikely that the efforts of Hambro on his personal mission to procure streptomycin substantially speeded up the release of streptomycin for export to Britain more generally.
4.3 British acceptance of the October allocation of streptomycin

I have described above the unsuccessful attempts by the British government to procure small quantities of streptomycin. The British Commonwealth Scientific Office, as we have seen, had little clout when it came to obtaining supplies, and also does not appear to have been especially competent in performing its role as coordinator of information. It is not altogether surprising then that the Ministry of Supply officials chose another route for their attempts to procure streptomycin. I now describe these efforts to procure small amounts of streptomycin.

We see in detail in Chapter Sir Charles Hambro's efforts to obtain streptomycin for his young grandson. A flurry of telegrams was exchanged around 12 Oct 1946. According to Hambro—an MRC secretary recorded—on 10 Oct, the US Department of Commerce convened a meeting to announce a forthcoming change in the nation's policy on export of streptomycin. In a letter from the British Supply Council (BSC), which as we recall was the MoS liaison point in Washington, we see that a representative of that office attended Commerce's meeting, namely Keith Macrae, a Supply Officer in the General Procurement Division. Following this meeting, the export policy was announced publicly in a bulletin issued by the CPA. This bulletin announced that small quantities of streptomycin would become available for export from the USA, as of November 1946, for "the most urgent needs." All these exports were limited by quotas, determined each month for each country by the Joint Committee, which had Commerce and CPA representation.

On the 11 October, as mentioned above, Macrae informed Frank

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110 FD1/6760.
111 [Couzens] to Green, 12 Oct 1946, FD1/6760.
113 CPA press release 581, 30 Oct 1946, FD1/6751. It also announced that 9 kg of streptomycin were to be devoted each month to a research program to be conducted under the authority of Dr Hinshaw of the Mayo Clinic.
Warburton at the Ministry of Supply that the US Department of Commerce was going to release 600g of streptomycin to the UK government.\textsuperscript{114} The next day, Green was told about this by Hambro’s office, as we may recall.\textsuperscript{115} On 15 Oct 1946, Mellanby recorded in a note, Raistrick called on the MRC and “said that Streptomycin in small quantities would begin to be handed over to us in about a fortnight’s time”.\textsuperscript{116} That same day, Thomson wrote to Everett, the Assistant Controller of Penicillin Production, saying that the MRC would accept a shipment of 600 grams of streptomycin, on the understanding that the cost would be about £2000 worth of dollars,\textsuperscript{117} which works out to a price of $13.33 per gram. It is recorded that John Cairncross, a Principal at the Treasury, was telephoned in connection with this purchase, by an MRC officer, who was not identified in the note.\textsuperscript{118} Presumably Thomson was referring to this conversation when he mentioned to Everett on 15 Oct that the issue of dollar exchange had already been raised with the Treasury authority.\textsuperscript{119}

Thomson relayed the £2000 figure in a letter the next day to David Stephens at the Treasury.\textsuperscript{120} The dollar issue in this instance, I should clarify, was a routine process whereby Treasury approval was required for any purchase in dollars, above a certain threshold; there is no evidence of Treasury objection to, or hesitation over, the spending of dollars on streptomycin at this point and in this

\textsuperscript{114} Macrae to Director of Medical Supplies, MoS, 11 Oct 1946, FD1/6751.

\textsuperscript{115} FD1/6760.

\textsuperscript{116} Extract from Sir Edward Mellanby’s Note dated 15:10:46, FD1/6751.

\textsuperscript{117} Thomson to [Everett] Assistant Controller, PPC, MoS, 15 Oct 1946, FD1/6751.

\textsuperscript{118} Thomson to Stephens, 16 Oct 1946, FD1/6751.

\textsuperscript{119} Thomson to [Everett] Assistant Controller, PPC, MoS, 15 Oct 1946, FD1/6751.

\textsuperscript{120} Thomson to Stephens, 16 Oct 1946, FD1/6751.
amount. Stephens agreed on 29 Oct to allow the MRC to spend this amount, and he informed the MRC that the MoS had been notified and were going ahead with the order. Thomson then told Stephens, early in November, that the MRC had been informed of a cut in the price, to "half of what we had previously been told". The new proposal, he wrote, was to purchase 1800 grams of Streptomycin at a cost of £3000, which works out of course to $6.67/g. Official approval a few days later suggests that Treasury officials dealt with this modified proposal routinely. These prices, as is made clear in later correspondence, were aggregates of the prices demanded by various manufacturers; Macrae specified in his original letter that the cost of a gram varied from $10 to $15. When the purchase was finally arranged, Macrae wrote that this allocation would be made up of 10 g from Wyeth Corp from Philadelphia, at a price of $10/g; 30 g from Parke, Davis & Co at $6.80/g; and 560 g from Merck at $6.27/g. Macrae also recorded that an extra 110 g of streptomycin was to be supplied by Lilly at a unit price of $6.67/g; he gave as explanation that "one of the other Foreign Governments had not picked up its

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121 Extract from Stephens to Thomson, 29 Oct 1946, FD1/6751; full letter filed in FD1/4211.

122 Extract from Stephens to Thomson, 29 Oct 1946, FD1/6751.

123 Thomson to Stephens, 5 Nov 1946, FD1/6751.

124 ibid. The documents do not present any reason for what may be presumed to be an additional allocation by the Dept of Commerce, nor do they identify which firm(s) had made the price cut.

125 Stephens to Thomson, 8 Nov 1946, FD1/6751.

126 Macrae to [Warburton] Director of Medical Supplies, MoS, 11 Oct 1946

127 Macrae to [Warburton] Director of Medical Supplies, MoS, [circa 31 Oct 1946], FD1/6751. The small shipment from Parke, Davis & Co was delivered at the end of October. telegrams BSO NY to MoS, 25 Oct 1946 and 26 Oct 1946, FD1/6751. It would appear that the Wyeth shipment fell through, as it is not listed in a later chart.
allotment". As the MRC was told by Connell, the Department of Commerce’s policy was that national allocations would be forfeited if an American export licence was not arranged by the end of the month; in order to get such an export licence one had to have in hand an agreement to purchase from the individual manufacturer. Moreover, Macrae warned, "in the event that we request less than our specified allotment in any month, we cannot have the difference added to the amount released to us on the following month." These policies were important, in that they contributed to the urgency of the negotiations to approve the large UK allocation for the month of November.

We can see that BCSO’s role in this procurement was marginal, through an exchange of letters between Mrs Connell of that organization and Thomson at MRC headquarters. On 16 Oct 1946, Connell sent a telegram to Thomson, via DSIR— her office’s parent Department, we may recall. She followed this up with an air letter to Thomson despatched the same day, saying, "You will probably be surprised to learn from my cable that after our unavailing efforts to obtain 5 grams of streptomycin for you, the Ministry of Supply had suddenly been offered an allocation of 600 grams for the month of October." Only that day had she been so informed by the Procurement Division of the British Supply Office, according to her letter, which Thomson received 6 days later. Thomson replied on 23 October regarding what he referred to (apparently in response to her wording) as "the surprising offer" of 600 grams of streptomycin.

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128 Macrae to Director of Medical Supplies, MoS, [circa 31 Oct 1946], FD1/6751.

129 telegram BCSO to Verry DSIR for Thomson, 16 Oct 1946, FD1/6751.

130 Macrae to [Warburton], [circa 31 Oct 1946], FD1/6751.

131 telegram BCSO to Verry DSIR for Thomson, 16 Oct 1946, FD1/6751. In December 1942, control of the BCSO was transferred from its original place within the DSIR to the Ministry of Production. The latter Ministry, a wartime creation, was abolished in the Attlee government, and control of BCSO reverted to DSIR.

132 Connell to Thomson, 16 Oct 1946, FD1/6751.

133 Connell to Thomson, 16 Oct 1946, FD1/6751.
He remarked, "[a]s a matter of fact we had already heard about it from the Ministry of Supply". 134 Before receiving this response Connell had confessed, in a letter Thomson received at the end of the month, "I am afraid streptomycin has not been one of the B.C.S.O.'s successes and I am still puzzled by the abrupt transition from a refusal to supply any to the offer of 600 grams!" 135 She stated her continuing willingness to help the MRC, while suggesting that the need did not seem likely to arise as this was "now purely a supply matter". 136

4.4 Conclusion

Let us recapitulate. The MRC's earliest enquiries about American streptomycin, through its contacts in Washington, yielded no supplies in 1945 or early 1946. The MRC's attempts to purchase the drug through official channels remained frustrated throughout the summer of 1946, although very small amounts were brought by NIMR staff. After considerable agitation by the MRC staff and their allies, the American authorities eventually released small quantities designated for non-clinical purposes. Beginning in October 1946, the amount of streptomycin leaving the USA increased dramatically; officially approved monthly export levels leapt from a few grams to around 80 kilograms per month, of which a substantial proportion was allocated to the UK. This export increase can be attributed partly to the tight domestic control which had been exercised previously by the COC.

Enquiries made to the US medical authorities who controlled streptomycin invoked a variety of arguments: the advancement of science, the desirability of international cooperation, reciprocity for penicillin, and personal favours. But it can be seen that demands for streptomycin within the USA took priority, especially the demand from the American military. Only when this demand was predicted to be satisfiable from American stocks of the drug were substantial

135 Connell to Thomson, 18 Oct 1946, FD1/6751.
136 ibid.
quantities released for export. And in the period prior to the institution of export quotas, the restrictions applied by the COC, in a stated attempt to prevent the development of a black market in streptomycin, can be seen as responsible for the failure of the MRC to procure the very small quantities it was seeking for laboratory research.
Chapter 6. Clinical Trials

6.1 Introduction

The literature on the streptomycin clinical trials acknowledges a link between the supply situation and the planning of clinical trials. It has focused rather narrowly, however, on the argument that the supply shortage made it ethical to run controlled experiments on human patients. This understates the breadth and strength of the influence of the supply position. The shortage made it all the more important for the Council to represent itself with authority, and this found expression in the appointment of expert committees of clinicians, described in Section 6.2. I then track in Section 6.3 the development over several months of the design of the trials, which has previously been portrayed in finished form, and suggest some connections between the shortage and a range of design issues. Section 6.4 is an historiographical epilogue in which I trace the evolution of the standard story of streptomycin clinical trials.

6.2 The MRC's clinicians and the choice of tuberculosis

In the summer of 1946, MRC headquarters turned to a select group of clinicians and scientists to advise the Council on the design, and ultimately the conduct, of the streptomycin clinical trials. This section describes the process by which the conferences and committees came to be appointed; the next section will analyze the design decisions taken at their meetings. One design decision, however, is inseparable from the selection of clinicians, namely the choice to focus on tuberculosis.

The first question is how tuberculosis came to be the leading priority for the clinical trials. Despite the importance of tuberculosis as a public health problem in Britain, this decision should not be taken for granted. I point out that there were additional diseases such as plague which were also taken seriously as options for study.
The second question in this section is why the MRC’s research program dealt with non-tuberculous conditions at all, once the priority of tuberculosis had been settled. I argue that the non-tuberculous conditions committee was created for two main purposes. It placated certain individuals who for political reasons could not easily be denied access to streptomycin altogether. And the non-tuberculous conditions clinical trials could absorb certain smaller shipments of streptomycin which the tuberculosis committee did not wish to use, without leaving any awkward surplus which would raise difficult issues of distribution. The third, and most obvious purpose, namely the generation of new knowledge about the effectiveness and best use of streptomycin was of relatively minor importance in the eyes of the MRC’s senior administrative staff in the case of non-tuberculous conditions.

The priority of tuberculosis

Although in hindsight it might appear obvious that streptomycin clinical trials should concentrate on tuberculosis, this was not at all a foregone conclusion. It was for the stated purpose of running clinical trials in treatment of plague that the MRC first attempted to procure streptomycin from the USA, in January 1946, as I have described. The plague bacillus was one of those reported susceptible to streptomycin in laboratory tests.¹ A member (on secondment from the MRC) of the MoS experimental station at Porton, Denis Herbert, conducted between April and August 1945 a series of in vivo experiments in plague, of which Thomson was informed in October of that year.² Herbert’s study, confidential at the time, was published in 1947.³ As I described in Chapter 3, the first request the MRC received for streptomycin, in September 1945, was for treating a typhoid carrier;


² Fildes to Thomson, 2 Oct 1945, FD1/6751.

this request cited a paper in the Journal of the AMA published on 19 May 1945. In the USA, the Committee on Chemotherapeutics decided in March 1946 that no further tuberculosis patients should be started on streptomycin therapy until the supply picture improved, on the grounds that it would take too long to generate results, and in the meantime, research would concentrate on treatment of other conditions, in which concrete information could be produced sooner.

What then accounts for the priority given to tuberculosis by the late spring of 1946? Tuberculosis had of course been one of the major areas of research by the MRC during the war. There was some encouragement from the Ministry of Health to investigate tuberculosis, as we shall see. It is possible that the choice of tuberculosis was one of the points at which politicians had a significant effect on the streptomycin story during the year; the evidence for this is circumstantial, however. It appears that Mellanby recognized in the spring of 1946 that research into tuberculosis, a health problem of great concern in the economically crucial coal industry among others, would be a good way to earn credit for the MRC with the Labour Government. In the spring the Lord President’s Committee, the Committee of Ministers which set domestic economic priorities, examined the MRC’s research programme. One of the projected schemes in the Research Programme was the creation of a Tuberculosis Research Unit. This had been under discussion prior to the war, and at the beginning of May 1946, Hart agreed to draft a proposal quickly, apparently in order that this could be incorporated into

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7 The Pneumoconiosis Research Unit was the largest of the MRC’s external units. As well, though I doubt this was a decisive factor, Mellanby’s own nephew was ill with tuberculosis, as I discussed previously.
a document Mellanby was preparing for the Ministers. On 28 June 1946, Mellanby went before the Lord President's Committee. The circulated paper, which had been prepared in May, included in its list of research activities: "The study of tuberculous disease, with special reference to the development of new methods for its prevention and treatment". Very typical of the concerns of postwar reconstruction was the report's list of areas calling for "a substantial and early increase in research": investigations bearing on industry, problems raised by house construction in relation to human comfort, the human factor in road accidents, medical and biological problems arising from atomic discoveries, chemotherapy ("especially the use of chemotherapeutic agents in tuberculosis"), and prevention and cure of the common cold, dental decay and gum disease.

In the June 1946 letter we have seen in Chapter 4, Dalrymple-Champneys suggested that the MRC might set up a Streptomycin Clinical Trials Committee. He conveyed the view from the MoS-MoH meeting:

It was thought that perhaps the best disease on which to test out this new antibiotic in order to discover whether facilities should be given for its manufacture in this country might be pulmonary tuberculosis in spite of the fact that the criterion of 'cure' must necessarily be applied at a long interval after the treatment."

He granted that such decisions would of course be left entirely to the discretion of the MRC's experts. No mention of tuberculosis is found in Mellanby's reply.

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8 FD1/0065. In the event, the details of his plan were not sent to Mellanby until the week after the Programme was written. The Tuberculosis Research Unit was formally recognized by the MRC in 1948, and moved to Hampstead in January 1949.

9 Sequence 13, Medical Research Council Programme, MRC.46/104, 10 May 1946, T227/1027.

10 ibid.

11 Dalrymple-Champneys to Landsborough-Thomson [sic], 21 Jun 1946, FD1/6751.

12 ibid. Likewise he wrote that it was naturally up to the Council whether to set up a Committee.
early in July. Immediately after Raistrick’s visit on the 24th of the same month, Mellanby wrote, "I said that it seemed to me, although I was not wedded to the idea, that it might be well to concentrate on tuberculosis." This would be in keeping with priorities of the inter-Departmental meeting held in June by the Ministry of Supply, which departed from the views expressed in the Raistrick-Keep report, written in May or early June. Tuberculosis was not mentioned in that report’s concluding set of provisional recommendations, one of which was "that animal and clinical trials on Streptomycin in the treatment of plague should be carried out in view of the importance of this disease in the British Empire."

Mellanby promised Raistrick that he would "move at once" on preparations for streptomycin clinical trials. The same day he called Harold Himsworth over from London School of Hygiene and Tropical Medicine to discuss these developments. At this latter meeting, Mellanby hedged his bets: "I said that I had the idea that since supplies of streptomycin were going to be small that tests should be limited to tuberculosis only, but that I was not sure. After discussion I thought it would be best to have a Tuberculosis Committee and later, as supplies increased, to have a more general committee covering other therapeutic trials." He recorded that Himsworth raised the question of testing the action of streptomycin in whooping cough, and possibly plague. Mellanby wrote, "I said that I thought the Americans would settle these points before we got started."

\[\text{References:}\]
13 Mellanby to Dalrymple-Champneys, 8 Jul 1946, FD1/6751.
14 Mellanby memo on Raistrick meeting, 24 Jul 1946, FD1/6756.
15 Copy of Raistrick-Keep report, FD1/6759.
16 Mellanby memo on Raistrick meeting, 24 Jul 1946, FD1/6756.
17 Mellanby memo on Himsworth meeting, 24 Jul 1946, FD1/6756.
18 Mellanby memo on Himsworth meeting, 24 Jul 1946, FD1/6756.
19 In hindsight we see that Mellanby was mistaken about the former. Waksman’s bibliography lists only one American publication on streptomycin in whooping cough prior to 1949, when the first British paper came out, namely, H. Schwabacher and R.H. Wilkinson, "Streptomycin in whooping-cough", \textit{Lancet} 256 (1949), 180-183. It appeared in 1948 in the premier volume of the little-known
The two men discussed who should come to MRC headquarters for a confidential Streptomycin Clinical Trials Conference. It was then that Philip Hart was nominated to be Secretary.\textsuperscript{20} Also at this point, Geoffrey Marshall, an eminent tuberculosis specialist, was selected to act as Chairman.\textsuperscript{21} The Conference was held on Monday 29 July, three days after the invitations were sent out.\textsuperscript{22} At the meeting, Mellanby announced that it had been agreed the MRC would have sole responsibility for clinical trials of streptomycin.\textsuperscript{23} The minutes of the conference recorded, "[Sir Edward Mellanby] asked the Conference for guidance on (a) whether the trials should include various infective conditions susceptible to streptomycin in the laboratory (as in current trials in U.S.A.) or should be confined to tuberculosis; (b) if confined to tuberculosis, how many cases and what type of case should be treated".\textsuperscript{24} It was concluded that the main clinical trials should be restricted to tuberculosis; leprosy, a disease resulting from a species of bacteria closely related to the tubercle bacillus, was declared a potential later addition.\textsuperscript{25} Given that almost all the Conference members' experience had involved tuberculosis (see biographical information in Appendix A on the backgrounds of the ten men who attended), I argue that Mellanby had already decided that tuberculosis was to be the focus, and sought a rubber stamp. As with

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\textsuperscript{20} Mellanby memo on Himsworth meeting, 24 Jul 1946, FD1/6756.
\textsuperscript{21} ibid.
\textsuperscript{22} Minutes of conference, 29 Jul 1946, FD1/6756; hereafter cited as First Conference Minutes.
\textsuperscript{23} First Conference Minutes, Section 1. This was apparently a reference to the 12 June agreement between the Ministries of Supply and Health. It was reported earlier in the month that Glaxo's officials would have preferred the Public Health Laboratory Service to conduct "controlled trials of Streptomycin in suitable infections", instead of the MRC "Clinical Trials Committee"—by which they apparently meant the MRC's Therapeutic Trials Committee. See Cruickshank to G.S. Wilson, 3 Jul 1946, FD1/6751.
\textsuperscript{24} First Conference Minutes, para 1.
\textsuperscript{25} First Conference Minutes, para 2.

