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The Role of the Medical Research Council

Carsten Timmermann

Center for the History of Science, Technology and Medicine

University of Manchester

Simon Building

Manchester M13 9PL

carsten.timmermann@manchester.ac.uk

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Introduction

This essay deals with the main funding body for medical research in the United Kingdom, the Medical Research Council (MRC), the closest relative, as it were, of the NIH in Britain. The MRC oversaw and actively promoted the rise of biomedical ideals and the proliferation of institutions devoted to biomedical research in the United Kingdom. My work in recent years has been mainly concerned with developments in medical research in the post World War II period. I have looked at high blood pressure, both debates over the etiology of hypertension and the introduction of new therapies, and at lung cancer, the search for its causes and, again, for effective therapies.[1] For anybody studying these issues it is impossible to ignore how post-war practices in clinical research were informed by a specific MRC ethos and informal MRC networks constituted in the inter-war period, and by research traditions that representatives of the council saw as embodying its ethos. In the first part of this paper I will discuss the emergence of these traditions and the people who shaped them.[2] In the second part I will discuss how these traditions left their imprint on post-war clinical research on high blood pressure and lung cancer. This paper is about continuity more than change. Some of the post-war administrative changes, however, especially those linked to the introduction of the British National Health Service, allowed the MRC to broaden its influence on British clinical research by vigorously promoting the traditions invented in the inter-war period. While these research traditions permeated and shaped the policies of the

postwar period, the new National Health Service provided the Council with an opportunity to re-evaluate what clinical science meant.

I will talk about the reorganization of clinical research later, but at this point let me briefly introduce the definition of clinical science the Council espoused at this time. Clinical research, according to the MRC's 1952 Annual Report, had to go "beyond the stage of observation and description of syndromes".[3] It was to engage with "planned investigations of illness".[4] The author of the article in the 1952 report clearly valued the experimental more than the observational, when he stated that "a branch of research which is debarred from using the experimental method is heavily handicapped in the general advance of science".[5] Experimentation in clinical medicine, however, was "limited to investigations which involve no risk to the patient and enlist his willing co-operation", and such practical limitations explained "the relatively slow development in the direct application of the investigational method to the study of illness."[6] But clinical research also included objects of study not susceptible to the experimental method: "clinical research covers not only work on patients in hospital but also field studies in epidemiology and social medicine, and observations in general practice".[7] The aim was to build on knowledge gained in the pre-clinical fields and to devise "accurate techniques for the investigation of illness in human patients".[8]

> It is the devising of such techniques in adequate variety and with increasing speed over the last two or three decades that is putting new opportunities within our grasp. Chemical and instrumental methods are now available for accurate investigation in many types of illness, without risk to the patient. The development of statistical techniques has refined the methods of planned observation and controlled clinical trials … Progress in clinical knowledge need, therefore, no longer depend entirely

> upon the chance observation of naturally occurring events. The clinical observer can now become, in addition, a clinical investigator.[9]

In other words, the time was rife for a new type of clinical research in Britain, based on the foundations laid and the traditions established by the MRC in the inter-war period and during the war, and on the new opportunities provided by the reorganization of healthcare. Before I return to the post-war period, in the first part of the paper I will discuss the origins of the MRC traditions and the context of academic medicine in Britain in the early twentieth century. A brief word of warning: this chapter is by no means a comprehensive account. Rather, I am attempting to highlight some of the trends that are most relevant for a broad comparison with contemporary developments in the US.

The origins of the MRC traditions

The Medical Research Committee, which in 1919 became the Medical Research Council, was set up in 1913 with funds provided by the British government in the 1911 National Insurance Act. Initially intended for research on tuberculosis, as Linda Bryder has shown, the Council's research agenda got much broader very quickly.[10] The MRC agenda was shaped to a considerable extent by a small group of men, some of them close friends, most with ties to Cambridge physiology, who ceased this opportunity to create a new platform for their brand of medical research.[11] A key figure was Sir Walter Morley Fletcher, MRC Secretary from 1914 until his death in 1933, a medically qualified physiologist and Fellow of the Royal Society.[12] His background and continued interest in physiology secured basic science an important place in the MRC research agenda, and the Cambridge tradition with its emphasis on neurophysiology, pharmacology and nutritional research was strongly represented in the research projects supported by the Council. According to his obituary,

Fletcher "loved Cambridge first and foremost", and Cambridge played a special role in the policies of the Council, as home for many of its institutions and also of the intellectual traditions the Council embraced.[13] Austoker argues that "Fletcher believed that all medical research should be influenced by the MRC" and ultimately come under some form of MRC control, and many of the MRC policies from the beginnings until well into the post-war period, under Fletcher as well as his successors, were designed to extend this influence to areas of medicine which they perceived as following different agendas, incompatible with MRC ethos.[14] One example was cancer research, which initially was dominated by the Imperial Cancer Research Fund (ICRF), an organization that had close ties with the Royal College of Physicians.[15]

While there was considerable emphasis on fundamental research, clinical research was part of the MRC program almost from the beginning. Fletcher's obituary for the Royal Society, for example, was written by his friend, Thomas Renton Elliott, the first full-time Professor of Medicine at University College Hospital (UCH) London, himself a Cambridge man and one of the central players when it came to importing Cambridge research traditions and MRC ethos into the clinic. It was Elliott who proposed Fletcher for the post of MRC secretary in 1913. Theirs was an approach to the clinic that was new for Britain, modeled on continental European examples refracted through the prism of US institutional reform. The men who shaped the policies of the Council in the early years believed that investigations in the physiology laboratory provided the best model for good clinical research and practice. As long as only a few 'rational' remedies were available, foundations had to be laid in the laboratory, which explains the initial emphasis on fundamental research. Medical education at the clinical level also was to be reorganized, following the model of the basic sciences, and students were to be taught by full-time clinicians who were also researchers. This may sound

banal to us, as most medical research and teaching is organized along these lines today, but it was not banal in inter-war Britain, where most medical schools, in the words of Donald Fisher, "remained essentially 'trade schools'", with clinical teachers holding part time appointments and living on income generated by private practice.[16] Most of London's medical schools were associated with voluntary hospitals, and they maintained a considerable degree of independence from the University of London until well into the twentieth century, despite joining the university as 'schools' in 1900. The promoters of the MRC disapproved of the prevailing attitude at these schools which viewed research as a "private hobby".[17] There was also, as Chris Lawrence has argued, more fundamental opposition to the approaches promoted by the MRC from members of the medical elite who objected to the extension of experimental practices to the clinic and insisted that clinical knowledge was different from the knowledge generated in the laboratory. It was incommunicable, they argued, and could only be acquired by way of bedside practice.[18]

