

**BRITISH PHARMACEUTICAL INDUSTRY,
SYNTHETIC DRUG MANUFACTURE AND THE
CLINICAL TESTING OF NOVEL DRUGS
1895-1939.**

**A thesis submitted to the University of Manchester for
the degree of Doctor of Philosophy in the Faculty of
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ABBREVIATIONS

A&H	Allen & Hanbury's
ABCM	Association of British Chemical Manufacturers
AGFA	Aktiengesellschaft für Anilinfabrikation, (Berlin)
BASF	Badische Anilin und Soda Fabrik
BDH	British Drug Houses
BIPM	British Institute of Preventative Medicine (later Lister Institute)
BMA	British Medical Association
BP	British Pharmacopoeia
CIBA	Gesellschaft für Chemische Industrie Basel
DSIR	Department of Scientific and Industrial Research
FRS	Fellow of the Royal Society
ICRF	Imperial Cancer Research Fund
ICI	Imperial Chemical Industries
IG (Farben)	Interessengemeinschaft (or community of interests)
LSHTM	London School of Hygiene and Tropical Medicine
M&B	May and Baker
MRC	Medical Research Committee 1913-1920 Medical Research Council 1920 onwards
NHI	National Health Insurance
NIMR	National Institute for Medical Research
PRO	Public Record Office
RAMC	Royal Army Medical Corps.
SCI	Society of the Chemical Industry
STC	Scientific and Technical Committee
UCH	University College Hospital
WBSR	Wellcome Bureau for Scientific Research
WCRL	Wellcome Chemical Research Laboratory
WPRL	Wellcome Physiological Research Laboratory

ABSTRACT

British Pharmaceutical Industry, Synthetic Drug Manufacture and the Clinical Testing of Novel Drugs 1895-1939.

This thesis addresses how and when British pharmaceutical firms first manufactured synthetic drugs, and how they persuaded doctors to test novel therapies in clinical trials. Edwardian Britain was reliant on Germany for synthetic drugs, so how did British firms meet this challenge in the First World War, and how was this new form of the British pharmaceutical industry nurtured in the interwar period?

Previous studies have covered the industry's origins in pharmacy roots and dyestuffs, and the growth of the American industry, but without an overall synthesis. There are several good company histories for Britain, and Robson and Quirke compared pharmaceuticals in France and Britain, whilst Tansey examined physiological research at Burroughs Wellcome; but little has appeared on chemical research and synthetic manufacture. I will emphasise the work of Francis Carr who developed synthetic drugs at Burroughs Wellcome, Boots and British Drug Houses. As for testing, the literature covers early statistics and the clinical trials of major biological drugs such as insulin; but these did not originate with industry. With synthetic and other novel drugs, as I show, firms found it difficult to arrange clinical trials and they turned to the MRC for assistance. I examine these negotiations and trials in some detail.

Chapter 1 reviews the historiography of the pharmaceutical industry and the clinical testing of drugs. Chapter 2 examines the varied origins of the industry, contrasting ethical and patent medicines, and comparing Britain with Germany and America. Chapter 3 shows how Burroughs Wellcome combined novel drugs in sophisticated dosage forms, adopting new sales strategies and establishing laboratories to standardise drugs. Their experience in small scale synthesis from 1896 enabled them to prepare German drugs when patents were abrogated in the First World War (chapter 4). The MRC and other firms poached Burroughs Wellcome researchers, and the MRC took standardisation as a central theme, so establishing an international reputation. Chapter 5 addresses the post-war campaigns for tariff protection, and the extension of MRC drug evaluations as British firms strove to remain competitive. Novel vitamin and hormonal drugs allowed them to expand their manufacturing capacity while gaining further experience of drug synthesis. Chapter 6 describes how British firms campaigned for clinical testing of drugs from 1922 – 1930 and explains why a Therapeutic Trials Committee (TTC) was established in 1931. Chapter 7 examines the strategy of Burroughs Wellcome post-war, by analysing the strategic debates within their Scientific and Technical Committee. Chapter 8 examines the TTC, how they favoured British drugs, and how studies complemented their own research interests; it provides insight into the research strategies of British (and foreign) firms, plus an assessment of the TTC as seen by the MRC and by companies. Chapter 9 offers general conclusions and contrasts the position of British manufacturers at the outbreak of the Second World War with their position at the outbreak of the Great War in August 1914. Some opportunities for further work are then identified.

DECLARATION

No portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other University or other Institute of learning.

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Thanks also to Julie Sheppard, archivist and her assistant Lesley Hall at the Contemporary archive centre and archivists at the Royal Society and the Imperial Institute and J. M. Leverton in the research library at Boots Pharmaceuticals and to Mrs. Barbara Roberts who kindly forwarded two books at one time owned by Thomas Henry of Burroughs Wellcome.

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CHAPTER ONE: General Introduction, Aims and Scope of this Thesis.

1.1 Background to the Thesis.

The central questions of this thesis are:

How did British pharmaceutical companies first prepare novel synthetic drugs, and how did they get doctors to test these and their other novel drugs in clinical trials?