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the issue, mentioned above, of the number of patients in the trial, Mellanby suggested to parties outside the MRC that it had been the clinicians who were responsible for the decision. Disingenuously, he wrote to Dalrymple-Champneys, on 30 July, the day after the Conference, "After discussing the matter with some clinicians, it seemed to me that we might start with a clinical trial on tuberculosis". He added, "If there is more streptomycin available, I think we shall also set up a more general streptomycin clinical trials committee for testing in other conditions, but this work I think will be subsidiary to the tuberculosis tests." That was indeed the priority that remained in effect.

On 13 August, somewhat out of the blue, Dalrymple-Champneys invoked the Raistrick-Keep report's recommendation that the MRC conduct animal and clinical trials in plague, in view of its importance in the British Empire; he enclosed a copy of the report, which the MRC had apparently not seen before. Green spoke to Mellanby about this letter. Mellanby's expressed priorities for "the small amount of material which may be made available through the Ministry of Supply in about three months' time" were, Green explained in a note to Thomson, tuberculosis, Haemophilus infections (responsible for a form of meningitis), and thirdly perhaps leprosy. Green expressed with apparent irritation his surprise that the DCMO had made no reference to Mellanby's letter of 30 July quoted above, about which he remarked, "that makes it pretty clear that in our view clinical trials in tuberculosis in this country should have the first call upon streptomycin supplies." Then at the end of August, Marchbank told Mellanby that the MRC's planned trials using 75kg of streptomycin over six months would not be able to get underway until April 1947. As well as urging that the MRC

26 Mellanby to Dalrymple-Champneys, 30 Jul 1946, FD1/6760.
27 Mellanby to Dalrymple-Champneys, 30 Jul 1946, FD1/6760.
28 Dalrymple-Champneys to Thomson, 13 Aug 1946, FD1/6759.
29 "Streptomycin", FD1/6759.
30 Green to Thomson, 19 Aug 1946, FD1/6759.
31 ibid.
have its arrangements in place so as to be ready as soon as supplies became available, he suggested, "the M.R.C. might at the same time like to consider the possibility of clinical trials in conditions other than Tb." This comment undoubtedly was based on the reasoning, which had been invoked also in the USA, that smaller quantities of the drug would be required for such trials. There was thus pressure from several sides for including various other conditions in the programme of streptomycin clinical trials.

The Tuberculosis Committee

Meanwhile the Second Conference was held on 27 August. A few more men were invited to this meeting (see Appendix C). Hart explained to Thomson early in September, "[T]here is no committee as yet and I am very anxious to see Mellanby before names are decided". I surmise that he wished to prevent invitation of one or more individuals but did not wish to veto them in writing. The MRC took relatively little action on streptomycin during September, as in succession Hart and Marshall went on leave for a fortnight each, precluding formation of a Committee. In mid-October, Mellanby met with Marshall and Hart to discuss names. At this meeting, Mellanby persuaded a reluctant Marshall to remain as chairman when the Committee was formed. According to Guy Scadding, one of two surviving members of the committee (along with Hart), Marshall played a crucial role in the project, not through his scientific contribution but by persuading the medical profession that this experiment was a respectable endeavour. At the October meeting, Mellanby and the others decided that

32 Marchbank to Mellanby, 29 Aug 1946, FD1/6756.

33 Hart to Thomson, 4 Sep 1946, FD1/6756.

34 Hart to Thomson, 27 Sep 1946, FD1/6760.

35 Mellanby note, 14 Oct 1946, FD1/6764.

36 ibid.

Raistrick should have observer status on the committee. However he pressed for full membership, and as he was the liaison to streptomycin supplies through the Ministry of Supply, it is no surprise that his request was accepted. On Friday 18 October, Council approved the formation of a Streptomycin in Tuberculosis Clinical Trials Committee.

The Non-Tuberculous Conditions Committee

I have noted above some of the pressures which might lead the MRC to conduct clinical trials in conditions other than tuberculosis. Concern with novelty of findings appears not to have been a major impetus for this research. Mellanby suggested on several occasions that he thought the Americans would cover the field first, eg, "In the meantime, of course, large numbers of papers on streptomycin are beginning to appear in the American press, and I expect they have taken the cream off the whole subject." An important example of this was the summary paper published in JAMA in September. Keefer and his colleagues at the COC reported on the use of streptomycin in 1000 cases, involving a wide variety of conditions. This body of research of course did not exhaust the possibilities, as the publication of several thousand papers over the next few years testifies. There were other motives for research, surely not least of which was the excitement of a novel scientific plaything. Some of those who wanted some streptomycin of their own to investigate enjoyed a great deal of prestige in the scientific world—if not necessarily respect at the highest levels of the MRC—and could not be put off easily. In particular, Sir Alexander Fleming was a Nobel Laureate. Though he was not regarded as an effective "committee man", he was invited in 1945 to become a member of the Medical Research Council, undoubtedly because of his celebrity in the scientific world. At the meeting of

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38 Mellanby note, 14 Oct 1946, FD1/6764.
39 Extract from Mellanby note, 15 Oct 1946, FD1/6751.
40 Extract from Council minutes, 18 Oct 1946, FD1/6764; original in FD6/7.
41 Mellanby to Dalrymple-Champneys, 8 Jul 1946, FD1/6751.
Council on 18 October 1946, when the tuberculosis committee was approved, Mellanby also raised the question of research into non-tuberculous conditions. This he had been asked to do by Fleming (who was not present), who as we saw in Chapter 3 had tried to get streptomycin from Boots for research. Council "willingly accepted the idea," according to Mellanby's later explanation to Fleming. Mellanby wrote that he had in mind for the new body a few members of the Penicillin Clinical Trials Committee (see Appendix A). Mellanby consulted Christie, who had been Secretary of the penicillin committee, apparently inviting him to serve in a similar capacity in the streptomycin programme, and proposing that Fleming be Chairman. Christie was reportedly unwilling to do this. He told Mellanby at the beginning of November he thought the best person to be Secretary of the Streptomycin Trials Committee would be Clifford Wilson of the London Hospital, whom he said had just been appointed Professor of Medicine. Wilson had served as chief assistant to Christie, who wrote, "he is a person who puts his back into what he undertakes, as well as being capable and thorough." In this context, surely it was damningly faint praise of Fleming for Christie to add, "With him [Wilson] as Secretary, I agree with you that Sir Alexander Fleming would do very well as Chairman."43 Mellanby secured Wilson's cooperation a few days later at a face to face meeting of which no record was kept. He then wrote to Fleming, listing the proposed members and asking, "Will you please be Chairman and look after them?"44 With the chairman and secretary arranged, Thomson then sent invitations on 18 November to the three ordinary clinical members of the Committee,45 and on the same date to Raistrick, who was (at first) the only

42 Mellanby to Fleming, 7 Nov 1946, FD1/7943.

43 Christie to Mellanby, 1 Nov 1946, FD1/7943.

44 Mellanby to Fleming, 7 Nov 1946, FD1/7943.

45 Thomson to Christie, 18 Nov 1946, FD1/7943; also to Garrod and Vaughan Hudson.
member in common with the Streptomycin in Tuberculosis Committee. On 22 November, Council approved the appointment of the Streptomycin Clinical Trials (Non-Tuberculous Conditions) Committee.

The choice of conditions to be tested clinically was tied to the question of distribution to particular physicians and surgeons. For example, it appears that Sir John Taylor pestered Thomson during the autumn to include plague in India, his pet project, in the programme of clinical trials in non-tuberculous conditions. Here as in the case of Fleming, there appears to be an attempt to placate a troublesome member of the MRC's circle, who was pressing for research that the senior staff did not favour. Thomson accordingly suggested in a letter to Wilson, which was shown to Taylor, that plague be considered for some of the committee's trials, "although not necessarily at the outset". A further note a few weeks later urged, "When your committee come to consider the question of trying streptomycin in cases of plague, it would be well for you to invite Sir John Taylor to attend the meeting." Thomson stressed, "As I have already mentioned in sending you a note of his, he is to be found in this office." Wilson's reply to Thomson later in the week acknowledged that the comments about plague had been noted, and promised to bring the issue up again in committee when supplies were available. Two kilograms were eventually shipped to India at the end of 1947.

46 Thomson to Raistrick, 18 Nov 1946, FD1/7943. Cruickshank later joined the Non-Tuberculous Conditions Committee as well as the Tuberculosis Committee, of which he was one of the original members.

47 Extract from Council minutes, 22 Nov 1946, FD1/7943. This was in advance of formal acceptance by all the nominees.

48 Thomson to C. Wilson, 27 Nov 1946, FD1/6759.

49 Thomson to C. Wilson, 17 Dec 1946, FD1/6759. This I interpret as a warning that discretion was necessary in correspondence with headquarters regarding Taylor's proposal.

50 Extract from C. Wilson to Thomson, 19 Dec 1946, FD1/6759.
6.3 Design of the Clinical Trials

The experimental design of the pulmonary tuberculosis trial has received the lion's share of the attention in the historical literature. I discuss the design this trial in relation to the other two initial tuberculosis trials, and the trial in non-tuberculous conditions. It is widely claimed that the shortage of streptomycin in Britain made it possible for the pulmonary trial to be conducted using a control group of patients who were treated only with bed rest. I argue that this greatly underestimates the importance of the supply position in the design of these clinical trials. As I showed in Chapter 3, the clinical trials were used as a way of managing the distribution of the drug while it was scarce. Key aspects of this plan were as follows: the precise and narrow definition of the type of patients who would be eligible to be treated with the available supplies; the restriction of clinical trials to a few selected clinical centres; the insistence on the need for large-scale trials; and the claim that the MRC was best qualified to carry out methodologically sound research.

In this section I track the continuities and changes in design features at meetings which took place during the latter half of 1946. The specific issues of concern here are: 1) definition of cases, 2) choice of centres as related to the problem of the scale of trials, and 3) control groups.

Let me begin by reiterating the sequence of the planning meetings which are discussed in this section. The First Streptomycin Conference was held on Monday 29 July. The following Sunday, 4 August, Marshall chaired a meeting at his house, attended by Prof R.V. Christie (the Secretary of the MRC Penicillin Clinical Trials Committee) and three members of the First Conference. The Second Streptomycin Conference was held on 27 August. The Streptomycin Clinical Trials (Tuberculosis) Committee first met on 21 November 1946. The Streptomycin Clinical Trials (Non-tuberculous conditions) Committee first met on 6 December. A chart of attendance is found in Appendix C.\textsuperscript{51}

\textsuperscript{51} Minutes of the last one of these meetings, that of the non-tuberculous conditions committee, are found in FD1/7943; minutes of all the other meetings are found in FD1/6756.
Definition of cases

The definition of the kinds of cases which might be enrolled in the clinical trials was of significance for two reasons. It is obvious that there was a scientific goal of ensuring that clinical observations could be attributed, as conclusively as possible under the circumstances, to the effect of the drug. Arguments regarding the uniformity of disease condition had been made long before, for example by Hill in 1937.\textsuperscript{52} Thus it was accepted by the tuberculosis committee that they should study patients who came from a population which was as homogeneous as possible. In the cases where controls were used, it was agreed that the control group patients should be in similar condition to the streptomycin patients. But definition of cases also served administrative goals. Definition of cases restricted the number of patients who were eligible to be admitted to the trial. In a time of shortage this was particularly important. And to the extent that the criteria were fixed and objectively determinable, this reduced the opportunity for political and economic pressure to be exerted upon the gatekeepers. The system of definitions helped to direct the distribution of streptomycin on the basis of medical need, rather than special influence, and as well to maintain an image of fairness.

It was decided at the First Conference that the clinical trials would be restricted at first to tuberculosis.\textsuperscript{53} Recall that as per Mellanby’s plan there would be some 100 cases. The main group would be "acute, rapidly progressing tuberculous broncho-pneumonia at ages 15-25".\textsuperscript{54} It was recorded, "Advanced pulmonary cases, with much destruction and fibrosis, were considered to be of little value for critical trials." The argument, that is, was that where the lung was extensively scarred, any effect of the drug might take a long time to become apparent. But ruling out advanced cases also meant that, at a stroke, the requests for streptomycin by a large proportion of tuberculosis sufferers were made

\textsuperscript{52} A. Bradford Hill, "Principles of medical statistics: I. The aim of the statistical method", \textit{Lancet} 1 (2 Jan 1937), 41-43.

\textsuperscript{53} Para 2.

\textsuperscript{54} Para 3.
inadmissible, on the grounds of being unsuitable for research. The First Conference also agreed that there would be small numbers of cases of three other acute tuberculous conditions.\textsuperscript{55} It was expected to be quickly apparent in these types of cases whether streptomycin treatment was having any beneficial effect.\textsuperscript{56} At the Second Conference, the question was raised of restricting the large main group to "bilateral involvement", i.e., tuberculous disease in both lungs.\textsuperscript{57} A patient who had one healthy lung might alternatively be treated by artificially collapsing the sick lung, it was argued; this would consequently create an ethical dilemma, it was said, in that a control patient whose condition deteriorated might be given collapse therapy, and thus complicate the analysis. But evidently some members of the Conference could not be persuaded on this point, and the point was left to the future Committee.\textsuperscript{58} In the matter of tuberculous meningitis, the problem was raised that diagnosis of the condition was quite uncertain, and by the time bacteriological evidence of infection of the cerebrospinal fluid was produced, it was quite possible that the patient would already be dead. Based on that argument, it was agreed that presumptively diagnosed tuberculous meningitis could be treated, "but possibly only if tuberculin-positive".\textsuperscript{59} It was decided that data from this group would be broken down into two categories: patients where bacteriological proof of tuberculous meningitis eventually followed, and those

\textsuperscript{55} Para 3. The specific definitions were "(i) tuberculous meningitis in children (small number); (ii) acute tuberculous broncho-pneumonia at ages under 5 (small number); (iii) acute miliary tuberculosis at ages 15-25 (small number)". The numbers in these groups were in no instance specified.

\textsuperscript{56} Curiously, there was a failed attempt at the First Conference to include the study of "tuberculosis in African negroes". In the American tuberculosis literature, racial categorization of patients was a routine practice.

\textsuperscript{57} Para 1.

\textsuperscript{58} ibid.

\textsuperscript{59} The tuberculin skin test was much quicker than testing of the CSF, but a positive tuberculin test indicated only that the patient had been exposed at some time in the past, not that he or she had active tuberculous disease; in some parts of the country, the background prevalence of infection was quite high.
where such proof remained absent. Aside from those changes, the types of cases remained identical to the definitions recommended at the First Conference.

At the first meeting of the Streptomycin Tuberculosis Committee the main Group A was defined: "Acute, rapidly progressive, bilateral pulmonary tuberculosis of recent development, unsuitable for collapse therapy, bacteriologically proven, age limits 15-25." That is, the issue of bilateral disease was finally resolved. Group B was defined: "tuberculous meningitis at ages under 5 without obvious evidence of tuberculosis bronchopneumonia (but including miliary cases)"; this was, following the recommendation of the Second Conference, divided into "initially proven" and "presumptive" cases. Group C was to be "acute tuberculosis bronchopneumonia ages under 5, without obvious evidence of meningitis on acceptance, Mantoux+." For the time being, the Conferences' plans to study miliary tuberculosis in adults were shelved. It was explained to an enquirer about a fortnight later that such cases were "too infrequent to have the first claim on the restricted supplies"; this I surmise is related to the question of the size of clinical trials, which I address in the next subsection.

There was a major contrast between formal definition of case types in tuberculosis committee, as just described, versus clinical discretion in the non-

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60 Para 1.

61 There was a failed attempt, by a person not identified in the Second Conference minutes, to add "fibro-caseous disease with contra-lateral exudative spread" to the groups. I suspect that this was an ad hoc attempt to set the criteria to fit a particular patient whom the doctor had in mind.

62 Para 2A.

63 Para 2B.

64 Para 2C. The Mantoux test was another tuberculin skin test for having been exposed to infection.

65 Para 2.

66 Green to F.S. Jackson, 26 Nov 1946, FD1/6760.
tuberculous conditions committee. The latter committee declined to impose objective standards of admission: "Use of the drug in other conditions should be left to the discretion of those taking part".67 This was apparently subject to the caveat that streptomycin should be used only in infections resistant to both sulphonamides and penicillin,68 although the minutes were silent on how resistance to these other drugs was to be determined. As well, no more than a quarter of the supplies at any centre were to be used on cases of urinary infection.69 This was likely a response to public and medical views on the justice of distribution of penicillin to combatants with gonorrhea and syphilis, at the expense of civilians with other kinds of infections. They also selected pulmonary infections involving two or more types of infectious organism (against which streptomycin might be tested in conjunction with penicillin), whooping cough, and—finally fulfilling Garrod's request—typhoid carriers.70

The clinical case records also reflect a difference in attitude between the two committees. In the non-tuberculous conditions clinical trials, the minutes declared, "The form of record keeping was left to the discretion of individual workers."71 In contrast, the tuberculosis committee developed standard case record forms covering the patients' history, data on admission, clinical record, treatment record, and final summary report; and other forms for pathological examinations, and meningitis cases.72 We can characterise this as a differing conception of patients: as members of a population, in the tuberculosis research; as individuals, in the non-tuberculous conditions research. The attempt to compare outcomes between groups was limited, however, by the policy that patients should

67 Para 4c.

68 Para 4a.

69 Para 4b.

70 Para 4c.

71 Non-Tuberculous Conditions First Minutes, para 5.

72 See draft forms, covered by a letter, Daniels to Committee, 10 Dec 1946, FD1/6756.
receive whatever treatment was deemed to be in their individual best interests; this resulted in collapse therapy being applied in several cases.