The conflicts between the Council and the Royal Colleges, the traditional representatives of all things medical in Britain, as David Cantor has shown, found their expression in controversies over the uses of radium for research and in treatment of cancer in the interwar period.[19] In 1919, the Medical Research Committee had acquired 5 grams of hydrated radium bromide, an extremely valuable and scarce resource that provided the basis for the MRC's programme of radiological research. This programme was initially predominantly clinical rather than biological, as it proved difficult for Fletcher to promote an experimentalist agenda in face of the increasing visibility of cancer and the growing belief that radium might provide a solution to the problem of therapy, as an alternative or in combination with surgery. Surgeons, initially extremely critical towards radium, became interested in the new therapeutic modality towards the late 1920s. In the 1930s, the creation

of a National Radium Commission and a division in the control of radium allowed the Council to expand experimental research. This was not defeat, however: the Commission, while controlled by the Colleges, allocated radium to the various centers under similar conditions concerning record keeping and data evaluation to those the MRC had imposed. The British Empire Cancer Campaign (BECC) was another example of an organization colonized by the Council. Initially founded by a group of London doctors, Fletcher managed to secure the MRC control over the Campaign's Scientific Advisory Committee. The controversies between the Council and the Colleges continued well into the post-war period, when the reorganization of the British healthcare system allowed the MRC to significantly expand its influence and the Colleges, too, changed their outlook.[20] Before I turn to these post-war developments, however, let me take a closer look at the traditions that prepared the ground for the post-war clinical research that I will discuss later, above all in two institutions, UCH and the MRC's own National Institute for Medical Research (NIMR).

Clinical science at University College Hospital and the role of the Rockefeller Foundation

The two major pioneers of the clinical science tradition in the MRC were Thomas Lewis and Thomas Renton Elliott.[21] Both had their institutional home at UCH, then the flagship for those who worked to develop British medical studies according to the German-American model. After World War I, University College Medical School and its hospital received substantial amounts of funding from the Rockefeller Foundation in order to enable its transformation into a university medical center modeled on Johns Hopkins University.[22] The UCL center was to serve as a model to other medical schools in Britain and in the Empire. Much of the funding went into the pre-clinical departments on one side of Gower Street, but

the Foundation also funded two clinical 'units' in the hospital across the road, staffed with full-time researchers and teachers and with direct access to laboratories. The MRC provided additional funding, as its statutes prevented it from making capital grants. Its architects intended the unit system as a model for clinical research in Britain. The Rockefeller Foundation subsequently also supported the establishment of units elsewhere in London and in the country and funded the transformation of the School of Tropical Medicine into the new London School of Hygiene and Tropical Medicine (LSHTM), a postgraduate school for hygiene and public health within the University of London, which was going to become the institutional home of Major Greenwood and Austin Bradford Hill and the influential MRC Statistical Unit, to which I will return later. [23]

T.R. Elliott's medical unit and Thomas Lewis's MRC funded department of clinical research and experimental medicine turned into important staging posts in the careers of many clinical researchers in Britain. Lewis, unlike Elliott and Fletcher, was not a Cambridge graduate. He studied at Cardiff before he went to UCH in 1902, where he met Elliott and Henry Dale, another member of the 'club' that was going to shape MRC research traditions.[24] An important influence on Lewis, besides his work in E.H. Starling's physiology laboratory, was a friendship with James Mackenzie. In his research Lewis focused on the heart, its functions and diseases. An active, hands-on researcher, he pioneered the routine clinical use of the ECG and of many other laboratory techniques. Elliott's early research at Cambridge followed the traditions established by Foster and Langley, his director of researches, and dealt with the physiology of the autonomic nervous system. Later, as professor of medicine his publications became infrequent and Elliott's more important roles were those of an administrator and teacher. Elliott and Lewis were close friends and even shared lodgings for a period of time. Lewis self-consciously and repeatedly described his

work as 'clinical science', as though he was laying claim to the term. He changed the title of the journal he founded and edited from *Heart* to *Clinical Science*. His approach to and understanding of clinical science was immensely important for the directions subsequently taken by the MRC. Many young medical graduates who were interested in research spent a year or more in either Lewis's department or Elliott's unit, often supported by Beit Memorial Fellowships, where they were exposed to approaches to the clinic that integrated technologies and practices from the physiology laboratory. [25] These disciples shaped medical research in Britain and the Empire in the decades to come. They included George Pickering and Frederick Smirk, about whom we will hear more later, as well as Harold Himsworth, secretary of the MRC from 1949 to 1968, and John McMichael, later director of the new Postgraduate Medical School in Hammersmith.[26]

The National Institute of Medical Research

The other important birth place of MRC traditions included under 'clinical research' in the post-war definition was the Council's National Institute of Medical Research (NIMR). The institute was set up originally for the Medical Research Committee just before the outbreak of World War I in 1914, in the buildings of the North London Hospital for Consumption, Mount Vernon.[27] During the war the buildings were used by the Army Medical Service, and Thomas Lewis did his research work on 'soldier's heart' at what was then Hampstead Military Hospital.[28] The Institute had four departments: Bacteriology, initially under the directorship of the eminent Sir Almroth Wright; Biochemistry and Physiology with Henry Dale as director; Applied Physiology under Leonard Hill, and Medical Statistics under John Brownlee. I will focus here on Dale's and Brownlee's departments, as these are important for the post-war case studies I want to look at. The four directors initially had equal standing

and the institute was run by a staff committee and a general secretary, but de-facto Dale gained more and more control over both day-to-day and strategic decisions. This arrangement was formalized in 1928 when Dale was appointed overall director of the institute.[29]