Clinical Centres and Research Scale

The choice of clinical centres to participate in the trials was a crucial one: physical facilities and skills of staff differed widely from one hospital to another around Britain. Some clinicians were trusted by the MRC administrators to share their views on what constituted proper scientific research; the great majority were not. The historian Daniel Fox has argued that what he called "hierarchical regionalism" was a dominant assumption in planning the delivery of medical services in Britain this century. That is, he suggested, those at the centre of power saw it as natural for new medical discoveries to be distributed via stratified regionally-based networks, with university teaching hospitals at the apex of each region's hierarchy. The MRC's plans broadly fitted with this model (and even more so did the MoH's plans for tuberculous meningitis treatment and research, which were implemented in 1947). The pattern of selection of centres for streptomycin was based on the MRC's experience in the penicillin clinical trials. Penicillin had been studied at four centres initially, extending to fourteen centres as supplies of the drug had increased. The four main penicillin centres each had a full-time registrar who was employed by the MRC but acted under direction of the local clinicians. Coordination of what would later be termed a "multi-centre" clinical trial involved more work than if the same number of patients had been

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73 See Abel-Smith, The Hospitals.


75 According to the penicillin committee secretary, Christie, the choice of penicillin testing centres had been dictated by the availability of bacteriological facilities; he recommended that in the streptomycin trials, centralization of the determination of bacteriological type and sensitivity to the drug would allow the centres to be chosen for their clinical facilities instead. Meeting at Marshall's home, FD1/6756.
concentrated at a single institution. Dr Marc Daniels, who had recently held a prestigious grant from the Royal College of Physicians (RCP) to complete its Prophit Survey of tuberculosis incidence, was nominated at the First Conference to serve for one to two years as the "registrar" who would coordinate field-work at the dispersed hospitals.76

At the First Conference, it was proposed that there might be five clinical centres in England and Scotland. The University of London’s British Postgraduate Medical School, housed at the (London County Council-funded) Hammersmith Hospital, and the Brompton Hospital were suggested. It was also thought desirable to have some participation by a Middlesex County Council institution, a Northern hospital—Manchester was mooted—and a Glasgow hospital.77 At the Second Conference, centres recommended were Alder Hey Children’s Hospital in Liverpool and the Children’s Hospital in Glasgow.78 Although the London County Council’s tuberculosis chief, Fred Heaf, evidently enjoyed Hart’s respect,79 there appears to have been no regular contact between the LCC and the MRC.80 The LCC had access to most of the cases of tuberculous meningitis in the metropolis, and it was brought into the programme.81 In November the Streptomycin in Tuberculosis Trials Committee finally confirmed the list of these centres: the Brompton Hospital; the Middlesex County Council Sanatorium at

76 First Conference Minutes, para 5. For Daniels’ qualifications, see memo on Staff, MRC.46/254, 11 Oct 1946, FD13/38.

77 First Conference Minutes, para 4. Tuberculosis was generally more prevalent in Scotland than in England, and Glasgow had among the highest rates of tuberculosis in the country.

78 Second Conference Minutes, Para 2.

79 Heaf was on the list of tuberculosis experts whom Hart proposed that Feldman should visit on his trip to England. Hart to Mellanby, 29 Apr 1946, FD1/3258.

80 See eg Daley to The Secretary, Medical Research Council, 29 May 1946, FD1/6760.

81 The Council treated about two thirds of London’s 145 reported deaths in 1938, the latest year for which figures were available. Allen Daley to Thomson, 13 Jun 1946, FD1/6760.

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Harefield; the LCC’s Colindale Hospital for case-type A (pulmonary tuberculosis in young adults); the British Postgraduate Medical School and Hammersmith for case-type B (tuberculous meningitis in children); the Alder Hey Hospital and Glasgow Children’s Hospital for case-types B and C (as above, and tuberculous bronchopneumonia in children).

The issue of scale of research was an important aspect of the MRC’s control scheme. As discussed above in the section on production for clinical trials, the most important decision of the Second Conference regarding clinical centres was that a pilot trial would be run in the autumn using surface production. This decision evidently came as a surprise to the headquarters staff, and was reversed at the Committee meeting in November. I propose the following explanation: The most obvious point is that as of the latter meeting, it was expected that 50 kilograms of streptomycin would soon be available to the Committee. Raistrick reported that this quantity of American streptomycin would last for six months, after which the committee could depend on British supplies at the rate of 15-20 kg per month. It might be thought that with ample supplies available in the immediate future, there then was simply no need for a pilot trial using a small amount of the drug. However, that view was not uniformly shared, even among the handpicked members of the Committee. It was suggested by a Committee member (not named in the minutes) that the small amount of streptomycin which was expected within the next week or so be used to start a pilot trial on three to six patients at a single centre. This proposal was turned down. In the penicillin clinical trials, there had been continual pressure for small amounts of the drug to be diverted to individual cases, and one of the arguments against doing so was that large-scale clinical trials were necessary to achieve scientific validity. Likewise, as I have shown, the MRC continually asserted to the public that the supplies of streptomycin had to be kept intact. If the MRC decided that it could run small-scale trials of streptomycin and learn something scientifically reliable by doing so, then, someone outside the organization might reason, so could other groups. The

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82 Tuberculosis Committee First Minutes, Paras 2 and 3.

83 Tuberculosis Committee First Minutes, Para 4.
pilot trial plan, in other words, ran contrary to the logic under which the MRC could justify its monopoly on supplies. In November, the Committee abandoned the plan of a pilot trial. I stress that the Committee resolved "to advise the Council that tuberculosis trials be started only when an adequate store of drug had been built up, and then at all of the selected centres."84 The Committee also recommended that the Council should issue a press statement on the tuberculosis trials, particularly to the BBC, making these points: "it is not practicable to commence trials until an adequate supply has been built up; small quantities are useless for tuberculosis, a course of treatment generally lasting at least 3-6 months and requiring 4-6 injections daily; there will be no supplies at present for private use."85

As for trials in non-tuberculous conditions, Raistrick explained at the committee’s first meeting early in December, that some 540g of streptomycin was available immediately, and further British supplies would be available within a few months.86 It was decided that until supplies increased, admissions were to be restricted to Bart’s, Middlesex, St Mary’s, and the London Hospital. These were the hospitals where members of the committee worked.87

Control Groups

The aspect of the streptomycin trials which has received the greatest historical attention is the explanation of the control groups. I raise three main questions. Why were untreated controls approved in the pulmonary tuberculosis trial? Why were untreated controls ruled out in the miliary tuberculosis and tuberculous meningitis trials? Why was it decided to use randomized allocation of treated and control cases in the pulmonary trial?

84 Tuberculosis Committee First Minutes, Para 4.
85 Tuberculosis Committee First Minutes, Para 6.
86 para 2.
87 Non-Tuberculous Conditions First Minutes, para 3.
The field of tuberculosis research has played a special role in the development of experimental methodology partly because the clinical course of the disease, especially in its pulmonary forms, exhibited spontaneous recoveries. In 1944, Hinshaw and Feldman presented numerous techniques to reduce the possibility of erroneous claims from anti-tuberculosis trials on human patients. Their concepts of clinical trial design attempted to extend controlled laboratory conditions to the bedside. Their guidelines included careful definition of eligible cases in order to ensure a homogeneous group of cases, independent assessment of roentgenograms (x-rays), blinded as to whether patients received treatment, and "some procedure of chance" in allocating patients, ideas all implemented in the MRC trial.\(^*\) Their own study, then underway, used the toss of a coin to select one member from each of several pairs of patients who had been matched for clinical condition.\(^9\) As well, there was a historical argument that blamed poorly controlled studies for the adoption of numerous treatments that were later discredited, as Hart declared in his Mitchell Lecture.\(^{90}\) Most notorious of these was sanocrysin, a gold compound that was popular for about a decade from 1925.

In 1931 a team from the Detroit municipal sanatorium divided 24 patients in two groups, with patients paired as closely as possible according to criteria including age and severity of disease. A single flip of a coin decided which group would receive sanocrysin and which, injections of distilled water. No benefit in the sanocrysin group over the untreated group was found.\(^{91}\)

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\(^{89}\) Curiously there was no mention of this in their November 1946 paper on clinical tuberculosis. See H. Corwin Hinshaw, William H. Feldman, and Karl H. Pfuetze, "Treatment of tuberculosis with streptomycin: a summary of observations on one hundred cases", *JAMA* 132.13 (30 Nov 1946), 778-782.

\(^{90}\) P. D'Arcy Hart, "Chemotherapy of tuberculosis: research during the past 100 years", *BMJ* 2 (30 Nov 1946), 805-810, 2 (7 Dec 1946), 849-855.

The first recorded discussion of control cases in the British streptomycin trials took place at the meeting at Marshall’s home. It began with Christie’s experience of the penicillin trials, and continued with more general discussion:

The obvious difficulties met with in refusing penicillin to suitable cases were reduced by the fact that supplies were short; in the present trials, the position might be much the same initially, but the use of control cases might be rendered difficult if and when supplies became more plentiful...

The question of control-cases was thought to be one which would require a great deal of discussion, but the general view was that these were unnecessary for meningitic and miliary cases, but that they were highly desirable, if not essential, for the main group of broncho-pneumonic cases; the physician, as well as the patient, would probably have to be kept in ignorance of whether a given case was being treated with drug or control.92

That is, the use of untreated controls was also a feature of the penicillin clinical trials, and likewise it was dependent on the supply position.

The Second Conference had little recorded discussion of control-cases:

"These were considered essential for case-type (iv) [pulmonary tuberculosis], but possibly not for the meningitis cases, provided these were proved bacteriologically at some stage of their progress."93 Note that the use of untreated controls in the pulmonary tuberculosis trial was agreed when there was expected to be a shortage, but before there was any discussion with Treasury about the payment for supplies from America. One of the physicians attending the Second Conference, D.G. Madigan, of the Kent County Council Sanatorium, is recorded as giving a brief report on his cases of tuberculosis treated with streptomycin.94 He was not invited to join the Committee, possibly on the grounds that all the patients in his

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92 Minutes of meeting, 4 Aug 1946, FD1/6756. Para 2, my emphasis.

93 Para 3e.

94 Para 4.
study were given streptomycin. His research was published in December 1947.\textsuperscript{95}

I quote in full the minutes of the first Committee meeting on the question of controls:

\textit{Control-cases.} The use of control-cases was fully discussed and it was \textbf{resolved} that controls were essential for case-type A (rapidly spreading disease in young adults) and advisable for case-type C (bronchopneumonia in young children) but unnecessary for case-type B (meningitis). It was felt to be impracticable to use injections of an inert substance for controls over a period of months. The proposal to use "untreated" controls was therefore approved.\textsuperscript{96}

I point out the change in policy from August, when control cases "were considered essential for [the pulmonary case type], but \textit{possibly} not for the meningitis cases, provided these were proved bacteriologically at some stage of their progress."\textsuperscript{97}

It has been suggested that it was obvious for the pulmonary tuberculosis trial not to use placebos.\textsuperscript{98} In fact, the meeting at Marshall's home had anticipated the need to arrange material for placebo injections.\textsuperscript{99} This plan was abandoned in November: "It was felt to be impracticable to use injections of an inert substance for controls over a period of months. The proposal to use 'untreated' controls was therefore approved."\textsuperscript{100}

Hindsight has declared that it was obvious for the Committee to provide \textit{all} patients in the tuberculous meningitis trial with streptomycin treatment, rather than

\textsuperscript{95} D.G. Madigan, P.N. Swift and George Brownlee, "Treatment of tuberculosis with streptomycin and sulphonamide", \textit{Lancet} 2 (20 Dec 1947), 897-903; He did use a control group, but comparing streptomycin alone versus streptomycin plus a sulphonamide. No patients received sulphonamide alone.

\textsuperscript{96} Tuberculosis Committee First Minutes, para 8. Emphasis original.

\textsuperscript{97} Second Conference Minutes, Para 3e. My emphasis.


\textsuperscript{99} Minutes of meeting, 4 Aug 1946, para 2.

\textsuperscript{100} First Committee minutes.
leaving some of them as a control group. The logic was the following: tuberculous meningitis was almost invariably fatal no matter what other treatment was tried; therefore, if any patient survived after treatment with streptomycin, this would constitute ironclad scientific proof that the drug was effective. It is rather puzzling that a few months earlier, the Conference had not been equally definite in its views. In August, the use of controls was considered only "possibly not" essential in tuberculous meningitis.

On the tantalizing third question, of randomization, we have little contemporary documentary evidence: the word "random" appears nowhere in the MRC's streptomycin files for 1946. In those files, Bradford Hill's scheme was referred to explicitly in a single letter, in which Daniels referred to "a statistical process of selection." The pulmonary tuberculosis trial report explained:

Determination of whether a patient would be treated by streptomycin and bed-rest (S case) or by bed-rest alone (C case) was made by reference to a statistical series based on random sampling numbers drawn up for each sex at each centre by Professor Bradford Hill; the details of the series were unknown to any of the investigators or to the co-ordinator and were contained in a set of sealed envelopes, each bearing on the outside only the name of the hospital and a

101 See e.g., Thomson, *Half a Century*, vol 2, p. 239.

102 The complicating factor was that a diagnosis of tuberculous meningitis could be established with certainty only by an examination of the cerebrospinal fluid for presence of tubercle bacilli; without this test, a claimed success in treatment might be challenged as not having been a case of tuberculous meningitis to begin with.

103 Second Conference Minutes, emphasis added.

104 Likewise, there is no mention of randomization in the minute book of the Whooping Cough Immunization Committee, which is said to have agreed slightly earlier than the streptomycin committee to use randomization. FD1/7509.

105 Daniels to G.S. Wilson, 10 Dec 1946, FD1/6756.

number. After acceptance of a patient by the panel, and before admission to the streptomycin centre, the appropriate numbered envelope was opened at the central office: the card inside told if the patient was to be an S or C case, and this information was then given to the medical officer of the centre. Patients were not told before admission that they were to get special treatment; C patients did not know throughout their stay in hospital that they were control patients in a special study.

Hill wrote shortly before he died that he had been hoping since before the war to conduct a clinical trial with all the methodological safeguards recommended in his publications. He claimed that he had wanted to use randomization but chose to advocate the simpler scheme of allocating alternate patients into treatment and control groups. That recollection involves an anachronism. Hill in 1937 considered alternation to be a form of random allocation, it is clear from a close reading of his articles. The leading article that accompanied the publication of the pulmonary tuberculosis paper justified the new technique and distinguished it from the method of random allotment based on alternation. In a trial with the latter design, the clinicians would be certain that the next patient to be admitted would, say, receive the treatment, and their decision whether to accept this patient might consequently be affected. In the era of the slogan, "fair shares for all", suspicion of favouritism was to be avoided. Under Hill's scheme, there could be no such worries, as the decision whether to include the patient in the trial was made in complete ignorance of which group the patient would join.

I argue that that randomization might was implemented at this particular juncture in order to depersonalize the responsibility for allocation. The new method of random allocation "removed personal responsibility from the clinician",


In particular, it would make the system less vulnerable to pressure at the point of admission. Looking ahead in the files to the spring of 1947, I observe that an MRC staff member wrote to Green with advice about how to handle a physician's request for admission of his patient to the pulmonary trial:

"the strongest point against any possible acceptance of his case is that with the control system we dare not take isolated cases of this kind-- we don't decide whether the case is to be a treated one or a control case." 111 When one senior physician fell ill with tuberculosis, the MRC obtained supplies for him outside the trial, rather than compromise the integrity of this admission system. 112 Ensuring comparability between groups was a secondary goal; alternation continued to be used in certain later streptomycin trials where the allocation between groups was less sensitive for the MRC. Supplies for the aforementioned clinical trial in treatment of plague, for example, were provided free of charge to researchers in India on condition that an alternating design was to be used. 113 The importance of Hill's method lay in protecting the admission process from external pressure.

In this section I have shown that the design decisions were not straightforward, in that there were a number of changes over the course of several months. These changes may be attributed to the different supply position, and to the fact that the membership of the meetings was somewhat different; it would seem that certain individuals who held views on design not shared by MRC headquarters were excluded from the decisive meeting in November. The shortage of streptomycin not only explains the acceptability of untreated controls, but also contributes to our understanding to the features such as the new method of random

109 ibid, p.792.

111 Agnew to Green, 19 Jun 1947, FD1/6756. Interestingly, Mrs Agnew suggested that this patient would be worse off if admitted to the control group, being in a hospital far from home in Northern Ireland, than if not admitted at all.


113 Copy of cable despatched Secretary of State for Commonwealth Relations to Scientific, New Delhi, circa 11 Nov 1947, FD1/6759.
allocation.

6.4 Epilogue: historiography

The report of the MRC committee in 1948 published in the British Medical Journal on 30 October 1948 may be viewed as the first significant account of streptomycin research in Britain. Almost all subsequent British historical accounts about streptomycin, as well as many American ones, cite it and are derived from its sketch of the economic circumstances of the trial. The report began, "When a special committee of the Medical Research Council undertook in September, 1946, to plan clinical trials of streptomycin in tuberculosis, the main problem faced was that of investigating the effect of the drug in pulmonary tuberculosis." It argued that only "adequately controlled clinical trials" could validate a claim that a new drug was effective in pulmonary tuberculosis, on the grounds that the natural course of the disease was highly variable. It explained, "In 1946 no controlled trial of streptomycin in pulmonary tuberculosis had been undertaken in the U.S.A. The Committee of the Medical Research Council decided then that a part of the small supply of streptomycin allocated to it for research purposes would be best employed in a rigorously planned investigation with concurrent controls." The feature of the trial that would later excite the most comment was the method of deciding which patients would be treated with streptomycin and bed rest, and which, the controls, with bed rest alone. This was accomplished with a scheme of random sampling numbers and sealed envelopes, designed by Bradford Hill. The report argued that use of untreated controls was ethically justified on two grounds, first that the value of the drug was still uncertain, and also "that all the streptomycin available in the country was in any case being used," the rest of the supply being taken up for two rapidly fatal forms of the disease, miliary and

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115 ibid.

116 ibid.
meningeal tuberculosis.\textsuperscript{117} Between January and September 1947, 109 patients were enrolled. On the basis of clinical, radiological and bacteriological comparison of the two groups, the report established conclusively that streptomycin was of value in the particular form of pulmonary tuberculosis studied.

Several months earlier, in April 1948, \textit{The Lancet} published the MRC tuberculosis committee's report on its other main clinical trial of streptomycin, in treatment of tuberculous meningitis in children.\textsuperscript{118} The trial report covered 105 patients who were admitted under the MRC scheme between January and September 1947. At the latter date the health Departments made streptomycin available to tuberculous meningitis patients at selected hospitals throughout the UK, on the basis of the MRC's preliminary findings and American reports. The MRC's patients remained under treatment for at least six months and were then observed in follow-up studies. About a third of patients in the trial survived, in contrast to the almost invariably fatal outcome previously. The meningitis paper is only occasionally cited, invariably to repeat the argument that the committee adopted untreated concurrent controls only when this procedure was considered scientifically valid and ethically sound.\textsuperscript{119} The Non-Tuberculous Conditions Committee produced an interim report in 1948,\textsuperscript{120} but Wilson was told by MRC headquarters in 1950 not to bother "going to the labour of preparing a final report" if there was "nothing very fresh to say".\textsuperscript{121}

\begin{thebibliography}{9}
\bibitem{117} ibid, p.770.
\bibitem{118} Medical Research Council, "Streptomycin treatment of tuberculous meningitis", \textit{Lancet} 1(17 Apr 1948), 582-596, hereafter cited as MRC, "Streptomycin treatment of tuberculous meningitis".
\bibitem{120} Clifford Wilson, "Streptomycin in non-tuberculous infections: Summary of a report to the Medical Research Council", \textit{Lancet} 2 (18 Sep 1948), 445-446; \emph{idem}, "Streptomycin in non-tuberculous infections: Summary of a report to the Medical Research Council", \textit{BMJ} 2 (18 Sep 1948), 552-553.
\bibitem{121} Ware to C. Wilson, 19 May 1950, FD1/7944.
\end{thebibliography}

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The standard story was amplified slightly in the MRC’s report for the year 1945-1948. Most importantly, the country’s foreign exchange problem was introduced as an explanation of the purchase of what it referred to as the limited amount of streptomycin. Conditions in Great Britain, the report explained, had been very different from the USA where streptomycin was readily available, for there was at that time (1946) no practical possibility of the drug being made in substantial quantity here, and its purchase in the United States must involve a heavy expenditure of dollars which were badly needed for the purchase of food and other necessities. The authorities in this country therefore decided to permit the purchase of only a limited amount of streptomycin from America until tests, organised by the Council on behalf of the Ministry of Health, had confirmed the practical value of the drug both in Tuberculosis and in the other infections in which it might be indicated, and had demonstrated the magnitude of risks attached to its use.\(^{122}\)

In a number of scientific publications over the years, the pulmonary tuberculosis trial was presented as a model of experimental design; often the standard ethical defence of the use of an untreated control group was repeated.\(^{123}\) A senior MRC official made a nationalist argument that confirmatory tests were sometimes needed when American reports on drugs launched in that country were inconclusive but


sufficiently encouraging to create an urgent demand in Britain.\textsuperscript{124} Landsborough Thomson’s official history of the MRC boiled down poignant earlier comments about "painful" refusals of numerous requests for the drug to the matter-of-fact statement that untreated controls were justifiable "in view of the shortage of supplies in Britain at that time, in relation to the large number of available subjects".\textsuperscript{125} In the 1970s, medical reformers promoted the randomized controlled trial (RCT); the MRC’s pulmonary tuberculosis trial is frequently credited with being the first RCT, or the first modern clinical trial.\textsuperscript{126} In the new journal \textit{Statistics in Medicine}, a special issue dedicated to Sir Austin Bradford Hill traced the spread of statistical methods in medicine to his 1937 series in \textit{The Lancet}.\textsuperscript{127} Clinical researchers have produced numerous retrospective accounts of developments in medical statistical methods.\textsuperscript{128} In recent years there has been


some debate about whether some other clinical trial might have priority over the MRC streptomycin study in the use of randomization.\textsuperscript{129}

The standard story of streptomycin clinical trials tends to present an idealized interpretation of the British government's streptomycin programme. For one, it selects the elements that show the ethical sensibilities of the trial planners in the most favourable light. The frame of the standard picture of ethical issues, includes only the patients enrolled in the MRC's trials. Doll, for example, suggests that the MRC committee was ahead of its time in showing ethical concern for experimental patients before formal ethical review panels had been institutionalized.\textsuperscript{130} With his focus on trials alone, he does not rebut or even address Waksman's claim that the government misled the British public about the toxicity of the drug.

The standard account is also idealized in another sense. The historian of medicine Harry Marks has criticized this tendency in much of the historical literature on controlled trials, in a 1988 paper, and more recently in The Progress of Experiment: Science and therapeutic reform in the United States, 1900-1990.\textsuperscript{131} He draws attention to the social and organizational factors involved, in quantitative approach to prevention of disease", Addition 92.6 (1997): 657-666.


\textsuperscript{130} Doll, "Development of controlled trials"; \textit{idem}, "Clinical Trials: Retrospect and prospect", p.338.

addition to conceptual factors, in making modern clinical trials possible. While the standard account in Britain acknowledges that the shortage of streptomycin played an *enabling* role, it is still idealized in that it treats scientific reasoning as the main driving force behind the trials. The standard account of streptomycin is based on a single explanatory factor. It has been assumed that *the* motivation for the streptomycin trials was the need to find new scientific knowledge in order to improve medical treatment. The government consistently presented its research to the public in such terms. As one contemporary statement put it, "The object is to obtain as much information as possible about the value of streptomycin and the methods of its use by the time supplies become generally available to the medical profession." The historical actors have, in retrospective accounts, continued this emphasis, portraying research into the properties of the drug as having been motivated by a desire to advance scientific knowledge. This is valid but it is only one part of the story. Original private documents from the time show that these same scientific writers treated research as a means to achieve administrative ends. Moreover, as I have seen, a general mandate for the advancement of scientific knowledge left considerable room for discretion in how it would be implemented. Thus, for example, scientific factors alone are not sufficient to explain why tuberculosis was given priority, why its priority was not made exclusive, or why the committee insisted that the scale of trials should be large.

It would be churlish to dwell on all the differences between the archival record and the standard accounts, which were surely put forward in good faith on the basis of familiar sources. There are straightforward reasons for the emphases found in the existing story. The unit of the Ministry of Supply that handled penicillin and streptomycin was soon transferred to the Ministry of Health, which may account for the complete absence of the MoS from the standard story. Self-effacing accounts by senior headquarters officials such as Green and Thomson are partly the cause of an overemphasis in the literature on the clinical committees, to the exclusion of most other actors. British production of streptomycin before 1948 was plagued by difficulties, and no one has rushed to call attention to it, whereas the achievement of effective chemotherapy in tuberculosis and the use of random allocation are success stories, so it is no wonder they have been emphasized.
Finally, as the use of untreated controls has remained controversial, it is understandable that accounts should emphasize how small the supply of streptomycin was in relation to the number of patients, rather than how large it was in absolute and financial terms.

6.5 Conclusion

Section 6.2 described the delegation of responsibility for clinical trials to clinicians. These men were important to the MRC partly as a link between its research programme and the medical profession. In this respect, the choice of Marshall as chairman reflects the need for legitimacy. As we saw in Chapter 3 that the MRC continually told enquirers that streptomycin supplies had to be reserved for clinical trials, it is clear that those designated to run these trials had to enjoy the respect of the profession.

Section 6.3 turned to the specific design of the clinical trials. This aspect of the introduction of streptomycin into Britain has received more historical coverage than any other; however, previous accounts have continued to follow the line originally presented to the medical profession and the public in the original publications in 1948. Here for the first time I presented archival evidence of how the planning took place. The word "random" and its derivatives occur nowhere in the MRC streptomycin files for 1946. The fuller picture I have presented of the context of the trials shows the importance of factors such as management of public requests for the drug during the shortage, and protecting the integrity of the admission process, in the design of the clinical trials.

Section 6.4 shows the evolution of the standard story, the progressive fading from memory of the involvement of British industry and of the intensity of public demand. It suggests why the story we have on record so far has been incomplete.
Chapter 7. Purchase of Streptomycin

7.1 Introduction

Three policy questions on streptomycin supplies are examined in this chapter. Would the British government agree to purchase a substantial quantity of streptomycin made available from American sources? Would it place an order with British firms for substantial quantities of the drug? And if it was decided to procure the drug from either or both sources, which governmental Department would be held responsible for the expenditure? It is well known within the contemporary history of medicine that the first of these questions was answered in the affirmative. This purchase allowed the Medical Research Council’s famous clinical trial of streptomycin in pulmonary tuberculosis to begin soon afterwards. But the circumstances of the purchase have not been explained fully until now. In mid-November 1946, a senior Treasury official approved the spending of some £80,000 on the purchase of streptomycin which had been offered for export by the American authorities. His decision constituted the British government’s first major financial commitment in the area of streptomycin. Appendix D consists of the MRC’s letter to him regarding the three questions with which we are concerned. The letter illustrates, in the most eloquent manner, the framing of information by the MRC in such a way as to achieve its own administrative goals. In this letter we see, in particular, the presentation of clinical trials as a way of addressing the government’s problems around streptomycin supplies. One such problem was the control over the distribution of the drug while it was in short supply. Another was the production of medical knowledge. In the discussions of both domestic and imported streptomycin for clinical trials, we shall see that the numbers representing the quantities of the drug constitute a rhetorical resource which reveals important institutional relationships.

In Section 7.2, I present the dispute between the Ministry of Supply and the MRC over which Department would be held responsible for the cost of British streptomycin for clinical trials, in the context of the agreement they had reached in the spring. Section 7.3 describes how the American offer came to be known to the
Departments, and the suspicious attitude with which the offer was greeted inside the Ministry of Health. Section 7.4 briefly describes the Treasury’s oversight of the MRC, giving the important financial context for the approval of the large imports in 1946. Section 7.5 contains a close analysis of the letter which argued that the Treasury should accept the American offer. Section 7.6 briefly summarizes the policy decisions which soon emerged.

7.2 The question of British purchases

Thomson wrote to Everett on 22 October regarding the supply of streptomycin of British manufacture for the stated purpose of clinical trial by the MRC. This subject, he recalled, had been discussed in their recent telephone conversations. Thomson stated that Everett had referred him to a letter from the MoS Permanent Secretary, dated 1 April, and, attached to that letter, the memorandum of the agreement reached between the MoS and MRC on 19 March. The memorandum stated in paragraph (4b):

The Ministry of Supply will be responsible for developing, at the request of the Medical Research Council, a method of producing a new substance in sufficient quantity for clinical trials and also for the production of that quantity. In carrying out this responsibility the Ministry will, wherever practicable, endeavour to carry out the work itself but there may be cases where the Ministry may find it necessary, after consultation with the M.R.C., to place a developmental contract with industry. The Ministry of Supply will carry out such services on an agency basis, the cost being borne by the M.R.C.\(^2\)

Franks, in the cited letter concerning what he referred to as "suggested

\(^1\) Thomson to Everett, 22 Oct 1946, FD1/6764.

\(^2\) Memo 295/Med/1627, Division of Responsibility between MRC and MoS as agreed at a meeting held by C.S.O. on 19 Mar 1946, FD1/7009. My emphasis.
arrangements" agreed at the meeting, had proposed to Mellanby, "if you agree we can now regard these arrangements as operative". Thomson asserted in October:

We have refreshed our recollection of this agreement and in our view it is not applicable to the particular case. What we had envisaged at that time was the production for clinical trial of new substances discovered in the course of our own research work. Streptomycin, on the other hand, is an American discovery, which in this country goes straight to the development stage. This argument may be purely academic, however, as you had agreed in any event that it would be appropriate for the cost of streptomycin supplied for clinical trial to be charged to the vote of your Ministry.4

It is possible, although the issue is unclear, that Thomson's argument was based on paragraph 2 of the agreement, which said, "It is agreed that the Medical Research Council will be responsible for fundamental research leading to the discovery of promising substances and then that the Ministry of Supply should, at the request of the M.R.C., develop and produce sufficient quantities of such substances for extended clinical trials."5 An interpretation giving weight to this paragraph could be taken to support the claim that the scope of the agreement covered only those substances discovered by the MRC. However, paragraph 4 of the agreement stated that it was in the national interest for the MoS "to provide assistance to the M.R.C., for the development of promising antibiotic and therapeutical substances up to small-scale production"—6 that is, without specification of the origin of these substances— and it was to this latter paragraph

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3 Franks to Mellanby, 1 Apr 1946, FD1/7009.

4 Thomson to Everett, 22 Oct 1946, FD1/6764.


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that the remarks I have quoted on cost were subsidiary. Furthermore, it is puzzling that Thomson claimed that the Ministry of Supply had agreed that it would be appropriate for their Department to bear the cost of streptomycin for clinical trials. The previous week, he himself had sought Treasury approval to pay for the 600 grams of streptomycin under the MRC's current grant-in-aid. And while it is possible that an oral suggestion regarding payment had been made to the MRC by one of the officials from Penicillin Production Control, in the course of the various planning meetings and telephone conversations, it is hard to believe that a bureaucratic Department like the MoS could have left unwritten a financial undertaking as important as this. It is puzzling that Thomson cited no supporting documentation. Finally, it is not entirely clear on what basis the Ministry of Supply could have been asked to pay for this material if it had, as Thomson argued, fallen outside the scope of the 19 March agreement—although we shall see below that as the production Department for medical supplies, the MoS was seen as accordingly responsible by Ministry of Health officials. In any event, Thomson closed his letter by informing Everett, who was on the production side of MoS based at Shell Mex House in the Strand, that an explicit request for the British streptomycin was being put to a colleague who was on the financial side of the Ministry, based at Portland House in Whitehall.

That same day, 22 October, Thomson wrote to that colleague, F.J. Doggett, Assistant Secretary for non-munitions supplies. The introductory information provided to Doggett in this letter suggests that this was the first time

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7 There is one final complication which suggests that the scope of the agreement had not been carefully thought through by the MRC officials. Namely, as Mellanby pointed out in a letter to Harington, the text of the agreement was open to the interpretation that it was not confined to antibiotics but covered all substances of chemotherapeutic interest, even though, as Harington recalled in a responding letter, "[t]he whole of the discussion on which the draft agreement... was based was concerned with antibiotics as such. A more correct wording would have been antibiotics of therapeutic interest." Mellanby to Harington, 9 Apr 1946; and Harington to Mellanby, 13 Apr 1946, FD1/7009.

8 Thomson to Stephens, 16 Oct 1946, FD1/6751.

9 Thomson to Everett, 22 Oct 1946, FD1/6764.
the MRC had corresponded with him on the subject of procurement of streptomycin. Thomson’s remarks bear quoting, as a characterization of the purposes for which clinical trials were propounded:

The Medical Research Council have been considering plans for implementing the proposal that they undertake clinical trials of the streptomycin about to be produced in this country, in order that full information as to its value in different conditions and the best methods of its use may be available by the time the manufacturing output makes possible some general distribution to the medical profession.¹⁰

This was immediately followed by the statement, "They have come to the conclusion that to carry out adequate trials in tuberculosis and other conditions 100 kilogrammes will be required".¹¹ This figure can only have come from the MRC staff. During the summer when the MRC held its conferences in July and August for the planning of clinical trials, the figure under discussion was 75 kilograms.¹² Moreover, Thomson’s letter to Doggett was sent almost a month before the first meeting of the MRC’s Streptomycin in Tuberculosis Clinical Trials Committee.¹³ Whatever the source of his figure of 100 kilograms might have been— and we shall see in Section 7.5 that its apparent arbitrariness is a matter of some interest— Thomson requested that the MoS carry out arrangements for obtaining this material. And although Everett had already claimed that MoS had no obligation to pay for the material, Thomson closed his letter by declaring, without any elaboration, "It is presumed that the cost would be borne by the Ministry of Supply."¹⁴ Doggett’s response, a week later, was terse. He insisted, quoting the

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¹⁰ Thomson to Doggett, 22 Oct 1946, FD1/6764.

¹¹ ibid.

¹² e.g., Mellanby minute, 24 Jul 1946; Extract from PPC MoS to Marchbank, 27 Aug 1946, both FD1/6756.

¹³ Minutes of first meeting Friday, 21 Nov 1946, FD1/6756.

¹⁴ Thomson to Doggett, 22 Oct 1946, FD1/6764.
agreement reached at the meeting on 19 March, "where the Ministry of Supply carried out services for the Medical Research Council... the cost would be borne by the Medical Research Council. This position still obtains."

He reported to Thomson that the cost of 100kg of streptomycin was estimated to be between £200,000 and £300,000, and he predicted that delivery of this material would be spread between February and November of 1947. He summed up, "If, in the light of the foregoing, you confirm your demand on us for 100 k.g. arrangements will be made to meet it." And there matters between the MoS and MRC rested, until the situation was further complicated by the American offer of streptomycin.

7.3 The question of a major American purchase

We left the story of imports from America at the point of the Treasury's agreement that the MRC could purchase the 600 grams of streptomycin which the US Department of Commerce had released to Britain for the month of October 1946. What happened next regarding the export quota for the month of November is rather hard to determine. According to Keith Macrae's letter to the MoS Director of Medical Supplies, F. Warburton, dated 11 October, N.H. Foster from Commerce had explained the export quota procedure at the meeting the previous day. This procedure would be that, towards the end of each month, the British Supply Council would be informed about the following month's allocation. It is thus very likely that late in October, Foster informed Macrae that the UK was to be allocated 50 kilograms of streptomycin. Moreover, at a meeting at Portland House on Thursday 31 October, on the establishment of a provisional British standard for streptomycin, Raistrick is reported to have assured those present that

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15 Doggett to Thomson, 29 Oct 1946, FD1/6764.