Dale, like Elliott was a Cambridge man and a product of the Foster School. Another major professional experience that shaped his approach to research and, more importantly, the ways in which Dale and the Council dealt with the pharmaceutical industry, was his time as director of the Wellcome Physiological Laboratories.[30] Dale had joined Wellcome's new research center in 1902 and, counter to what some of his colleagues assumed, this excursion out of the university and into the expanding corporate world of the pharmaceutical industry did not ruin his academic career. Wellcome left Dale plenty of freedom to pursue his own research. The Wellcome laboratories were the first corporate research establishment of this kind in Britain and Dale's appointment may have provided a model for other companies. As Tilly Tansey has shown, Dale managed to combine productive research in the Cambridge physiology tradition with commercial exploration.[31] He also valued the experiences he gained with routine tasks and in his later career at the NIMR used what he learned about the every-day work in a corporate laboratory, for example on the bread and butter issue of standardizing biological compounds. Dale managed to turn the Institute into not only a national, but an international center for the standardization of therapeutic substances. The Institute under Dale also actively promoted therapeutic substances that were products of laboratory research and thus embodied the new ethos of scientific medicine as embraced by the MRC, such as insulin or penicillin.[32]

The NIMR's Department of Medical Statistics, and later the London School of Hygiene and Tropical Medicine, were home to another tradition that shaped the self

understanding of the MRC in the post-war world and, with its work on the health effects of smoking, also the public image of the Council.[33] The first director of the Department, John Brownlee in this regard was far less effective than a Ministry of Health employee transferred to the NIMR in 1920, Major Greenwood.[34] Both were disciples of the eugenicist Karl Pearson.[35] Greenwood was a personal friend of Walter Fletcher. By then chair of the MRC Statistical Committee, he accepted an appointment to the London School of Hygiene and Tropical Medicine and when Brownlee died in 1927, the Council decided to bring all statistical work under his direction. In 1945 Greenwood was succeeded by Austin Bradford Hill and the LSHTM group became the MRC Statistical Research Unit.[36] As we will see, this unit left its mark on many of the MRC's post-war activities, not least through its crucial involvement in the iconic streptomycin trials and work on smoking and health.[37]

Post-war reorganization

Rockefeller money and MRC initiatives turned the UCH center into a moderate success (researchers there complained about the heavy teaching load), but such activities initially were mainly centered on London, and the status of medical academics remained precarious, in relation to other consultants or compared, for example, to professors in the US or Germany. From three in 1939, the number of MRC clinical research units rose to eighteen by 1948.[38] However, organized clinical research struggled, as Helen Valier has shown, until the massive influx of funds to British medicine in the years following WWII provided a new basis for its organization.[39] In1948 the National Health Act came into operation. Centrally funded through general taxation and national insurance contributions, the new National Health Service, encompassing general practice, hospital medicine and public health, was designed to provide care from cradle to grave and free at the point of use. [40] This provided

the MRC with an opportunity to broaden its remit. Britain's hospitals were now owned by the state. The MRC, since the interwar period the body on which the government drew in most questions of medical research, was the ideal partner for new negotiations over access for researchers. Harold Himsworth, Secretary of the Council from 1949, along with other members of the influential '42 Club' of medical academics (many of them with MRC links) had liaised with Ministry of Health officials and members of parliament about provisions for teaching and research even before the National Health Act was passed.[41] There was by now also a sufficient supply of trained researchers to staff new positions. The reorganisation provided an opportunity to secure their career paths and 'export' MRC ethos to provincial hospitals.

One important vehicle through which the Council broadened its control over clinical research was the Clinical Research Board (CRB), set up following the report of a Joint Committee chaired by Sir Henry Cohen, published in 1953 as a government White Paper.[42] The remit of the CRB, whose members were appointed by the MRC after consultation with the Health Departments, was to advise on the placement of new research units and the running and staffing of existing ones, as well as on decentralized research (i.e. research not organized and funded by the MRC), research grants and training awards. MRC spending on investigations directly concerned with patients rose from circa £400,000 in 1951-52, before the Cohen Report to circa £700,000 in 1955-56.[43] Much clinical research in Britain, if not funded by the MRC, responded to MRC advice, was performed by researchers trained in the clinical units, or drew on extensive, formal and informal MRC networks. In the following sections I will look at two complexes of postwar research that exemplified the role that these networks played in disseminating the traditions established in the interwar period, on the etiology and treatment of high blood pressure and on bronchial carcinoma.[44]

Hypertension

Much attention in medical research in the postwar era turned from infectious to non-infectious and chronic conditions such as cancer or cardiovascular disease. British researchers left their marks in both these fields, and in the following I will look at the role of MRC networks in this research. In hypertension, two major shifts could be observed, one in the understanding of its etiology and the other therapeutic.[45] Firstly, high blood pressure turned into a disorder where the boundary between normal and pathological was blurred, defined by statistics and notions of risk. Secondly, while the origins of essential hypertension remained obscure and contested, new therapies, including drugs became available for the treatment of high blood pressure. The early drugs had quite drastic side effects, and their use was only justifiable for malignant hypertension, cases where the high blood pressure had led to clearly diagnosable and often life threatening pathological changes. These drugs demonstrated that it was possible to use drugs for the management of blood pressure over long periods of time, and new drugs with less drastic side effects made it acceptable to treat ever lower blood pressures.[46] Both in controversies over the etiology of high blood pressure and in the development of new drugs, formal and informal MRC networks played major parts.

At the node of one of these networks was George White Pickering, member of the second generation of full-time professors and director of one of the new clinical units in London, at St Mary's Hospital Medical School. Pickering was a Cambridge graduate and a Lewis disciple who had joined the UCH department with a Beit fellowship.[47] At UCH he had taken up research on blood pressure. Before the war, this research was mostly physiological, concerned with mechanisms and particularly the hormonal regulation of blood pressure.[48] After the war, triggered by a publication by Robert Platt, Manchester's first full-time