16 ibid.

"ample supplies" of streptomycin of a certain potency would be available within 6 months.\textsuperscript{18} This potency, 300 units per milligram, was above what the British manufacturers had said at the meeting they would be able to achieve on that schedule.\textsuperscript{19} The discrepancy aroused the interest of Marchbank, who described this to Dalrymple-Champneys, in a memo written on the following Monday, as the only point of doubt in his mind.\textsuperscript{20} He went on, "I asked M/S. [the Ministry of Supply] to-day how Raistrick could give such an assurance in face of the expressed views of the manufacturers. The answer (very hush, hush!) is that U.S.A. manufacturers are offering M/S streptomycin at cut prices for the M.R.C.!!\textsuperscript{21} Dalrymple-Champneys responded on Tuesday with a note that he had spoken with Everett about the situation.\textsuperscript{22} The Deputy CMO's recorded recollection of this conversation provides information which is notable for its inaccuracy, although it is (barely) conceivable that Everett was the source of the erroneous details. "It appears that M.R.C. have accepted an offer of 500 Gms. from U.S.A. towards their clinical trials & on Friday next are to consider a much bigger offer (I think 5 Kg.) from Merck via. Glaxo."\textsuperscript{23} In the first place, no other document had mentioned the figure of 500 grams since the abortive attempts in the spring to procure that amount for the stated purpose of clinical trials in plague. By this date, 5 November, the officials of PPC were aware that there were 1800 grams on offer-- we know from the fact that Thomson had been so informed-- up from the initial October allocation of 600 grams.\textsuperscript{24} Second, the figure which it turned out

\textsuperscript{18} Meeting Held at Portland House, 31 Oct 1946, Subject-- Specification of Streptomycin, MH58/636.

\textsuperscript{19} ibid.

\textsuperscript{20} Marchbank to DCMO, 4 Nov 1946, MH58/636.

\textsuperscript{21} ibid.

\textsuperscript{22} Dalrymple-Champneys annotation to Marchbank, 5 Nov 1946, on Marchbank to DCMO, 4 Nov 1946, MH58/636.

\textsuperscript{23} ibid.

\textsuperscript{24} Thomson to Stephens, 5 Nov 1946, FD1/6751.
was to be considered by the MRC, 50 kilograms, was ten times that mentioned by Dalrymple-Champneys, and if the total quantity required per patient was \( \frac{3}{4} \) of a kilogram, it is hard to imagine 5 kilograms being alluded to by Raistrick as "ample". Third, I have seen no evidence elsewhere that Glaxo was involved at all as an intermediary in this transaction. The DCMO continued, "I think that in the circumstances we cannot object to anything which will speed up the clinical trials by the M.R.C., but I have told Mr E. I am not happy as to the future of our own manufacturer[s] (if the report of the S. Clin. Trials Ctee. is favourable) & he has promised... to watch the position and keep me informed."

On the next day, Wednesday, Marchbank drew the DCMO's note to the attention of Alan Marre, the Assistant Secretary responsible for medical supplies: "You may like to see this. We, of course, cannot wish to stop supplies of penicillin streptomycin being sent here for clinical trial, but large scale commercial importation before British firms are through their teething troubles may be disastrous. Glaxo, who are building a £500,000 plant, will be 12 or 15 months before they are in full production. This argument was amplified in his memo, dated the following Tuesday, 12 November:

> In view of the publicity given to Streptomycin as a cure of T.B. and of conditions due to bacillus coli and other organisms against which Penicillin is useless, we should be on very weak ground in refusing the [sic] accept all we can get (at a reasonable price) for the treatment of T.B. pending British manufacture getting into its stride.
> But I think we should (as with Penicillin) keep purchase and distribution under close Government control for the dual purpose

25 Dalrymple-Champneys annotation to Marchbank, 5 Nov 1946, on Marchbank to DCMO, 4 Nov 1946, MH58/636.

26 Marchbank to Marre, 6 Nov 1946, MH58/636. It is possible that at least the first slip in Marchbank's handwritten annotation was made deliberately, though the association between streptomycin and penicillin might have been so close in his mind that it was genuinely inadvertent. In either case, the parallel is clear between the streptomycin situation and that which the MoH had previously faced with regard to American penicillin competing against the domestic product.

27 Marchbank to Marre, 12 Nov 1946, MH58/636.
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(a) directing supplies into the most profitable channels and preventing waste and mis-use. Streptomycin is almost certainly subject to the same dangers to the community as is Penicillin if used inexpertly and indiscriminately;
(b) preventing for the present commercial importation which may kill any hope of establishing British manufacture.

Marchbank's memo was written in response to an invitation Dalrymple-Champneys had received, to an inter-Departmental meeting at the MRC on the 15th. It would seem that this meeting was the one which of which Everett had spoken to Dalrymple-Champneys on the 4th or 5th, as planned for "Friday next".

Regarding the figure of 50 kilograms, the earliest explicit reference I have found comes from the correspondence between Thomson and the Treasury in mid-November. This figure is, on the face of it, rather surprising. It was announced in the CPA bulletin of 30 October that the American research programme to be run under the direction of Hinshaw would be allocated a supply of 9 kilograms of streptomycin per month for six months. Thus it is quite remarkable that the British researchers should have had access to a total quantity only 4 kilograms less than that available to their American counterparts. Second, there is the question of how Commerce settled upon this figure. There is a curious coincidence, which might be purely accidental or might suggest that the Ministry of Supply was able to exert some influence on the American authorities. Back in the summer, Mellanby had requested 75 kilograms of streptomycin in discussion with Raistrick, and we can be certain that this figure was well known throughout PPC because Raistrick's query had been made for the purpose of setting production targets for British industry. It is possible that the 75kg figure was made known as well to Macrae in Washington, perhaps at the time of Hambro's request for streptomycin in October. It was recorded in the minutes of the British meeting on specification of streptomycin, attended by six officials from MoS, that the American standard

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28 FD1/6764.

29 CPA press release, FD1/6751.
had been set at 400 micrograms per milligram in July 1946.° The material on
the American market in November had a potency of 600 micrograms per
milligram. Thus 50 kilograms of this latter material would contain exactly the
same amount of the active ingredient, the streptomycin base, as 75 kilograms of
material having the potency which it would seem some MoS officials believed,
erroneously, to have been standard when Mellanby made his estimate of
requirements. Thus it is just possible that the U.S. Department of Commerce set
its quota for November exports of streptomycin to the UK on the basis of
Mellanby's original suggestion of what would be necessary for clinical trials in
Britain. One missing link in this speculation, of course, is the nature of the
discussions between Washington-based MoS officials and the American authorities,
on which I have not been able to locate any information in the files of the Office
of International Trade.

Whatever the reasons were that Commerce set the November export quota
to Britain at 50 kilograms, the American decision set in motion a train of events in
Britain of lasting significance. The British government's acceptance of the
allocation has been seen as crucial to the form that the MRC's clinical trials took,
and it also initiated a series of major expenditures. Thus the arguments which the
MRC put to the Treasury regarding the streptomycin position deserve close
scrutiny.

7.4 Treasury oversight of the MRC

° Meeting Held at Portland House, 31 Oct 1946, Subject-- Specification of
Streptomycin, MH58/636. We know now that the standard of the FDA (which
then belonged to the Department of Agriculture) was actually "300 micrograms of
streptomycin base per milligram of dry powder". FDA Specifications for
Streptomycin, effective 15 Jul 1946, FD1/6752. It would appear, however, that
this information on potency was not known to Macrae until mid-December, as it
was only then that he told Lester, "You will note that in the enclosed pamphlets on
streptomycin given to me by Dr. Welch of the Department of Agriculture, it states
that the minimum potency of commercial streptomycin shall represent not less than
the equivalent of 300 micrograms of streptomycin base per milligram of dry
powder". Macrae to Lester, 16 Dec 1946, FD1/6752.
To this point I have been discussing the relations among the various "spending Departments" of the British government. But these must also be understood in their relation to the Treasury, which exercised control over the annual Votes of the Departments, and somewhat lesser control over the detail of the Grant-in-Aid which was received by the MRC. It is a commonplace in Whitehall that Treasury officials had the fullest overview of the government's activities, in contrast to the narrower scope of the departmental views as documented in other files. Thus the negotiations with the Treasury over streptomycin purchases can be seen to reveal the interplay of departmental interests. Furthermore, I suggest that it was largely through Treasury that the overall priorities expressed by the Cabinet came eventually to affect the Departments' handling of the streptomycin issue.

The entire grant in aid provided by Parliament for the current expenditure of the Medical Research Council for 1946-47 was £380,000, of which approximately £130,000 was for clinical research. In the fiscal year 1946-47 the MRC overspent its original Estimate. Discussion of this amongst Treasury officials suggests that they were more concerned that proper process be followed than they were with the gross amounts being spent. One example of this is the question of virement, that is, the spending of money for a purpose other than that for which it was originally budgeted. It happened that the MRC had budgeted to spend £100,000 during fiscal year 1946-47 on new buildings at the NIMR in Mill Hill, but spent only half that, reportedly because the lack of building materials had slowed down construction. The question was put to Treasury whether that money could be spent elsewhere by the MRC, as it simultaneously had gone over its main Estimate by £35,000. The increase in the Council's research programme, Thomson suggested, had arisen from "the return towards peacetime conditions in general and from specific requests by Government Departments in particular." These

31Sequence 10, Stephens to Thomson, 10 May 1946, T227/1024.

32This happened again in FY1947-48, Sequence 127, Thomson to Hale, 18 Dec 1947, T227/1024.

33eg, sequence 62, Hale to Sugars, 9 Dec 1946, T227/1024.
included, he wrote, an increase in the Council's "effort in respect of pulmonary
disease among coalminers and of the application of new knowledge of nuclear
physics to medical problems." The Under Secretary, Hale, wrote to a Treasury
official, "I don't think we can question the need of an additional £35000 on the
main grant in aid." The saving, however, presented a potential problem of
accounting, on which Hale asked this official, Sugars, for an opinion. Sugars
replied on 16 Dec that TOA (the Treasury Officers of Accounts) advised against
virement.

The MRC's overspending, at a time when the government was under
financial pressure, occasioned some discussion among Treasury officials as to how
they might exercise control; a surviving example is a memo from Stephens to
Hale. The former, a Principal, reminded the Under Secretary that the whole
MRC program had been put to the Lord President's Committee in Jun 1946. There
the program was noted with approval, Stephens quoted, "on the understanding that
the Chancellor of the Exchequer was not committed to finding the necessary
money to finance the proposals. [sic] in the programme". Stephens went on in

34sequence 60 and 61, Thomson to Hale, 5 Dec 1946, T227/1024.

35sequence 62, Hale to Sugars, 9 Dec 1946, T227/1024.

36sequence 62, Hale to Sugars, 9 Dec 1946, T227/1024.

37[annotation on] sequence 62, Hale to Sugars, 9 Dec 1946, T227/1024. Sugars wrote that the saving would appear as a deduction in a Supplementary
section.

38Sequence 89, Stephens to Hale, 4 Feb 1947, T227/1024.

39L.P. (46)142 and 23rd conclusions of 28 Jun 1946, CAB132/1; as well as the
excerpt quoted by Stephens in T227/1024, a full copy of the Conclusions is filed
in T227/1027. This research program had included, under the heading,
Tuberculosis, "The study of tuberculous disease, with special reference to the
development of new methods for its prevention and treatment". It mentioned a
projected Tuberculosis Research Unit, and cross-referenced the research proposals
for Chemotherapy, which specified, "The preparation, preliminary testing in
animals, and trial in man of new chemical substances for the prevention or
treatment of bacterial infection and of tropical diseases such as malaria". Sequence
13, Medical Research Council Programme, MRC.46/104, 10 May 1946,
T227/1027.
his letter to Hale:

This latter proviso gives us some liberty of action, if we wished to make a cut. But if a cut were imposed, [it] would have to be of a general character, made on the grounds that, in the present state of the national finances, there is only, say, £400,000 and not £500,000 of public money available for medical research—*leaving it to the M.R.C. to determine their own priorities*. I do not see any particular point at which we can usefully prune the present proposals.40

That is, in this and other documents, Treasury did not propose to exercise line-item control over scientific research—in contrast to their detailed scrutiny of some other aspects of spending by Departments.

### 7.5 The MRC's Appeal to Hale

We have already seen the disagreement between the MRC and the MoS over which of the Departments would be financially responsible for the placing of a large and expensive order with British firms for streptomycin for clinical trials. Added to this situation was the allocation by the U.S. Department of Commerce of an export quota to Britain for November of 50 kilograms of streptomycin, which was very clearly also an expensive proposition. It was in this context that Landsborough Thomson wrote on Monday 11 November 1946 to Edward Hale, Under Secretary at the Treasury, to outline the position, which he said "urgently calls for discussion". His three-page letter, which I have dubbed the Appeal to Hale, or simply the Appeal, is reproduced in full in Appendix D.41 Thomson informed Hale that the MoS and MRC were to hold a meeting at MRC headquarters in Old Queen Street on Friday 15 November. He ended his letter by saying, "I hope to hear that you or someone else from the Treasury will be able to attend our meeting, as we cannot get much further without some guidance on financial policy." Thomson sent copies of this letter, with brief covering notes, to

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40 Sequence 89, Stephens to Hale, 4 Feb 1947, T227/1024, emphasis added.

41 Thomson to Hale, 11 Nov 1946, FD1/6764.
Everett at the MoS, and to Dalrymple-Champneys at the MoH. The latter note contains the suggestion to the Deputy Chief Medical Officer, "I hope that you or one of your people will be able to attend our meeting here... I imagine that you may wish to bring an administrative colleague, who will likewise be welcome." This I interpret as a coded attempt by Thomson to have the Ministry of Health represented at the meeting by someone he regarded as more competent than Dalrymple-Champneys. This interpretation is consistent with correspondence among those MoH administrators, who made a point of seeing that whoever attended would be well-briefed, although the DCMO himself did not seem averse to being accompanied, asking Marchbank if he would go. Marchbank suggested to Marre on the Tuesday, "A talk with D.C.M.O. before Friday might be helpful." On this letter, Marre made an annotation on Wednesday addressed to Enid Russell Smith, then a Principal Assistant Secretary. He told her, "As I shall be away all tomorrow also, can I pl. drop this on you? The D.C.M.O., I gather, wd. like a word." Marre also suggested, regarding H.B. Riddle, the Ministry’s Deputy Accountant-General, "perhaps he ought to be at the meeting". In any case, we shall see that Dalrymple-Champneys went alone from the Ministry of Health.

We know little about how the Appeal to Hale was prepared within the MRC. No early draft of the document survives, and there is no record of who was consulted about it prior to posting. No written record survives of discussion

42 Thomson to Everett, 11 Nov 1946, FD1/6764.

43 Thomson to Dalrymple-Champneys, 11 Nov 1946, FD1/6764.

44 Dalrymple-Champneys annotation to Marchbank, on Thomson to Hale, 11 Nov 1946, MH58/636.

45 Marchbank to Marre, 12 Nov 1946, MH58/636.

46 Marre annotation to Russell Smith, 13 Nov 1946, MH58/636.

47 ibid.

48 The carbon copy kept at MRC headquarters was at some time initialled by Green, Whittaker and the Finance Officer, D.V.T. Fairrie.
within the Ministry of Supply. The Treasury file which covers the MRC's annual grant-in-aid shows signs of heavy weeding.\(^49\) It contains one of Stephens' letters regarding the MRC's purchase of the 600 grams, but no copy of the Appeal nor indeed any document whatsoever referring to the 50 kilograms of streptomycin.\(^50\)

As for the Ministry of Health, we have an interesting discussion, some of which we saw in the previous Section.

As we look at the Appeal in overview, two points stand out. First is that in the rhetorical structure of the Appeal, the potential purchases of American and British streptomycin are treated as parallel cases. This should be borne in mind to keep in perspective the fact, which is emphasized throughout the historical literature on the subject, that the American purchase was approved. Second, I stress the centrality of clinical trials to the argument put forward in making this claim on the government's economic resources. Repeatedly in this document, clinical trials are presented as a rational means of dealing with the various problems with which the government was confronted.

We can identify three basic questions which Thomson put forward to Hale for arbitration: (Paragraph 4) Should the British government purchase a large quantity of domestically-produced streptomycin? (Paragraph 6) Should the British government purchase a large quantity of American streptomycin? And (Paragraph 7) if either purchase were made, which Department should be responsible for the expenditure?

The third of these questions involves what are perhaps the most straightforward arguments. Thomson reported the Ministry of Supply's assertion that it was not permitted to pay such costs. He anticipated a claim which might be made against the MRC's resources, namely that under the agreement (which he did not identify) the Council would be responsible for the costs of material

\(^{49}\) T227/1024. This file was previously labelled SS71/01, which according to the PRO "Yellow Book" incorporated S.11047/2, which was the file reference on any Treasury correspondence regarding streptomycin which I have found in MRC files. The file S.55498, which Treasury later opened on streptomycin finances, presumably removing relevant documents from S.11047/2, was incorporated into SS53/02, which is listed as having been destroyed.

\(^{50}\) sequence 58, Stephens to Thomson, 29 Oct 1946, T227/1024.
produced for clinical trial. But he responded to this claim by reiterating the Council's position that this agreement was inapplicable to the case of development of a drug discovered elsewhere. His main argument for the MRC not being saddled with the cost was simply that it would be very large in relation to the organization's total budget. Recall that the MRC had for 1946-47 a Grant-in-aid of £380,000 and special grant in aid of the completion of the NIMR building £100,000. The Council's spending on clinical research during the financial year 1946-47, was later estimated at approximately £130,000. We can be fairly sure that this estimate, generated in response to a Parliamentary Question from an opponent of animal experimentation, did not understate the amount the Council spent on research using human subjects. Thus the figures of £80,000 for American streptomycin and £100,000 to £300,000 for British streptomycin do indeed look large by comparison. The third possible Department which might be asked to pay for streptomycin, the Ministry of Health, had, as Thomson wrote, not been consulted as yet. His suggestion that they might be considered responsible was greeted within the MoH by Marchbank's declaration: "On the question of purchase, surely this should be borne by the Ministry of Supply vote. At the recent meeting of the D.R.A.C. [Drug Requirements Advisory Committee.] Ministry of Supply laid down that procurement of drugs was solely for the Ministry of Supply." Marre responded, "Mr. Riddle needs to be consulted on the question of the Dept. on whose account the charge would have to be borne. I

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51 Sequence 10, Stephens to Thomson, 10 May 1946, T227/1024. Hale was informed in October by Stephens that the MRC were contemplating a Supplementary Estimate, but this was not formally submitted until December. Sequence 59, Stephens annotation to Hale, 29 Oct on sequence 58, Stephens to Thomson, 29 Oct 1946, T227/1024.