professor of medicine, Pickering turned to the etiology of high blood pressure and the role of inheritance.[49] With colleagues at St Mary's he sought to organize an epidemiological study to test Platt's assumption that hypertension was a single-gene trait whose inheritance followed a simple Mendelian pattern. While Platt had studied the relatives of patients treated for high blood pressure in his Manchester clinic, Pickering and his colleagues surveyed the blood pressures of surgical outpatients at the hospital, a sample that they hoped to be representative of the wider British population.[50] Initially unsure about the best way of dealing with the data, Pickering turned to an expert within the MRC network, the geneticist and statistician John Alexander Fraser Roberts at the London School of Hygiene and Tropical Medicine, who devised a score method that allowed correcting for age and sex.[51] As a consequence of the study, as I have discussed in greater detail elsewhere, Pickering and his colleagues came to challenge the predominant view of hypertension as distinct disease entity, contributing to its conceptual transformation into a quantitative rather than a qualitative phenomenon.[52] Guided by Fraser Roberts, Pickering looked to Galton and Pearson, the founding fathers of the biometric tradition for examples, comparing blood pressure to body height. Hypertensive patients, according to Pickering, did not suffer from a specific disorder. Rather, like for very tall or very short people, the difference was quantitative. The distribution of blood pressure in the population could be described by a normal distribution, and patients with high blood pressure found themselves on one extreme of the bell curve. Blood pressure rose with age and close relatives resembled one another in blood pressure as in other characteristics. According to the MRC Annual Report, these "observations suggested that what is called essential hypertension is not an entity but a convenient label given to those with arterial pressures above a level selected on arbitrary grounds".[53] Pickering disseminated his thinking about high blood pressure as author of some of the most

important textbooks on the subject.[54] He continued to collaborate with epidemiologists at the MRC's pneumoconiosis research unit in South Wales.[55] Moving from St Mary's to Oxford, where he was appointed as Regius Professor of Medicine in 1956, he played an important role in the reorganization of medical research and medical teaching in Britain for years to come.

The transformation of high blood pressure was associated not only with changing views about its etiology but also with new treatment methods, and here, too, MRC networks were important. One of the first drugs for the treatment of hypertension, hexamethonium, was the product of such a network, and I have analyzed the development of this drug elsewhere in detail.[56] Pickering's work on the etiology of high blood pressure gained its decisive innovative impetus from contacts between the clinical science and statistical traditions. In the development of hexamethonium, pharmacology in the Dale tradition met clinical science, with the MRC assuming the role of a booster. The node of the network in this case was William Paton, a physiologist and pharmacologist in Henry Dale's former laboratory at the NIMR.[57] Paton stumbled over the methonium drugs while testing a antibiotic compound for a colleague in the institute in 1947. As became clear fairly quickly, the methonium compounds, depending on the length of the carbon chain, had a variety of effects on the autonomic nervous system – a subject of much research in Cambridge physiology. They were characterized as ganglion blockers, a label that had been used by pharmacologists at Harvard to describe the effects of Tetraethylammonium (TEA), a drug with a related structure. [58] While in previous decades such experimental compounds rarely made it into the clinic, this was different for the methonium compounds in the post-war period. Curare and its active principle had long been subjects of research at the NIMR.[59] As Paton and colleagues established in animal tests and heroic self experiments, decamethonium

(C10) had clinical potential for use in surgery as a synthetic curare analog, while pentamethonium and hexamethonium (C5 and C6) promised to be useful in the treatment of high blood pressure and stomach ulcers.[60]

The search for clinical applications was actively promoted by the MRC and Paton put in charge of an ad-hoc committee for evaluating the drug in further clinical experiments.[61] Clinicians in a number of centers in the UK were contacted, and a number of small-scale clinical trials organized whose results were published between 1948 and 1950, when the Council hosted a conference on these clinical tests.[62] The responses for blood pressure treatment were optimistic, but very cautious, due to difficulties with dosage and considerable side effects. The decisive break-through came from Frederick Horace Smirk, a clinician who, supported by a Beit Fellowship, had trained with Elliott at UCH in the 1930s.[63] In 1940 he found himself in the dominions, as the first full-time professor of medicine at Otago Medical School in Dunedin, New Zealand, where he attempted to construct a center modeled on UCH. In 1949, during a sabbatical spent at the Postgraduate Medical School in Hammersmith on invitation of John McMichael, another former Beit fellow at UCH, Smirk was introduced to the effects of hexamethonium on blood pressure. He had long been screening compounds for their antihypertensive effects and on his return to New Zealand took a supply of hexamethonium with him, provided by the drug house May and Baker at the initiative of the MRC. Smirk was a therapeutic enthusiast, believing (like Edward Freis in the US) that clinicians were justified in treating patients with high blood pressure even without much knowledge about its causes.[64] With his colleagues Smirk developed a regime that overcame the problems of dosage by administering the drug subcutaneously with a tuberculin syringe and training the patients to do this themselves (like diabetics injected their insulin). They also developed a number of simple fixes for the most

common side effects.[65] Partly thanks to Smirk's advocacy – like Pickering he wrote a textbook[66] – it became acceptable to treat hypertensive patients, initially those with malignant hypertension, over long periods of time, with the intention not to cure the disorder but to manage the blood pressure.[67]

Lung Cancer

Hypertension research was one example of the MRC extending its influence by promoting approaches from a combination of traditions established in the interwar period. Clinical cancer research was another case, and here I want to look particularly at lung cancer.[68] The MRC had sought to incorporate the prestigious field of cancer research into its activities from early on in its history.[69] The restructuring of the British health system with the introduction of the NHS in 1948 enabled the Council to assume the central role long aspired to by its officers and advocates. However, the territory of cancer research that the Council attempted to colonize in the 1950s and 1960s was contested. Clinicians and scientists interested in cancer research already had the resources of the ICRF, the BECC, and cancer centers such as the Marsden and Christie hospitals to draw on.[70] However, as we have heard, the MRC already played a central role in the organization of radiotherapy. Below I will take a brief look at two further inroads into cancer research, based on traditions established in the inter-war period. The first of these is lung cancer epidemiology, especially the work by Richard Doll and Austin Bradford Hill on the effects of smoking, and the second is the attempt to organize therapeutic trials for cancer on the back of the successful trials of streptomycin in the treatment of tuberculosis.

Lung cancer emerged after World War II as the major cause of cancer deaths and a particular public health problem. A rare disease at the turn of the century, incidence and

mortality had been increasing noticeably and exponentially since the 1920s. Initially it was controversial if this was a real increase or just coincidental as changes in the health system and insurance coverage led to more men dying in hospital and subsequently being autopsied, the only way of conclusively diagnosing the disease. After the war the increase was generally accepted as real and controversy turned to its causes. Cigarette smoking was one of the chief suspects, along with air pollution, industrial exposure or tarring of the roads.[71] The controversy over "Tobacco Smoking and Cancer of the Lung" was one of the few occasions on which the MRC, in 1957, issued a public statement.[72] The statement drew on the innovative epidemiological work on the subject by Hill and Doll at the Statistical Research Unit at LSHTM.[73] Doll and Hill first undertook a retrospective investigation, in the course of which they collated interview data relating to nearly 5,000 hospital patients, including circa 1,500 suffering from lung cancer, revealing only one significant difference between patients with and without lung cancer: lung cancer patients were much more likely to be cigarette smokers and to smoke heavily.[74] Still, many in politics and the wider public remained unconvinced, especially as experimental research on the effects of tobacco smoking yielded inconclusive results.[75] In response to such doubts, Doll and Hill devised a prospective study, sending out a questionnaire to all registered members of the medical profession. More than 40,000 doctors replied, were classified according to their smoking habits and followed up.[76] This study produced results that led to the 1957 MRC Statement and a Report of the Royal College of Physicians in 1962, and to a broad consensus in the UK that cigarette smoke was the main cause of lung cancer.[77]

Lung cancer was not only a subject of epidemiological research, but also part of the MRC's strategy to develop therapeutic cancer research, and here the statistical tradition was combined with clinical research in a narrower sense. In the early 1950s, before the link with

smoking became general consensus, carcinoma of the bronchus was not yet framed as a disease that had to be prevented rather than cured. While the expectations of survival were bleak for lung cancer patients, they were not significantly worse than for other malignant diseases. In 1957 the MRC held a Conference on the Evaluation of Different Methods of Cancer Therapy. The conference, under the chairmanship of the renowned Professor of Radiotherapy at Middlesex Hospital Medical School, Brian W. Windeyer, recommended that the Council "should consider undertaking an investigation into the treatment of certain tumours which appeared particularly suitable for short-term study".[78] The purpose of the meeting was to prepare a series of therapeutic studies for cancer along the lines of the Council's preferred, biomedical model of controlled intervention. Lung cancer was included in the list of cancers that were thought suitable explicitly because much was known about its etiology and because of its short natural history after diagnosis.[79] The agenda set by the recommendations of the 1957 conference was heavily geared towards the evaluation of new approaches in radiotherapy. Radiotherapy was the form of therapy from which British cancer specialists most expected innovative impulses. [80] The studies were motivated, as much as by the urge to tackle a major public health problem, by the desire to extend the MRC's remit by applying and combining a set of promising new technologies in which the Council had invested, besides radiotherapy the randomized controlled trial (RCT), a set of methods that had gained public attention and professional acclaim through use in the evaluation of the effects of streptomycin in the treatment of tuberculosis.[81] The central role assigned to statistics was reflected by the fact that Bradford Hill, credited with some of the more innovative aspects of the RCT approach, was a member of most of the working parties set up for the different cancers. He was joined by radiotherapists and by specialists who traditionally treated the respective organs, in the case of lung cancer chest physicians and

surgeons. The chairman of the lung cancer working party, J.G. Scadding, and its secretary, J.R. Bignall, both based at the Brompton Hospital for Diseases of the Chest in London, were also veterans of the streptomycin trials.

The organization of the lung cancer trials proved difficult, not least, as I have argued elsewhere, because with surgical resection of the affected lung (or parts of it) there was a mature, generally accepted therapy in place.[82] The working party was confronted with long and frustrating debates over the ethics and the feasibility of trials, focusing especially on randomization and the withholding of surgery. Was it acceptable to treat operable patients with radiotherapy? How reliable were the results of experimental radiotherapy if only "surgical rejects" were treated?[83] Trials that were practically feasible and addressed questions of interest could not be justified ethically, and ethically justifiable trials addressed problems that were comparably marginal. Radiotherapists and chest surgeons, when invited for consultations, were distinctly unenthusiastic (in many ways continuing some of the controversies of the inter-war period). The working party finally, in 1961, decided on a trial that compared surgery and radiotherapy for small cell lung cancer, a cell type that metastasized particularly quickly and for which the use of surgery was controversial, and a second trial looking at two different forms of adjuvant chemotherapy. The studies were organized by the MRC Tuberculosis Research Unit under Philip d'Arcy Hart, the unit that had also been in charge of the streptomycin trials. However, while the latter assumed iconic status, the results of the lung cancer trials were disappointing, and along with the problems that had emerged during their preparation left their organizers frustrated.[84] And this had nothing to do with bad organization: a note in the administrative file dealing with the study states: "It seems to me that there is nothing at all controversial about this report, which is a straightforward account of a difficult but well organized clinical trial, the outcome of which

has been as depressing as it was predictable."[85] Along with the increasing recognition of the link with smoking, this frustration about the results of therapeutic trials contributed to a shift of focus from therapy to prevention and the prevailing notion that lung cancer was a particularly hopeless cancer.

Conclusion

Lung cancer therapy, in contrast with hypertension research, as I have argued, was a case where the Council's strategy did not work particularly well, the strategy of combining MRC networks, traditions and methods developed with MRC investment to facilitate the desired extension of the Council's influence and ethos, ultimately to all areas of medical research in Britain. Radiotherapists, especially those in well established regional centers like, for example, Manchester's Christie Hospital, had developed their own statistical methods and their interest in an RCT comparing radiotherapy with surgery was limited. They felt, with some justification, that their work was already sufficiently scientific. The surgeons proved difficult to convince, too. And these were not the most conservative of surgeons, either. Thoracic surgery at the time was an innovative field, and lung resection had only very recently become a routine operation.[86] Such a failure to convince crucial specialists was unfortunate, as the RCT, probably like few other methods, embodied the ethos that the MRC wanted to see applied to clinical research. It represented the successful use in the clinic of experimental methods: a carefully planned investigation and more than just observation, this was what the MRC Annual Reports meant when they called for use of 'the scientific method' in clinical research. However, other working parties were more successful, and by the 1970s the MRC organized whole series of randomized controlled trials for different forms of malignant disease, working alongside with ICRF and CRC (the successor

organization to the BECC).[87] This may have less to do with the MRC's activities, however, and more with contemporary developments in the US, especially the successes with experimental chemotherapy in the treatment of leukemia and lymphomas, leading to the notion in the 1970s that these diseases were curable.[88] For leukemia and lymphomas, it seems, the trial organizers managed to create and maintain the sense of hope that activists are now keen to bring to lung cancer research.