52 Thomson to D.O. Henley, 18 Feb 1947, FD1/4214.

53 The projected costs to the Treasury of the streptomycin were astonishing; the upper estimate for domestic streptomycin, £300,000, was close to one thousandth of the entire British central government spending for 1946 on health, labour and insurance. (The figure of £334 million under this heading is quoted in Butler and Butler, British Political Facts, 6th ed, p.390.)

54 Marchbank to Marre, 12 Nov 1946, MH58/636.
Let us turn now to the questions of whether streptomycin should be purchased, and if so from which source or sources. The potential British acquisition was described by Thomson as being for the purpose of "a series of controlled clinical trials". Here we see that clinical trials were presented as responding to a need for medical knowledge: "It is clearly desirable that before Streptomycin becomes more generally available to the medical profession there should be soundly based knowledge of its value in different conditions, but particularly in tuberculosis, and of the methods of its use." He went so far as to suggest that the medical question of the value of streptomycin in tuberculosis could be "settled". Thus we see the need for clinical trials being reasserted by Thomson. These clinical trials were undertaken by the MRC at the request of the Ministry of Supply, he wrote, to test the British product. The British firms, he said, were expected to produce "limited quantities" of streptomycin "within the next few months. The fly in the ointment, as we see Thomson arguing, was that this was "not quite so soon as had been hoped". It is in this context that we see the offer of the American product introduced in Paragraph 5 as a potential solution to this problem of the delay in the clinical trials in Britain. The time saving entailed by acceptance of the American offer was projected, in the following

55 Marre annotation to Russell Smith 13 Nov 1946, MH58/636. Riddle's named was asterisked, referring to a marginal note with the proposal I have previously mentioned, that he attend the Friday meeting.

56 Para 4.

57 ibid.

58 Para 1.

59 Para 2.

60 Para 2. Marchbank wrote early in the month that Glaxo would be "12 or 15 months before they are in full production". Marchbank to Marre, 6 Nov 1946, MH58/636. But we have no documents internal to the various Departments as to their current best estimates for the arrival of British production on a scale suitable for clinical trials. In hindsight, it appears Glaxo produced a total of 50kg only by the spring of 1949. See Green to Daniels, 10 May 1949, FD1/7944.
paragraph, as "some months". Part of the force of this argument lies in the statement that this American product was "for immediate delivery".

It is also notable that the amount said by Thomson to be required for clinical trials was "estimated at between 50 and 100 kilograms". This must be contrasted with his declaration when he placed the MRC's order with Doggett, a month earlier: "to carry out adequate trials in tuberculosis and other conditions 100 kilogrammes will be required". There are two possible explanations for this change. At the time of the earlier estimate, the MRC said it presumed that another Department would pay for the material, thus Thomson in November appears partly to be covering the MRC against the eventuality that it might be required by Treasury to pay for the streptomycin itself. More importantly, however, unless 50 kilograms was taken to constitute an adequate quantity for clinical trials, there would be no argument, on grounds of the advancement of medical science, for the Government to accept the American offer.

We can also see that this argument on scientific grounds relies on an interesting assumption, when we look at the question of the comparison of the various commercial preparations of streptomycin. In the case of a drug produced by fermentation-- and, as Thompson pointed out, not yet available in a pure preparation-- doubts might well be raised as to whether the different companies' products would have the same effect on patients. Such doubts were raised at the first meeting of the MRC's Streptomycin in Tuberculosis Trials Committee, just over a week later: "In the discussion the general view was that there was no

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61 Para 6.

62 Para 5. This would seem to be stretching the limits of the phrase, on Thomson's part, although it is not altogether clear just when the material was expected by the Departments. In the event, the first half of the 50kg allocation was delivered on 20 December, more than five weeks after the Appeal was written. Telegram, 20 Dec 1946, FD1/6751.

63 Para 4.

64 Thomson to Doggett, 22 Oct 1946, FD1/6764.

65 ibid.
objection to the bulk American supply coming from two or three firms, but that each centre should have similar proportions of the products of these firms, while each patient should have, so far as practicable, one batch from one firm. Observe as well the way that Thomson presented as clinically homogeneous, by consistent use of the phrase, "the British product", the products of what he then knew to be three different British firms, each presumably with different manufacturing processes. Likewise he acknowledged in his Appeal no distinction that might be made among the ten or twelve American firms from which "the American product" might come. He conceded in a parenthetical remark that further trials with "the British product" would "still be necessary" if the MRC ran its clinical trials using the 50 kilograms of American streptomycin. The purpose of these further trials, he stated, would be "to confirm that it gives similar results". One of his arguments for the acceptance of the American offer, we can see, hinged on the assumption that all these products were essentially similar.

Finally, it should be stressed that in making a scientific argument for the British government to purchase American streptomycin, Thomson made no explicit mention of the ongoing American program of clinical trials. In paragraph 1, he referred to "American evidence", without specifying the nature of the research by which this evidence had been generated, and notably without saying that the body of research continued to accumulate at a very rapid pace. Moreover he portrayed it as inconclusive, particularly in the case of tuberculosis. The acceptance of the American offer was proposed on the grounds that "clinical trials may be instituted in this country" earlier than would otherwise be possible. His argument on grounds of medical research, for conducting clinical trials, as quoted above from Paragraph 3, made no reference to the desirability of any particular site for such

66 Minutes of first meeting, 21 Nov 1946, FD1/6756.

67 Para 5, etc.

68 Para 6.

69 ibid. My emphasis on singular.

70 Para 6, emphasis added.

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research. It would seem that it was important for Britain itself to run clinical trials of streptomycin on grounds other than those Thomson considered to be strictly "of a research nature".\textsuperscript{71}

We have seen, to sum up so far, that there were several scientific or technological objections which could have been raised against the use of American streptomycin in British clinical trials, but that Thomson framed his argument in such a way as to gloss over them. He explicitly anticipated two other objections against accepting the offer, however: "The disadvantages of this course are, obviously, the use of dollars... and the possible repercussions on British manufacture."\textsuperscript{72} On the latter point, he made no direct rebuttal; the prospect of these repercussions considerably exercised Marchbank, among others, in days to come.\textsuperscript{73} On the former point, which is mentioned frequently when the story of British clinical trials of streptomycin is told, some clarifications are in order. In these accounts, it is suggested that the dollar shortage experienced by the British government determined the size of its purchase of American streptomycin for clinical trials.\textsuperscript{74} Against this interpretation the evidence is strong. First I note Thomson's own parenthetical remark, namely that "the actual cost in sterling is less".\textsuperscript{75} That is, the spending of dollars, an admitted disadvantage, was described by Thomson as mitigated by a potential saving of between £20,000 and £220,000; American streptomycin at a cost equivalent to £80,000 would serve nearly as well as British streptomycin costing anywhere from £100,000 to £300,000. Second, let us recall from Chapter 5 that Treasury routinely approved the spending of dollars in the case of the allocation for the month of October (which was of course much

\textsuperscript{71} The phrase comes from Para 8. There is, we can see, no substance to the suggestion sometimes made that the British government discounted the scientific value of the American research on grounds that controls were impossible in the American context of relative abundance of streptomycin.

\textsuperscript{72} Para 6.

\textsuperscript{73} eg Marchbank to Marre, 12 Nov 1946, MH58/636.

\textsuperscript{74} e.g. Thomson 1975; etc. etc.

\textsuperscript{75} Para 6.
smaller and cheaper). Third, let us look at a letter Everett wrote in December to Thomson, with copies to Doggett and Marchbank, primarily on the subject of the control of non-Governmental imports of American streptomycin. There Everett remarked, "Incidentally, there is the point that import of Streptomycin from U.S.A. means expenditure of dollars and this fact could be used as an argument for withholding import licences until the Ministry of Health is satisfied as to the merit of the drug." Thus we can see an element of opportunism in the way the dollar shortage argument was invoked by civil servants dealing with those outside government. Fourth, at the time the Appeal was made, the dollar shortage itself was not severe, according to Sir Alec Cairncross, who is widely seen as the leading historical authority on the workings of the Treasury under the Attlee governments. Cairncross has written, "The dollar problem itself did not come to the front until 1947 although officials could see it coming in the middle of 1946". Cairncross also offered the view that in 1946, imports into Britain were "artificially low" because American exporters in general were unable to keep pace with the orders they had received, and consequently there was at that time a shortage of goods on which British holders of dollars could spend them.

Finally, I reason that if dollar expenditure had been a major issue in November 1946, Hale would have needed a serious consultation with his Treasury colleagues who were primarily responsible for the expenditure of dollars, and one can hardly imagine that this matter could have been arranged, without advance notice, in the space of the four days before the meeting on the 15th. I contrast Hale’s handling of the situation in November with his actions as reported in a letter he wrote in May 1947—by which time he described the "dollar position" as "really most

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76 Everett to Thomson, 18 Dec 1946, FD1/6751.


78 Cairncross, pp.114-115.
difficult." He told Russell-Smith, "At our meeting on the 29th April I agreed to the purchase of a further 50 kg. in the United States, but said that I could not go further without authority from my colleagues who are responsible for dollars." And in the course of this letter he stated that he had authorized the original 50 kilograms. It is thus abundantly clear that in November 1946, the factor limiting the amount of streptomycin purchased for the MRC's clinical trials was the American export quota, and not any pressing concern at Treasury over the conservation of dollars.

The closing argument in the Appeal revolved around what Thomson presented as the question of "controlling the issue of streptomycin while it is in short supply". He argued, "The need for such control will arise as soon as there are supplies in excess of the amounts required for clinical trial." Thus, he wrote, if the supplies of streptomycin from either American or British sources were not wholly taken up for clinical trial, the government would have to face the issues of sale of the drug. As the background to the questions he raised in his preceding paragraphs, he painted a public "clamour for supplies" which was "likely to continue"; we have seen illustrations of the public demand in Chapter 3. The prospect of a black market in streptomycin was obvious, and had been discussed explicitly in the American context. Commercial sale could be

79 Hale to Russell-Smith, 5 May 1947, MH58/636.
80 ibid. My emphasis.
81 ibid.
82 Para 8.
83 Para 8.
84 Para 9.
86 One illustration, for example, was the Washington Star article in April 1946. FD1/6751.
predicted, moreover, to lead to economic inequality in distribution of the drug. In
the case of a drug which Thomson pointed out was claimed to be life-saving, and
in light of the political sensitivities surrounding tuberculosis among the members
of the working classes, public perceptions of unfairness in the distribution of the
drug might prove disastrous to the Labour government. On similar reasoning,
penicillin had been provided free of charge to those in Britain for whom it was
deemed medically necessary, until 1 June 1946. Only at this time, once the supply
"pipe lines" were said to be "assured" and the price had dropped to about 25
shillings per mega unit of penicillin, was that drug moved to commercial
distribution on prescription.87 In the meantime, thus, while supplies of
streptomycin remained short, distribution via clinical trials was presented by
Thomson as a fair and rational system. He wrote that control of the issue of
streptomycin would be done "so that it may be allocated to the most suitable
cases."

88 "The indiscriminate use of streptomycin... would be wasteful and often
harmful".89 An alternative mechanism for controlling distribution would be a
Control Order, as Everett was soon to discuss.90 Such an Order could be issued
by the MoH and the Department of Health for Scotland, as Thomson suggested.91
But in that case there would still remain a problem for the government of
legitimating this approach in the eyes of the public. Allocation of all the supplies
in Britain to clinical trials, while subject to some objections as we have seen in

87 "Brief for P.A.C. 1946", MH136/70.
88 para 8.
89 Para 9.
90 Everett to Thomson, 18 Dec 1946, FD1/6751.
91 Para 8. An Order could have been authorized under the Defence
Regulations. See Note of a Meeting, 16 Jan 1947, FD1/6764. In the autumn of
1947, an interdepartmental meeting discussed scheduling of streptomycin under the
Therapeutic Substances Act, 1925, which restricted the importation of various
medicines of biological origin, or the Penicillin Act, 1947. Such scheduling was
described by Marchbank as involving administrative machinery which would be
"rather cumbersome" and which would take some months to implement. Extract
from minutes of meeting, 7 Oct 1947, MH58/622.

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Chapter 3, at least was widely seen as a policy which would contribute to the advancement of science.

In the Appeal to Hale, we see reflected, and carefully framed, many of the key issues surrounding the supply of streptomycin in Britain in 1946: the uncertainty about the clinical value of streptomycin, the problem of public clamour for the drug, the risk of waste and harmful usage, the claim that clinical trials would advance medical knowledge, the tensions among Departments over financial responsibility. The Appeal is intriguingly almost silent on other aspects of the streptomycin position, however, in which certain information would be damaging to the MRC’s case: the problem of comparing streptomycin preparations from different firms, and the relationship of the MRC’s research to clinical trials in the USA. The Appeal stands as a brilliantly argued document. With such a powerful case laid before Hale, it now seems hard to imagine that he could have responded with any decision other than acceptance of the American offer.

7.6 The meeting and its aftermath

The inter-Departmental meeting on 15 November appears now to be somewhat of an anticlimax. It is significant, surely, that Hale himself did not attend the meeting, and that his delegate, J.F. Cahan, was on a very junior Administrative grade and clearly outranked by the other participants. From this, I infer, it is likely that all the main conclusions of the meeting were settled beforehand within the Treasury. It is noteworthy that of the three main questions which Thomson put to Hale, the only one which, by the end of the meeting, had in fact been resolved, was whether the government would accept the offer of

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92 Cahan was one of eighteen Temporary Administrative Officers at the Treasury. His salary range was £600-950. ICCL 1946. In contrast, Dalrymple-Champneys earned £1,750, Doggett’s range was £1,050-1,200, and Everett, who did not appear in the Imperial Calendar that year, was listed the next year with a fixed salary in the range £1,011 to £1,161. Thomson was in 1946 given the salary of an Under Secretary, which was the same as Hale’s. See Council Minutes 18 Oct 1946, FD6/7.

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American streptomycin. And that decision to accept the 50 kilograms, we have seen above, had been made by Hale himself.

There were no official minutes taken, but the following day Doggett sent Cahan a letter, with copies to Dalrymple-Champneys and Thomson, confirming the agreement reached at the meeting.⁹³ Thomson, remarking that he himself had been on the point of drawing up a similar document, wrote to Doggett, "as your letter records the conclusions very adequately I need not proceed with that."⁹⁴ (We also have Dalrymple-Champneys' note to his colleagues within the MoH, from which we learn that Mellanby took the chair and that Raistrick also attended).⁹⁵ Doggett recorded that the following were agreed:

(a) the Ministry of Supply would proceed at once with the purchase from America of 50 kilogrammes of Streptomycin at an approximate cost of £80,000 - £100,000.

(b) the cost would not be borne on the Ministry of Supply vote, but either on the Ministry of Health vote or out of the grant to the Medical Research Council.

(c) the Ministry of Health and the Medical Research Council would agree between them which should bear the cost, but that so far as the Ministry of Supply was concerned it would look to one or other of them for repayment.

(d) the Ministry of Health would consider the possibility of placing an additional demand on the Ministry of Supply for the purchase from production in this country of 100 kilogrammes of Streptomycin. (No action on this will be taken until the demand is

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⁹³ Doggett to Cahan, 16 Nov 1946, FD1/6764.

⁹⁴ Thomson to Doggett, 20 Nov 1946, FD1/6764.

⁹⁵ Dalrymple-Champneys minute, 15 Nov 1946, MH58/636. We also learn that Dalrymple-Champneys did not know Doggett, whom he identified as "Another", from the Ministry of Supply. Although according to Marchbank's note to Marre, early in the week he sent the Department of Health for Scotland a copy of the Appeal, remarking, "they have asked particularly to be kept informed of Streptomycin developments," no one from that Department attended. Marchbank to Marre, 12 Nov 1946, MH58/636.
received. Here again the Ministry of Supply will look to either the Ministry of Health or the Medical Research Council for repayment).

(e) unless the demand from the Ministry of Health referred to at (d) is received within a reasonable time, in order to avoid any misunderstanding on the part of the firms, the Ministry of Supply would make it clear to the British firms developing Streptomycin production that they were acting entirely at their own risk and that there could be no assumption that the Government would purchase their output.

The Treasury soon decided that the Ministry of Health should bear the cost of the 50 kilograms. And after rather protracted discussion, it was agreed in January 1947 at a meeting at the Treasury, this time chaired by Hale himself, that the Ministry of Supply be authorized to place orders with Boots, Glaxo and Distillers for 20 kilograms each, on what were referred to as "the best terms obtainable". These terms, it was recorded, were expected to be considerably more than the current price of American streptomycin, £1,000 per kilogram. The matter of the amount to be provided for in the Ministry of Health Estimates was to be discussed further between that Department and the Treasury. Thus the Treasury was prepared to spend £60,000 on British streptomycin plus the dollar equivalent of £80,000 on imported streptomycin. Placed under the Ministry of Health vote, the £80,000 did not appear in the figures for the growth of the MRC's spending. In late February 1947 Mellanby and Thomson appeared as witnesses before the Parliamentary Select Committee on Estimates, which was conducting an investigation of spending on scientific research. The MRC's written evidence included the statement, "A recent project undertaken by the Medical Research Council, which has created much interest, is the wide scale tests being made to see whether streptomycin, an antibiotic substance discovered in America, is curative of tuberculosis. This, again, has involved a big organisation and tests are being made

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96 Stephens to Riddle, 26 Nov 1946, FD1/6764.

97 Note of a meeting held at the Treasury, 16 Jan [1947], FD1/6764.
in various parts of the country on different forms of tuberculosis. In addition to tuberculosis, other tests are being made to see whether streptomycin is curative of other diseases.  

No questions were asked about streptomycin. And the select committee remarked in its report, "The Council have full liberty, untrammelled by considerations of day-to-day administration, to pursue an independent policy towards the advancement of medical science." Such was the period’s idealized image of science.