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[1] Carsten Timmermann, "Lung Cancer, Clinical Trials, and the Medical Research Council in Post-War Britain," *Bulletin of the History of Medicine*, 2007, *81*: 312-34; idem, "Hexamethonium, Hypertension and Pharmaceutical Innovation: The Transformation of an Experimental Drug in Post-War Britain," in *Devices and Designs: Medical Technologies in Historical Perspective*, ed. Carsten Timmermann and Julie Anderson (Basingstoke: Palgrave Macmillan, 2007), 156-74; idem, "A Matter of Degree: The Normalisation of Hypertension, circa 1940-2000," in *Histories of the Normal and the Abnormal*, ed. Waltraud Ernst (London: Routledge, 2006), 245-61; idem, "To Treat or Not to Treat: Drug Research and the Changing Nature of Essential Hypertension," in *The Risks of Medical Innovation: Risk Perception and Assessment in Historical Context*, ed. Thomas Schlich and Ulrich Tröhler (London: Routledge, 2006), 133-47.

[2] The main works on the history of the MRC are a two-volume history by a senior administrator of the Council, A. Landsborough Thomson, *Half a Century of Medical Research* (London: HMSO, 1973, 1975) and a collection of essays edited by Joan Austoker and Linda Bryder, *Historical Perspectives on the Role of the MRC* (Oxford: Oxford University Press, 1989). Especially relevant for this paper is Christopher C. Booth, "Clinical Research," in ibid., 205-41. See also idem, "From Art to Science: The story of clinical research," in *A Physician Reflects: Herman Boerhaave and other Essays* (London: Wellcome Trust Centre for the History of

Medicine at UCL, 2003), 79-101; idem, "Clinical Research," in *Companion Encyclopedia of the History of Medicine*, ed. William F. Bynum and Roy Porter (London & New York: Routledge, 1993), 205-29. Many of the important figures in the early history of the Council were fellows of the Royal Society, and their biographies have been published in the *Obituary Notices*, later *Biographical Memoirs of Fellows of the Royal Society*. I will cite these where I draw on them.

[3] MRC Annual Report 1951-1952, p. 3.

[4] Ibid.

[5] Ibid., p. 4.

[6] Ibid.

[7] MRC Annual Report 1955-1956, p. 5. This passage is a quote from the 1953 Cohen Report.

[8] MRC Annual Report 1951-1952, p. 4.

[9] Ibid.

[10] Linda Bryder, "Tuberculosis and the MRC," in *Historical Perspectives*, ed. Austoker and Bryder (n. 2), 1-21.

[11] On the Foster school see Gerald L. Geison, *Michael Foster and the Cambridge School of Physiology: The Scientific Enterprise in Late Victorian Society* (Princeton: Princeton University Press, 1978). On networks that had their roots in the Cambridge school, see also Abigail O'Sullivan, *Networks of Creativity: A Study on Scientific Achievement in British Physiology, c. 1881-1945* (D.Phil. dissertation: University of Oxford, 2002).

[12] Joan Austoker, "Walter Morley Fletcher and the Origins of a Basic Biomedical Research Policy," in *Historical Perspectives*, ed. Austoker and Bryder (n. 2), 23-33. See also Thomas R.

Elliott, "Sir Walter Morley Fletcher," *Obituary Notices of Fellows of the Royal Society*, 1935, *1*: 153-63.

[13] Ibid., p. 163.

[14] Austoker, "Walter Morley Fletcher" (n. 12), p. 24.

[15] On the history of the ICRF, see Joan Austoker, *A History of the Imperial Cancer Research Fund 1902-1986* (Oxford: Oxford University Press, 1988).

[16] Donald Fisher, "The Rockefeller Foundation and the Development of Scientific Medicine in Great Britain," *Minerva*, 1978, *16*: 20-41, p. 23.

[17] Ibid., p. 25.

[18] Christopher Lawrence, "Still Incommunicable: Clinical Holists and Medical Knowledge in Interwar Britain," in *Greater than the Parts: Holism in Biomedicine 1920-1950*, ed. Chistopher Lawrence and George Weisz (New York & Oxford: Oxford University Press, 1998), 94-111.

[19] David Cantor, "The MRC's Support for Experimental Radiology During the Inter-War Years," in *Historical Perspectives*, ed. Austoker and Bryder (n. 2), 181-204.

[20] See Christopher C. Booth, "Smoking and the Gold-Headed Cane: The Royal College of Physicians Enters the Modern World," in *A Physician Reflects* (n. 2), 155-160.

[21] Henry H. Dale, "Thomas Renton Elliott," *Biographical Memoirs of Fellows of the Royal Society*, 1961, *7*: 53-74; A.N. Drury, R.T. Grant, "Thomas Lewis," *Obituary Notices of Fellows of the Royal Society*, 1945, *5*: 179-202.

[22] Fisher, "The Rockefeller Foundation" (n. 16).

[23] Ibid. See also Helen K. Valier, *The Politics of Scientific Medicine in Manchester* (PhD dissertation: University of Manchester, 2002).

[24] On Dale, see W.S. Feldberg, "Henry Hallet Dale," *Biographical Memoirs of Fellows of the Royal Society*, 1970, *16*: 77-174; E.M. Tansey, "What's in a name? Henry Dale and Adrenaline, 1906," *Medical History*, 1995, *39*: 459-76; idem, 'Sir Henry Dale and Autopharmacology: The Role of Acetylcholine in Neurotransmission,' *Clio Medica*, 1995, *33*: 179-93.

[25] The Beit Memorial Trust was founded in 1909. Both Lewis and Elliott received Beit Memorial Fellowships. Lewis was the first Beit Fellow in 1909. Cf Dale, "Thomas Renton Elliott" (n. 21), p. 68.

[26] Cf Booth, "Clinical Research" (n. 2). See also idem, *A Physician Reflects* (n. 2); Douglas Black and John Gray, "Sir Harold Percival Himsworth, K.C.B.," *Biographical Memoirs of Fellows of the Royal Society*, 1995, *41*: 200-18; Colin Dollery, "Sir John McMichael," *Biographical Memoirs of Fellows of the Royal Society*, 1995, *41*: 282-96.

[27] Joan Austoker and Linda Bryder, "The National Institute for Medical Research and Related Activities of the MRC," in *Historical Perspectives*, ed. Austoker and Bryder (n. 2), 35-57.

[28] Joel D. Howell, "'Soldier's Heart': the Redefinition of Heart Disease and Speciality Formation in Early Twentieth Century Great Britain," *Medical History*, 1985, *Supplement No 5*: 34-52.

[29] Austoker and Bryder, "The National Institute for Medical Research" (n. 27).

[30] See references in note 24.

[31] Tansey, "What's in a Name?" (n. 24).

[32] See Jonathan Liebenau, "The MRC and the Pharmaceutical Industry: the Model Insulin," in *Historical Perspectives*, ed. Austoker and Bryder (n. 2), 163-180; idem, "The British Success with Penicillin," *Social Studies of Science*, 1987, *17*: 69-86.

[33] Edward Higgs, "Medical Statistics, Patronage and the State: The Development of the MRC Statistical Unit 1911-1948," *Medical History*, 2000, *44*: 323-40.

[34] Lancelot Hogben, "Major Greenwood," *Obituary Notices of Fellows of the Royal Society*, 1950, *19*: 139-154.

[35] Eileen Magnello, "The Introduction of Mathematical Statistics into Medical Research: The Roles of Karl Pearson, Major Greenwood and Austin Bradford Hill," *Clio Medica*, 2002, *67*: 95-123.

[36] Richard Doll, "Austin Bradford Hill," *Biographical Memoirs of Fellows of the Royal Society*, 1994, *40*: 128-40.

[37] J. Rosser Matthews, *Quantification and the Quest for Medical Certainty* (Princeton: Princeton University Press, 1995). On streptomycin, see Alan Yoshioka, "Streptomycin in Postwar Britain: A Cultural History of a Miracle Drug,' *Clio Medica*, 2002, *66*: 203-27; idem, "Use of Randomisation in the Medican Research Council's Clinical Trial of Streptomycin in Pulmonary Tuberculosis in the 1940s," *British Medical Journal*, 1998, *317*: 1220-3. On smoking, see S.A. Lock, L.A. Reynolds, and E.M. Tansey, eds, *Ashes to Ashes: The History of Smoking and Health* (Amsterdam & Atlanta: Rodopi, 1998).

[38] MRC Annual Report 1951-1952, p. 5.

[39] Valier, *The Politics of Scientific Medicine* (n. 23).

[40] For an overview of the origins and development of the NHS see Charles Webster, *The National Health Service: A Political History* (Oxford: Oxford University Press, 1998); Rudolf Klein, *The New Politics of the NHS*, 3rd edition (London: Longman, 1995); Geoffrey Rivett, *From Cradle to Grave: Fifty Years of the NHS* (London: The King's Fund, 1998).

[41] Cf L.A. Reynolds & E.M. Tansey, eds, *Clinical Research in Britain, 1950-1980: A Witness Seminar held at the Wellcome Institute for the History of Medicine, London, on 9 June 1998* (London: Wellcome Centre, 2000), pp. 12, 16; Christopher C. Booth, "Pioneers in the World of Academe: History of the '42 Club'," in *A Physician Reflects* (n. 2), 103-115.

[42] Medical Research Council, Ministry of Health, Department of Health for Scotland, Central Health Services Council, Advisory Committee on Medical Research in Scotland, *Clinical Research in Relation to the National Health Service* (London: HSMO, 1953).

[43] MRC Annual Report 1951-1952; MRC Annual Report 1955-1956.

[44] For the official MRC take on these episodes, see MRC Annual Reports 1948-1950, pp. 20-21; 1952-1953, pp. 30-33; 1953-1954, pp. 4-8; 1955-1956, pp. 10-14.

[45] For reflections on these changes, see Colin T. Dollery, "A Clinician Looks at the Future," *British Journal of Clinical Pharmacology*, 1982, *13*: 127-32.

[46] See Timmermann, references in note 1; Jeremy Greene, "Releasing the Flood Waters: Diuril and the Reshaping of Hypertension," *Bulletin of the History of Medicine*, 2005, *79*: 749-94.

[47] On Pickering, see John McMichael and W.S. Peart, "George White Pickering," *Biographical Memoirs of Fellows of the Royal Society*, 1982, *28*: 431-49.

[48] MRC Annual Report 1952-1953, pp. 30-33.

[49] Robert Platt, "Heredity in Hypertension," *Quarterly Journal of Medicine*, 1947, *16*: 111-33. The debate is documented in J.D. Swales, *Platt Versus Pickering: An Episode in Recent Medical History* (London: The Keynes Press, 1985).

[50] M. Hamilton, G.W. Pickering, J.A. Fraser Roberts, G.S.C. Sowry, "The Aetiology of Essential Hypertension. 1. The Arterial Pressure in the General Population," *Clinical Science*, 1954, *13*: 11-35.

[51] On Fraser Roberts, see P.E. Polani, "John Alexander Fraser Roberts," *Biographical Memoirs of Fellows of the Royal Society*, 1992, *38*: 306-22.

[52] Timmermann, "A Matter of Degree" (n. 2).

[53] MRC Annual Report 1952-1953, p. 32.

[54] For example, George W. Pickering, *High Blood Pressure* (London: Churchill, 1955); idem, *The Nature of Essential Hypertension* (London: Churchill, 1961); idem, I.W. Cranston, and M.A. Pears, *The Treatment of Hypertension* (Springfield, Ill: Charles C. Thomas, 1961)

[55] Pickering Papers, Wellcome Library London, PP/GWP/C.6/51.

[56] Timmermann, "Hexamethonium" (n. 2).

[57] For Paton's account of the story, see William D.M. Paton, 'Hexamethonium', *British Journal of Clinical Pharmacology*, 1982, *13*: 7-14. See also H.P. Rang and P. Walton, "Sir William Drummond MacDonald Paton, CBE," *Biographical Memoirs of Fellows of the Royal Society*, 1996, *42*: 290-314.