7.7 Conclusion

In the course of planning clinical trials in relation to British production, a stalemate developed at the end of October between the Ministry of Supply and Medical Research Council, neither Department wishing to bear the financial burden of an order. A further complication emerged as these Departments and the Ministry of Health learned that a large allocation of American streptomycin was on offer. It was agreed that the major financial questions surrounding these possible purchases called for an inter-Departmental meeting, and Edward Hale from the Treasury was called to arbitrate. A powerful letter to Hale, drafted by Landsborough Thomson, served as the basis of discussion of the streptomycin position at the meeting on 15 November. But the crucial decision on the import from America had already been made by Hale. Within a few months, the other issues were also settled.

We can now see clearly the major features of the archival record which are not apparent from the received story of the purchase of the drug from America. First, the size of this import was determined by the export quotas set by the

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99 See Minutes of Evidence taken before the SCE (Sub-Committee B), Wed 26 Feb 1947, ibid, pp.64-76.

100 ibid, p.li.
American government. It is not true that a shortage of dollars on the part of the British government was a major factor in the purchase of streptomycin for the MRC's clinical trials. Second, the typical repetition of the MRC's argument for using a group of untreated controls (as discussed in Chapter 6) has led to a downplaying of the essential fact that the quantity of streptomycin imported was large, 50 kilograms, and its cost was extremely great, about a quarter of a million dollars for the November allocation, or £80,000. Third, it has been forgotten that the import was approved in the context of clinical trials arranged to solve a British industrial production problem. Finally, although the literature repeats the assertion that issue of the drug had to be controlled while it was in short supply, one would not guess that a key argument in the approval of the purchase had been precisely that the absorption of supplies by clinical trials in progress would temporarily remove the need for other administrative controls over distribution.
8. Conclusion.

8.1 Recapitulation

The body of the thesis has presented a large amount of new material on official policy developments, divided into narratives on each theme. In order to remind the reader of these events and to highlight the connections between these threads of the story, I now recapitulate the material in chronological order.

Streptomycin was isolated at Rutgers University in the autumn of 1943. Early in 1944 it was announced that the new antibiotic was active in vitro against a variety of organisms that were not susceptible to penicillin or sulphonamides, among them the tubercle bacillus. In 1944 and 1945 Feldman and Hinshaw at the Mayo Clinic conducted meticulous experiments with guinea pigs, which proved that streptomycin could reverse tuberculous disease in living animals. The British government first became involved with streptomycin in February 1945 when Raistrick asked the National Collection of Type Cultures for a sample of Actinomyces griseus, so that the Ministry of Supply experimental station at Porton could study the drug’s effect on plague in laboratory mice. Waksman sent a fresh culture of the microorganism to the NCTC, and Porton produced enough streptomycin to complete its study that summer. Workers at the National Institute for Medical Research meanwhile unofficially brought back tiny samples of the drug for use in laboratory work, but they had none to spare in September 1945 when a physician with close ties to the Medical Research Council sought to try the drug on a typhoid carrier under his care. At the very end of 1945, the MRC asked the British Commonwealth Scientific Office whether the substance could be procured for a clinical trial in plague in India.

In the USA, production of streptomycin remained under the control of the Civilian Production Administration, which allocated most of the output to military and naval use in certain urinary tract infections caused by gram-negative organisms. The BCSO, marginalized by the Washington medical authorities, never managed to accomplish much on the MRC’s behalf in the streptomycin situation. In Britain, Glaxo decided in January 1946 to invest a quarter of a million pounds
in streptomycin production. The MoS, whose approval was needed for this project, consulted the MRC in March 1946. The latter recommended development of medium scale production, sufficient for clinical trials, which were the Council's stock in trade. At the same time, Mellanby approached Richards of Merck on a personal mission to obtain streptomycin for treatment of his nephew, but American civilian demand had grown to the point that by March 1946 the CPA asked the COC to ration the substance, as it had done during the war with penicillin. Tuberculosis patients, other than those already enrolled in studies at the Mayo Clinic and elsewhere, were not permitted access to streptomycin treatment, on the grounds that the course of treatment for this disease required too much of the drug. Nor would the COC countenance even tiny exports of streptomycin. In the spring, word of the drug began to spread more widely in Britain and a trickle of requests reached the MRC and MoH, mostly from individual physicians and sanatoria. Anticipating that extreme demand for streptomycin might develop before large-scale production could be established in Britain, Jameson warned the MRC not to add further to the publicity, but it had already arranged for Feldman to come on tour.

In June 1946 a senior official in the MoS decided to approve priorities for streptomycin manufacture, partly on the basis of the MRC's arguments, but declared that financial support was out of the question. Representatives of the MoS and MoH met immediately, and delegated Dalrymple-Champneys to ask the MRC how much streptomycin it would need to run a proper clinical trial. He delayed for weeks, until finally, after the stakes had been raised by Feldman's lectures about streptomycin at the RIPH and in Oxford, Raistrick went directly to Mellanby to find the Council's requirements. Mellanby decided to ask that British firms produce enough of the drug to treat a hundred patients with tuberculosis. At the end of July, he called a conference of clinicians who were experienced with tuberculosis, and unsurprisingly they went along with his recommendations to concentrate on that disease. A follow-up conference in August decided that untreated controls would be used in the pulmonary tuberculosis trial, but not in the tuberculous meningitis or miliary tuberculosis trials. The second conference also decided that since the British manufacturers did not expect to produce enough
streptomycin using deep fermentation for a large scale trial until the following spring, they would like one company to produce small quantities using surface fermentation, a simpler but less efficient technique. Over the objections of Everett from the MoS, the clinicians decided to run a pilot trial using surface-produced material that was expected from Boots in a few months.

In September the MoS issued a press release presenting its plans for British manufacture, and mentioning forthcoming clinical trials under the auspices of the MRC, which had not been consulted about this announcement. This sharply increased the flow of enquiries, now coming from patients as well as doctors, and the MRC had to prepare a standard statement on the streptomycin position early in October. In the middle of that month, once Merck’s new plant came online, an interdepartmental US government committee that had taken over responsibilities for distribution from the CoC, broadened the access to the drug through American hospitals and for the first time set small export quotas for various countries including Britain. Hambro from the MoS requested a share in this British allocation, for the treatment of his grandson, but ended up obtaining the drug through private channels, probably the burgeoning black market. Five grams of American streptomycin meanwhile had been sent to NIMR for the purpose of establishing a British standard, which was needed both for industrial manufacture and for eventual regulation by the MoH under the *Therapeutic Substances Act*. Also in October the MRC created a committee for clinical trials of streptomycin in tuberculosis, with a technical subcommittee of pathologists.

At the start of November 1946 the BBC broadcast an emergency appeal for streptomycin to treat a small boy dying of tuberculous meningitis. In response the British subsidiary of an American manufacturer rushed their tiny sample to the boy. Though he died, such appeals continued, much to the consternation of the MoH and MRC, which deprecated the raising of people’s hopes when the drug was not available in adequate quantities. Later in that month, Feldman and Hinshaw published a report on 100 clinical cases of tuberculosis treated with streptomycin, including four long-term survivors of tuberculous meningitis. The American committee raised its export quotas for the month of November sharply over those of the previous month, and the MoS found itself being offered 50
kilograms of the drug, at a cost of a quarter of a million dollars. This offer raised important questions, first, whether it should be accepted in order to allow the MRC’s trials to begin earlier than they would have done if they waited for sufficient British production. Second, whether this import would hinder the commercial prospects of the British firms, and whether therefore it would be advisable for the government to protect them by promising to purchase their initial output. Third was which Department should bear the cost of any such purchases. A senior Treasury official decided to allow the import, and to bill this to the MoH. A few days later, at the first meeting of the streptomycin in tuberculosis committee, the pilot trial was scrapped, because the 50 kilograms promised imminently. As well, the legitimation of the MRC’s control strategy depended partly on an argument that only large-scale trials would provide reliable information about the value of the drug. The committee decided to use Hill’s scheme, of randomization based on sealed envelopes, which relieved the MRC’s clinicians of the responsibility for deciding which patients would receive the drug. The same month the Council created a second committee for clinical trials of streptomycin in non-tuberculous conditions. In December this latter committee was given control over the small shipment representing the October quota. This stock was used in several small clinical trials, mostly without a control group of patients. The BMJ ran a notice prepared by Green, warning that the value of streptomycin was still unproven, and meningitis patients might be left permanently deaf or deranged following treatment.

In 1946, the first half of the 50 kilograms representing the November quota arrived. The first patients in the MRC’s tuberculosis trials were admitted to the participating hospitals. Late in the month the MoH made a statement to The Times similar to the BMJ’s earlier warning. This time around Waksman received word, and objected to the imputation that streptomycin was toxic. Also this month the Treasury committed the government to purchasing streptomycin from British producers. Finally, in February 1947, a Parliamentary investigation of scientific expenditure overlooked the recent creation of this major medical research project.

Epilogue. In April 1947 the tuberculosis committee told the MoH that
streptomycin definitely prolonged the lives of tuberculous meningitis patients. The MoH made streptomycin treatment for this condition available throughout the country in September 1947. The MRC's tuberculous meningitis report was published in April 1948, and the pulmonary tuberculosis report six months after that. The MoH's scheme of treatment and research progressively widened to include other tuberculous conditions, and the MRC's program extended to the use of streptomycin in conjunction with surgical treatment and the new drug paraaminosalicylic acid. Streptomycin became available on prescription in November 1949.

8.2 A bigger picture

Although very many clinical trials over the years have been dependent on pharmaceutical firms in various ways, and firms have made ample use of clinical research in their production and marketing strategies, there is relatively little engagement between the newer historical literature dealing with clinical trials and the literature on the pharmaceutical industry. A key theme emphasized in this

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thesis is the connection between clinical trials and pharmaceutical production. However, specific analysis of economic aspects of clinical trials has tended to concentrate on the demand side, where the products have entered a network of patients, doctors and hospitals, rather than on production. On the other hand, business historians have tended to write, not entirely surprisingly, as if all that mattered was that companies' products were subjected to scientific tests, and not the nature of those tests, since clinical research is but one stage in the development of pharmaceutical products.

In light of the British government's concentration of its streptomycin program on the treatment of tuberculosis, it is worth considering how a new account of streptomycin may modify our historical understanding of this disease, on which there is now a rich literature. The bulk of such work has not come to grips with the way tuberculosis was dealt with in the postwar world. Several social histories which are valuable on the early twentieth century relegate the postwar period to a cursory epilogue in which critical perspective is abandoned in favour of the optimistic voices of medical scientists. Or they breeze through the several decades from the discovery of streptomycin in 1944 to the resurgence of tuberculosis in the developed countries in the 1980s. Most of the other work originates from medically trained writers who focus rather narrowly on the history of innovation*, History and Technology 13.2 (1996), 83-100; W.J. Reader, Imperial Chemical Industries: A history. II. The first quarter century 1926-1952, (Oxford: 1975); Geoffrey Tweedale, At the Sign of the Plough: 275 years of Allen & Hanbury's and the British Pharmaceutical Industry 1715-1990, (London: John Murray, 1990). See however Louis Galambos and Jane Elliot Sewell, Networks of Innovation: Vaccine Development at Merck, Sharp & Dohme, and Mulford, 1895-1995, (New York: Cambridge UP, 1995).


of research.\textsuperscript{5} Bryder, in contrast, provides a salutary overview of the multifaceted problems faced by the British tuberculosis services from the Second World War onward, in the final chapter of \textit{Below the Magic Mountain}, but there is room for much more work on the subject.\textsuperscript{6} The current thesis, along with a few local and national case studies of how tuberculosis control was actually implemented in an era of chemotherapy, points to the sheer complexity of this task and how it interlocked with other administrative objectives.\textsuperscript{7} The spread of powerful new drugs raised a set of social questions that were no less vexed than those of an earlier era.

8.3. An assessment

There has been much debate in recent historical literature on the Attlee years over whether the government put the formation of the welfare state ahead of economic productivity. Correlli Barnett, who argues that the Labour government threw away its chances to build an efficient modern economy because it was too preoccupied with the utopian dream of the New Jerusalem, has been sufficiently influential that several economic historians have taken the pains to demonstrate that his work is methodologically substandard. Others have suggested somewhat more credibly that the balance still tipped towards the welfare side, but much


recent scholarship reminds us of efforts to rebuild and modernize the nation’s productive capacity. The streptomycin story may serve as a reminder that projects served multiple objectives. This thesis clearly shows that industrial planning was a major impetus for the government’s streptomycin research programme. Even with regard to the distribution of treatment, however, the story demonstrates a proccupation with efficiency. This exceptionally valuable substance was conserved very carefully. There is no sign in the case of streptomycin that the government overextended itself in an attempt to distribute health care more widely than it could afford. Nor, however, does the government appear to have been excessively stingy with streptomycin under the circumstances: once the MRC weighed in with its evidence that streptomycin saved lives in deadly tuberculous conditions the Ministry of Health moved quickly to widen distribution to patients with such conditions. The Treasury, cast in much of the clinical trials literature in the role of inadvertent hero for making it possible to use untreated controls, appears in a rather different light in the story I tell. It cooperated fully with the MRC’s requests for resources for scientific research, and it went along with the MoH’s scheme to make streptomycin available in tuberculous meningitis and miliary tuberculosis (and not long afterwards in tracheo-bronchial tuberculosis). Not everyone was satisfied, of course, with the strictly limited availability of streptomycin, since the drug offered a real hope of improvement of chronic and often life-threatening illnesses. But it is not only with the benefit of hindsight, knowing now that streptomycin alone does not often lead to permanent recovery from tuberculous conditions (because of the tendency for drug-resistant bacteria to develop), that the restrictions lasting up to November 1949 on using streptomycin seem reasonable. At the time it was unclear what the long-term benefit would be from streptomycin treatment of pulmonary tuberculosis, and with so many other pressing demands for imports on its hands, the government gave priority to items whose value was more definite, such as timber for new housing, and food. Once the Ulverston plant was online, availability of streptomycin ceased to be a problem, and the government left it to medical practitioners to decide when streptomycin treatment was advisable.

Within the bounds of the streptomycin problem as defined by the
bureaucracy, the course of action taken under the circumstances seems eminently reasonable; indeed it is hard to imagine how it could have turned out much differently. The questions that may arise now about the streptomycin story are about what has been left outside the frame. As contemporary critics of planning argued, the trouble tends to lie in unintended consequences of the system. In fairness to the bureaucrats, these are questions they had no way of answering, and there was at the time no point in spilling ink over them. What, for example, might be the long-term effects of the toxicity scare? In the short term, of course, it was predicted that the Ministry’s warning would apply a brake to the growing demand for streptomycin for treatment of tuberculous meningitis. Waksman and Bryder suggest on the basis of the Ministry of Health’s promotion of streptomycin in 1950 that physicians continued to under-use the drug against this condition even after it became readily available. But to what extent did the paternalistic approach of the civil service contribute, say, to public cynicism about government health warnings? As stated in the introduction, different sources are needed to address such questions about what streptomycin meant to patients and to members of the wider public. What this study has provided is a comprehensive picture of how the central government handled streptomycin, one facet of which was the management of information. The way the story of the streptomycin trials has continued to be told seems far too neat. Looking back from the distance of half a century, we have different expectations than did our predecessors. Having emerged from the long shadow of the Second World War, and now beyond the Cold War, we find open government espoused as a virtue if not necessarily followed in practice. We are less optimistic that the progress of science and technology will solve our problems. And we are used to watching exposés of the great and the good. To our eyes, orderly narratives raise suspicions that there must have been a coverup. When we look into what the government did with streptomycin, we do find a much more complicated story, but not a hidden scandal. If the problem was to use the available streptomycin to best effect for purposes that included research and treatment, there is little to fault in the way the system worked, given the human and material resources available. If the ethical imperative was that patients within the trials should receive the best available treatment, the experimenters emerge
with due credit. Optimal use of material resources was how these historical actors conceived their task, and at that task they succeeded admirably. Handling of information was for them a means to an end, whereas to us it may seem an integral part of the task of government. Looking back from a different age, we find sound reasons for the secrecy in which the government dealt with streptomycin, and sound reasons for the shape of the historical record, and with that historical sympathy in mind it is now possible to ask a new set of questions.
Appendix A. Dramatis Personae

Note: Biographical data is given where readily available, eg, from Medical Directory 1946 (London: Churchill, 1946) or The British Imperial Calendar and Civil Service List (London: HMSO, 1946). Honours, qualifications and civil service salary ranges are given as of 1946 except where otherwise noted.

Mrs Charlene Agnew. Secretary to Hart at National Institute for Medical Research Farm Laboratories, Mill Hill.

Rt Hon Aneurin Bevan MP. Minister of Health, £5,000.

Prof J.W.S. Blacklock. Member, MRC Streptomycin Clinical Trials (Tuberculosis) Committee. Professor of Pathology, Glasgow University. Research on tubercular disease in children.

Mr Lawrence Brown. Director, Chemicals Division, Civilian Production Administration, USA. Oversaw streptomycin control.

Mr J.F. Cahan. Temporary Administrative Officer, Treasury, £600-950. Involved in drug imports.

Mr John Cairncross. Principal, Treasury, £800-1,100. Involved in streptomycin imports. Brother of economic historian Alec Cairncross.

Prof Hugh Cairns. Professor of Neurosurgery, Radcliffe Infirmary, Oxford. Used streptomycin to treat meningitis of both tuberculous and non-tuberculous varieties.

Prof Charles Cameron. Member, MRC Streptomycin Clinical Trials (Tuberculosis) Committee. Professor of Tuberculosis, University of Edinburgh. Research on miliary and meningeal tuberculosis.

Prof Norman B. Capon. Member, MRC Streptomycin Clinical Trials (Tuberculosis) Committee. Professor of Child Health, University of Liverpool; Consultant, Alder Hey Children's Hospital, Liverpool.

Ernst Chain. Microbiologist. Nobel Laureate 1945 for role in development of penicillin, and helped to promote streptomycin.

Prof R.V. Christie. MD DSc FRCP. Member, MRC Streptomycin Clinical Trials (Non-Tuberculous Conditions) Committee. Secretary, MRC Penicillin Clinical Trials Committee.

Mrs Vivian Connell. Technical Assistant to Director, British Commonwealth Scientific Office, Washington DC. Attempted unsuccessfully to procure streptomycin for the MRC.