[58] George H. Acheson, "Tetraethylammonium, Ganglionic Blocking Agents, and the Development of Antihypertensive Therapy," *Perspectives in Biology and Medicine*, 1975, *19*: 136-

48; Gordon K. Moe, Walter A. Freyburger, "Ganglionic Blocking Agents," *Pharmacological Reviews*, 1950, *2*: 61-95.

[59] MRC Annual Report 1948-1950, pp. 20-21.

[60] Ibid. See also "The Methonium Compounds" [editorial], *British Medical Journal*, 1950, *i*: 474-5.

[61] Green to Paton, 18 July 1950, UK National Archives, FD1/1172.

[62] Conference on Clinical Tests of Methonium Drugs, 22 June 1950, Minutes of the Meeting, UK National Archives, FD1/1172.

[63] Austin E. Doyle, "Sir Horace Smirk: Pioneer in Drug Treatment of Hypertension," *Hypertension*, 1991, *17*: 247-50.

[64] For Freis's views, see Edward D. Freis, "Recent Developments in the Treatment of Hypertension," *Medical Clinics of North America*, 1954, *38*: 363-74.

[65] F. Horace Smirk, *Instructions for Patients on C6 Injections*, and *Organisation of a Hypertensive Clinic, more particularly for patients on methonium treatment*, typescripts, October 1951, UK National Archives, FD1/1172.

[66] F. Horace Smirk, *High Arterial Pressure* (Oxford: Blackwell, 1957); F.N. Fastier, "Biography: Sir Horace Smirk: Professor Emeritus," *New Zealand Medical Journal*, 1968, *67*: 258-65.

[67] "Methonium and Hypertension" [editorial], *Lancet*, 1951, *257*: 395-6. See also MRC Annual Report 1952-1953, p. 33.

[68] For a more detailed analysis, see Timmermann, "Lung cancer" (n. 2).

[69] An early, successful chapter in the history of the Council was, for example, its role in the distribution of radium in the interwar period. See Cantor, "The MRC's Support for Experimental Radiology" (n. 19).

[70] On the ICRF, see Austoker, *A History of the Imperial Cancer Research Fund* (n. 15).

[71] On the debates over smoking and health, see Lock, Reynolds, and Tansey, eds, *Ashes to Ashes* (n. 37). For the US, see also Allan M. Brandt, *The Cigarette Century: The Rise, Fall, and Deadly Persistence of the Product That Defined America* (New York: Basic Books, 2007).

[72] Medical Research Council, "Medical Research Council's Statement on Tobacco Smoking and Cancer of the Lung," *Lancet*, 1957, *272*: 1345-7. Cf Thomson, *Half a Century* (n. 2), Vol. 1, p. 185.

[73] On smoking and epidemiological innovation, see Luc Berlivet, "'Association or Causation?' The debate on the scientific status of risk factor epidemiology, 1947-c.1965," *Clio Medica*, 2005, *75*: 39-74.; Colin Talley, Howard I. Kushner, and Claire Sterk, "Lung Cancer, Chronic Disease Epidemiology, and Medicine, 1948-1964," *Journal of the History of Medicine and Allied Sciences*, 2004, *59*: 329-74; Gerry Hill, Wayne Millar, and James Connelly, "'The Great Debate': Smoking, Lung Cancer, and Cancer Epidemiology," *Canadian Bulletin of Medical History*, 2003, *20*: 367-86.

[74] Richard Doll and Austin Bradford Hill, "A Study of the Aetiology of Carcinoma of the Lung," *British Medical Journal*, 1952, *ii*: 1271-86.

[75] Cf Virginia Berridge, 'Science and Policy: The Case of Postwar British Smoking Policy', *Clio Medica*, 1998, *46*: 143-62.

[76] Richard Doll and Austin Bradford Hill, "Lung Cancer and other Causes of Death in Relation to Smoking: A Second Report on the Mortality of British Doctors," *British Medical Journal*, 1956, *ii*: 1071-81.

[77] Royal College of Physicians, *Smoking and Health: A Report of The Royal College of Physicians on Smoking in Relation to Cancer of the Lung and Other Diseases* (London: Pitman Medical Publishing, 1962). See also Booth, "Smoking and the Gold-headed Cane" (n. 20).

[78] Evaluation of Different Methods of Cancer Therapy, Recommendations of the Council's Steering Committee, NA, FD7/327.

[79] Ibid.; Working Party for the Evaluation of Different Methods of Therapy in Carcinoma of the Bronchus, Minutes of the meeting held on 24 June 1958, NA, FD7/327.

[80] On radiotherapy, see Caroline C.S. Murphy, *A History of Radiotherapy to 1950: Cancer and Radiotherapy in Britain 1850-1950* (PhD dissertation: University of Manchester, 1986), and Cantor, "The MRC's Support for Experimental Radiology" (n. 19).

[81] See Yoshioka references in note 37.

[82] Timmermann, "Lung cancer" (n. 1).

[83] Minutes of a Special Meeting with Consultant Surgeons and Radiotherapists, 25 July 1961, NA, FD 7/327.

[84] J.G. Scadding *et al.*, "Comparative Trial of Surgery and Radiotherapy for the Primary Treatment of Small-Celled or Oat-Celled Carcinoma of the Bronchus: First Report to the Medical Research Council by the Working-Party on the Evaluation of Different Methods of Therapy in Carcinoma of the Bronchus," *Lancet* 1966, *288*: 979-86; J.G. Scadding, "Treatment of Bronchial Carcinoma" [letter], *Lancet*, 1967, *289*: 157; Medical Research

Council Working Party, "Study of Cytotoxic Chemotherapy as an Adjuvant to Surgery in Carcinoma of the Bronchus," *British Medical Journal*, 1971, *ii*: 421-8.

[85] Note by J.R.H. [Herrald?], 22 August 1966, NA, FD 7/1151.

[86] Cf Roger Abbey Smith, "Development of Lung Surgery in the United Kingdom," *Thorax*, 1982, *37*: 161-8.

[87] Cf Helen C. Tate, Janet B. Rawlinson, and Laurence S. Freedman, "Randomised Comparative Studies in the Treatment of Cancer in the United Kingdom: Room for Improvement?," *Lancet*, 1979, *314*: 623-625.

[88] Cf Gretchen M. Krueger, *"A Cure is Near": Children, Families, and Cancer in America, 1945-1980* (PhD dissertation: Yale University, 2003).