Dr Robert Coope. Lecturer in Clinical Chemistry at the University of Liverpool;
Physician, Liverpool Hospital for Consumption. Attended Second Streptomycin Conference.

Dr John Crofton. Streptomycin Registrar, Brompton Hospital.

Miss Couzens. Clerical assistant to Green, MRC. Handled Hambro enquiry.

Prof Robert Cruickshank. Member, MRC Streptomycin Clinical Trials (Tuberculosis) Committee. Member from April 1947, MRC Streptomycin Clinical Trials (Non-Tuberculous Conditions) Committee. Founding Director, Central Public Health Laboratory at Colindale.

Sir Henry H. Dale CBE MD FRCP FRS. Director of National Institute for Medical Research, 1928-1942. Assisted Mellanby with attempt to procure streptomycin from USA.

Dr William Allan Daley. Medical Officer of Health, London County Council. Sought successfully to bring the LCC into the MRC's streptomycin research programme.

Sir Weldon Dalrymple-Champneys Bart DM FRCP. Deputy Chief Medical Officer, Ministry of Health. £1,750. Responsible for medical supplies including streptomycin.

Dr Marc Daniels. Registrar, MRC streptomycin clinical trials. Coordinated research at clinical centres.

Mr F.J. Doggett, Assistant Director, Contracts (Purchases), Ministry of Aircraft Production, £1,050-1,200. Handled streptomycin purchase.

Dr Richard Doll. Statistician. Later collaborator with Bradford Hill on smoking and lung cancer studies. No formal role in early streptomycin clinical trials.

Sir Jack Drummond DSc FRIC FRS. Director, Research Department, Boots Pure Drug Co, Nottingham. Adviser to Ministry of Food during WWII.

Dr E.S. Duthie. Dunn School of Pathology, Oxford and Lister Institute. Penicillin researcher. Supplied streptomycin to several laboratory researchers.

Mr F.C. Everett ARCSc, ARIC. Assistant Controller, Penicillin Production Control, MoS, £1,011-1,161 (1947). Coordinated British production of streptomycin and penicillin.

Mr D.V.T. Fairrie. Finance Officer, MRC. Liaison with Treasury.

Dr William H. Feldman. Division of Experimental Medicine, Mayo Clinic. Leading researcher in field of chemotherapy of tuberculosis.
Prof Sir Alexander **Fleming** MB FRCS FRCP FRS. Chairman, MRC Streptomycin Clinical Trials (Non-Tuberculous Conditions) Committee. Member, Medical Research Council 1945-1949. Nobel Laureate 1945 for discovery of penicillin.

Prof Howard Walter **Florey**. Dunn School of Pathology, Oxford. Nobel Laureate for penicillin. Diverse involvement in research and development of antibiotics.

Lady M. Ethel **Florey**. Penicillin researcher, Dunn School of Pathology, Oxford. Used streptomycin to treat wound infections.

**Foster**, Office of International Trade, US Department of Commerce.

Mr Oliver S. **Franks**. Permanent Secretary, Ministry of Supply, £3,500. Negotiated with MRC about arrangements for antibiotic production.

Prof J.H. **Gaddum** ScD MRCS FRS. Member, MRC Streptomycin Clinical Trials (Tuberculosis) Committee. Professor of Materia Medica, University of Edinburgh.

Dr T.O. **Garland**. Principal Assistant Medical Officer, Middlesex County Council. Attended MRC Streptomycin Conference.

Prof L.P. **Garrod** MD FRCP. Member, MRC Streptomycin Clinical Trials (Non-Tuberculous Conditions) Committee.

Dr H.H. **Gerrans**. Secretary, Royal Institute of Public Health and Hygiene. Invited Feldman to deliver the Harben Lectures.

Dr S. Roodhouse **Glowne**. Dean at the London Chest Hospital and Consulting Pathologist at Midhurst Sanatorium. Selected for Streptomycin Clinical Trials (Tuberculosis) Committee, but was replaced by Cruickshank without ever serving.


Dr Frank H.K. **Green**, Publications Officer, MRC. Handled public and press enquiries regarding streptomycin.

Mr Edward O. **Haenni**, Government Presiding Officer, Civilian Production Administration, USA. Oversaw streptomycin control.

Mr Edward **Hale** CB. Under Secretary, Treasury, £2000. Approved first major import of streptomycin.

Sir Charles **Hambro**. Head of Hambros Bank and former Director General, British Raw Materials Mission, Washington DC. Procured streptomycin for grandson.

Dr Charles R. **Harington** PhD FRS, Director, National Institute for Medical
Research. Negotiated with MoS about antibiotic production.

Dr Philip D'Arcy Hart MD FRCP. Secretary, MRC Streptomycin Clinical Trials (Tuberculosis) Committee. Former Secretary, MRC Tuberculosis in War-Time Committee and later Director, MRC Tuberculosis Research Unit.

Dr Frederick R.G. Heaf BA MD MB MRCP MRCS. Member, MRC Streptomycin Clinical Trials (Tuberculosis) Committee. Senior Medical Officer in the Public Health Department of the London County Council, and administrator of the LCC's tuberculosis scheme. Conducted research on promin.

Dr Wallace Herrell. Division of Medicine, Mayo Clinic. Conducted early clinical studies of streptomycin in non-tuberculous conditions.

Prof A. Bradford Hill. DSc PhD. Member, MRC Streptomycin Clinical Trials (Tuberculosis) Committee. Head of the MRC's Statistical Research Unit, and Professor of Medical Statistics at LSHTM.

Prof Harold P. Himsworth MD FRCP MRCS. Professor, London School of Hygiene and Tropical Medicine. Later Secretary of the Medical Research Council.

Dr H. Corwin Hinshaw. Division of Medicine, Mayo Clinic. Leading researcher in field of chemotherapy of tuberculosis.

Surgeon John W. Hornibrook, US Public Health Service. Conducted research on streptomycin in plague.

Dr L.E. Houghton MD. Member, MRC Streptomycin Clinical Trials (Tuberculosis) Committee. Dr Lionel E. Houghton, Physician at the County Hospital, Harefield, Middlesex.

Dr J. Clifford Hovle MD FRCP. Member, MRC Streptomycin Clinical Trials (Tuberculosis) Committee. Physician at the Brompton, and Editor of the British Journal of Tuberculosis.

Sir William Wilson Jameson KCB MA MD FRCP DPH. Chief Medical Officer, MoH, £3,000. Discouraged publicity about streptomycin.

Dr Chester S. Keefer. Chairman, Committee on Chemotherapeutic and Other Agents, National Research Council. Coordinated major research project on streptomycin, controlled domestic distribution and prevented exports.

Mr T.B. Keep. Controller, Penicillin Production Control, MoS. Not listed in any published reference. Investigated American streptomycin facilities.

Mr Alexander King. Director, United Kingdom Scientific Mission, British Commonwealth Scientific Office, Washington DC. Attempted to procure streptomycin for MRC.
Dr Harold King DSc FRS. Head of chemotherapy research, National Institute for Medical Research. Negotiated with MoS about antibiotic production.

Sir John Edward Lennard-Jones. Chief Scientific Officer, MoS. Solicited MRC’s views on proposals for industrial production of streptomycin.

Mr H.T. Lester AIC FRIC. Chief Technical Assistant, Penicillin Production Control, MoS. Oversaw streptomycin production.

Dr H.M.C. Macaulay. Chief Medical Officer of Middlesex County Council. Invitee to Streptomycin Conference.

Dr James E. McCormack. Technical Aide, Division of Medicine, Committee on Medical Research, USA.

Dr C.J. Mackenzie, National Research Council of Canada. Provided the MRC with small sample of Canadian streptomycin.

Sir Arthur S. MacNalty. KCB DM FRCP. Retired 1940 as Chief Medical Officer, Ministry of Health. Chairman of the MRC Tuberculosis Committee throughout the 1920s. Sought unsuccessfully to include Papworth Village Settlement in MRC’s streptomycin research.

Mr Keith W. Macrae, Supply Officer, General Procurement Division, British Supply Office, Washington DC. Arranged streptomycin imports.

Dr D.G. Madigan. Senior Tuberculosis Officer of Kent County Council. Attended Second Streptomycin Conference, where he described his treatment of a variety of cases of tuberculosis. He was not invited to join the committee.

Mr Frank F. Marchbank. Principal, Ministry of Health, £800-1,100. Responsible for medical supplies including streptomycin and penicillin. Originally joined the Local Government Board in 1913 as Clerk Second Class.

Mr Alan Marre. Promoted during 1946 to Assistant Secretary, Ministry of Health. Responsible for medical supplies.

Dr Geoffrey Marshall OBE MD FRCP. Chairman, MRC Streptomycin Clinical Trials (Tuberculosis) Committee. Eminent Harley Street physician, and Senior Physician at the Brompton Hospital for Consumption and Diseases of the Chest, the nation’s most prestigious tuberculosis facility.

Dr W.J. Martin. MRC Statistical Research Unit. Attended MRC Streptomycin Conference.

Sir Edward Mellanby. Secretary, Medical Research Council. Attempted to procure streptomycin from USA for nephew; organized Streptomycin Conferences.

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Mr George W. Merck. President of Merck & Co, New Jersey, the first and largest industrial manufacturer of streptomycin.

Dr Ashley A. Miles, Director, Department of Biological Standards, National Institute for Medical Research. Oversaw setting of British standard for streptomycin.

Dr Hans Molitor. Director, Merck Institute for Therapeutic Research, Rahway, New Jersey.

Rt Hon Herbert S. Morrison (1888-1965). Lord President of Council, in which capacity he was the Minister responsible for the MRC. Also Deputy Prime Minister and Leader of Commons.

Prof Harold Raistrick ScD FRS. Member, MRC Streptomycin Clinical Trials (Tuberculosis) Committee. Member, MRC Streptomycin Clinical Trials (Non-Tuberculous Conditions) Committee. Liaison between MRC and MoS regarding streptomycin production. Professor of Biochemistry, London School of Hygiene and Tropical Medicine.

Dr A. Newton Richards. Chairman, Committee on Medical Research (CMR). Professor, University of Pennsylvania. Scientific Director, Merck & Co.

Sir Arthur Rucker KCMG CB CBE, Deputy Secretary, MoH, £2500.

Miss Enid M.R. Russell-Smith, Principal Assistant Secretary, Ministry of Health, £1,525. Involved in streptomycin toxicity warning.

Dr John Guyett "Guy" Scadding MD FRCP. Member, MRC Streptomycin Clinical Trials (Tuberculosis) Committee. Assistant physician, Brompton Hospital. During war ran a controlled trial of a sulphonamide.

Dr Albert Schatz. Microbiologist, Rutgers University. Discovered streptomycin in 1943.

Dr F.R. Selbie MD PhD. Member from April 1947, MRC Streptomycin Clinical Trials (Non-Tuberculous Conditions) Committee.


Dr A. Landsborough Thomson. Promoted during 1946 to Principal Assistant Secretary, MRC, £2000. With Green handled the Council’s public relations strategy around streptomycin.

Dr Geoffrey S. Todd. Medical Superintendent of the famous King Edward VII Sanatorium at Midhurst.
Prof W.H. Tytler. MD. Member, MRC Streptomycin Clinical Trials (Tuberculosis) Committee. Davies Professor of Tuberculosis, University of Wales, Cardiff. Director of Research, Welsh National Memorial Association.

Dr F.C.O. Valentine MRCP. Member from April 1947, MRC Streptomycin Clinical Trials (Non-Tuberculous Conditions) Committee.

Mr R. Vaughan Hudson FRCS. Member, MRC Streptomycin Clinical Trials (Non-Tuberculous Conditions) Committee.

Prof Selman A. Waksman. Microbiologist, Rutgers University. Credited with discovery of streptomycin.

Mr F. Warburton. Director, Directorate of Medical Supplies, MoS, £1,500.

Mr J.D. Whittaker. Supplies Officer, MRC.

Mr H. Wilkinson, Directorate of Medical Supplies, Portland House, Ministry of Supply.

Rt Hon John Wilmot MP. Minister of Supply 1945-47.

Prof Clifford Wilson DM MRCP. Secretary, MRC Streptomycin Clinical Trials (Non-Tuberculous Conditions) Committee.

Dr Graham Selby "G.S." Wilson MD FRCP DPH KHP. Member, MRC Streptomycin Clinical Trials (Tuberculosis) Committee. Director of the Public Health Laboratory Service.
Appendix B. The MRC's standard statement, sent during Autumn 1946, in response to requests for streptomycin for treatment of tuberculosis.\footnote{FD1/6760.}

MRC 46/248
8 Oct 1946
RESTRICTED

STREPTOMYCIN

In view of the publicity given to their plans for the trial of the new drug streptomycin in tuberculosis the Medical Research Council wish to make clear the following points:-

1. The object is to obtain as much information as possible about the value of streptomycin and the methods of its use by the time supplies become generally available to the medical profession.

2. The investigation will begin as soon as the first supplies come to hand from the manufacturers, but it will involve extensive tests of the suitability and safety of the material for administration to human beings before actual trials on patients can justifiably be undertaken.

3. The supply is, in the first instance, likely to be sufficient for only a very small number of patients, possibly in a single institution.

4. Even the larger scale trials which it is hoped to undertake at some date in 1947 will necessarily be limited to a few institutions.

5. In these circumstances, requests for supplies, or for the inclusion of particular institutions or individual patients in the scheme of trials, cannot be entertained.

6. The evidence from such trials as have already been made in America leaves it at present quite uncertain whether streptomycin is likely to prove of great value in tuberculosis, and it may eventually prove that its chief uses lie in the treatment of certain other conditions.
Appendix C: Attendance at Streptomycin Clinical Trials (Tuberculosis) Planning Meetings

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**TB Committee members**

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**Key**

- P Present
- X Apologies
- • Not invited

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Dear Hale,

Streptomycin

Following conversations between the Medical Research Council and the Ministry of Supply on the above subject, we are holding a meeting here at 11 a.m. on the 15th November at which we hope the Treasury will be represented as well as the Ministry of Health, to whom we are also writing, and the Ministry of Supply. The position which urgently calls for discussion may be outlined as follows: -

(1) Streptomycin is a new anti-biotic, discovered in the U.S.A., which appears on the American evidence to have a curative effect in some diseases not susceptible to treatment with penicillin or other known substances. Tuberculosis is claimed, not yet with certainty, to be among the diseases for which streptomycin is valuable, and this is the important medical question to be settled. On the answer, moreover, the scale of the eventual demand will very largely depend.

(2) Streptomycin has until now been practically unobtainable in this country, but the Ministry of Supply have encouraged several British firms to undertake production and limited quantities should become available within the next few months-- not quite so soon as had been hoped.

(3) On the 24th July the Medical Research Council were asked by the Ministry of Supply to undertake clinical trials with the British product, when forthcoming, and shortly afterwards the Council were also in touch with the

1 Thomson to Hale, 11 Nov 1946, FD1/6764.
Ministry of Health about this proposal. It is clearly desirable that before Streptomycin becomes more generally available to the medical profession there should be soundly based knowledge of its value in different conditions, but particularly in tuberculosis, and of the methods of its use. The Council have made preliminary arrangements to this end.

(4) This raises the question of acquiring the first output of the British firms for a series of controlled clinical trials. The amount required for the purpose is estimated at between 50 and 100 kilograms, the cost of which (at from £2,000 to £3,000 per kilogram) is likely to be from £100,000 to £300,000.

(5) Meanwhile, an unexpected - and at present confidential - offer of 50 kilogrammes of the American product for immediate delivery at a cost of about £80,000 (in dollars) has been received. (rather less than 2 kilogrammes, costing about £3,000, had already been ordered from America, with Treasury approval for the use of dollars.) This is a relatively impure preparation, compared with what may be expected later, but that is likely to be true also of the first output of the British manufacturers.

(6) The question arises whether this offer should be accepted, in order that clinical trials may be instituted in this country some months earlier than will otherwise be possible. (It would still be necessary to make some further trials with the British product, to confirm that it gives similar results, but probably not on a large scale.) The disadvantages of this course are, obviously, the use of dollars (although the actual cost in sterling is less) and the possible repercussions on British manufacture.

(7) If it be decided to purchase a substantial quantity of streptomycin from either source for the purpose of clinical trial, the further question arises as to which Department should be responsible for the expenditure. The Ministry of Supply state that they are now debarred from bearing such costs on their own vote, which we had originally assumed would be the
procedure. (There is an agreement between the Council and the Ministry that the former will reimburse the latter for the cost of making material for clinical trial, but this was intended to cover the development of discoveries made in the course of the Council's own research work and production on a medium scale in the Ministry's own technical establishments.) The Medical Research Council would be rather reluctant to handle a supplementary grant-in-aid for a single item so large in relation to their total budget. The Ministry of Health have not so far been consulted on the point, but might be considered appropriate as having a general responsibility for making new forms of treatment available: under the National Health Service Act they will presumably become the largest purchasers of streptomycin, for use in hospitals, if its value proves to be great.

(8) Another question, not of a research nature, is that of controlling the issue of streptomycin while it is in short supply, so that it may be allocated to the most suitable cases. The need for such control will arise as soon as there are supplies in excess of the amounts required for clinical trial. This is presumably a matter for the Ministry of Health and the Department of Health for Scotland.

(9) All these questions have to be viewed against the background of publicity given to the discovery of streptomycin and to the claims made for it as a life-saving drug, especially in tuberculosis. This publicity has aroused hopes, whether justifiable or not, which have already caused a clamour for supplies. Until these supplies are forthcoming, or unless and until it becomes possible to state definitively that the value of the drug is limited to a few relatively uncommon conditions, the clamour is likely to continue. Thus, if it is decided not to use the American supplies for clinical trial here, it may be necessary to face the question of permitting their purchase by agents for sale in this country. Equally, the question of releasing British supplies for sale will arise if these are not being wholly taken up for
clinical trial, although this is in any event likely to be later. The indiscriminate use of streptomycin, if placed on sale before controlled clinical trials have been made, would be wasteful and often harmful: it would also not yield any reliable information about the real value of the drug or the best methods of its use in treatment.

I hope to hear that you or someone else from the Treasury will be able to attend our meeting, as we cannot get much further without some guidance on financial policy.

Yours sincerely,

(Sgd.) A. Landsborough Thomson

E. Hale, Esq., C.B., Treasury Chambers, St. George St., S.W.1.
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