The question arose because the modern pharmaceutical industry is based largely on novel synthetic drugs. During the First World War the importance of a British pharmaceutical industry became recognised and British firms switched from preparing drugs at the request of physicians, to offering completely novel agents that were to be tested for the first time in man. Many of these had previously come from Germany. Not all were synthetic, but they were unique in their potency. The wider questions that emerged concern how Britain competed with Germany in the interwar period, and how British firms defined their strategies of drug development, to decide whether to commit to producing synthetic drugs as opposed to plant and animal extracts, inorganic drugs and antisera, and what internal and external factors were considered in making these decisions? Was it necessary for British firms to follow a German model or indeed an American model of drug research?

The thesis is therefore broader in scope than originally planned and demonstrates how close inter-relationships were forged in Britain between industry, academia, government and medical research, particularly for the period 1914-1939. It evaluates significant structural changes within the framework of the British Pharmaceutical industry, from small family owned firms operating independently, to larger businesses that recognised their interdependence and the values of collaboration and negotiation through a representative trade body.

When the First World War was declared, Britain was dependent on Germany for synthetic drugs, as well as many alkaloids and chemical intermediates.¹ How did British pharmaceutical firms synthesise complex essential drugs within weeks of the outbreak of

¹ W. Ormandy, "Britain and Germany in Relation to the Chemical Trade" in W. M. Gardner, The British Coal Tar Industry, Its Origin, Development and Decline (London: Williams & Norgate, 1915): 335-350.

war? What were the precedents on which they built? Having prepared these drugs on a manufacturing scale in the absence of German competition under the emergency conditions of war, how did British firms compete with Germany post-war?

I examine how the British companies used the recognition of their achievements in the Great War to negotiate a better deal in the interwar period, when they were offered various forms of protection in addition to tariffs, including new methods for testing the purity and standardisation of drugs, and then a system of clinical trials which seemed to favour the testing of British drugs. It is important to recognise that British firms themselves requested these operational frameworks and they were not imposed.

The ultimate measure of the success of British firms should not relate simply to the success of individual products. This type of appraisal has previously led to the conclusion that British firms achieved little of consequence in terms of novel discoveries. Rather, I prefer to compare how independent of Germany, Britain had become by the outbreak of the Second World War. In taking this approach I identify a series of factors that contributed to this success, including the large-scale manufacture of novel therapies other than synthetics, and in particular organotherapies (hormones) and vitamins. The common theme was that continued investment was important and a wide range of products contributed to an increase in manufacturing capacity. This then brings recognition of the importance of large-scale manufacture and chemical engineering. A theme throughout the whole thesis is the prominent role of individuals originating from Burroughs Wellcome and I give particular prominence to Francis Howard Carr. Following his training at the Imperial Institute and Pharmaceutical Society, Carr was responsible for the daily running of the Chemical Works reporting to Hooper A. D. Jowett at Burroughs Wellcome for 16 years, and then established synthetic drug manufacture at both Boots and British Drug Houses. He also played a prominent role in the establishment of the Association of British Chemical Manufacturers and their campaigns for protection and clinical trials, and following his success in large-scale production of insulin, he took the influential role of President of the Society of the Chemical Industry and campaigned for better education of chemists, further protection of the British industry, synthetic drug manufacture and again for the establishment of clinical trials. In a sense he becomes the central 'hero' of the thesis, and yet his career has previously received limited attention.

In the latter chapters I examine a series of factors that influenced how British firms got their new drugs tested. Firstly they collaborated with the MRC and the Pharmaceutical Society to demonstrate that biological compounds were standardised, and then they negotiated a means of clinical testing. A key point about these chapters is that they consider the drugs that British industry was producing and not successful imported drugs such as insulin. The MRC built up a network of research centres that became their centres for clinical trials, but they controlled access to the physicians, so much so that when British firms did develop important novel compounds, they began to employ their own physicians in the 1930's to manage the process of establishing clinical trials. A combination of factors therefore led to the success of the British firms - protection from Germany, synthetic chemists with manufacturing expertise, the establishment of laboratories, the introduction of novel organotherapies and vitamins and physiology support, and the associated increased manufacturing capacity. Importantly, collaborations were also established with university chemists and with the MRC, which then allowed the rapid development of novel variants of sulphonamides from 1936. The British pharmaceutical industry was a key partner in driving this forward.

1.2 General Introduction and Historiography.

Although there are several general accounts of American and British pharmaceutical firms, there has not yet been a general synthesis of how the modern British pharmaceutical industry developed, and of the external factors involved.² There have been accounts of individual companies with long pedigrees in pharmacy, but none focusing on chemistry and large-scale drug synthesis.³ The historiography of drugs has focused almost exclusively on

² J. T. Mahoney, The Merchants of Life: an Account of the American Pharmaceutical Industry (New York: Harper, 1959); S. Miall, History of the British Chemical Industry (London: Ernest Benn, 1931); F. N. L. Poynter, The Evolution of Pharmacy (London: Pitman, 1965); C. J. Thomas, "The Pharmaceutical Industry" in Duncan Burn (ed.), The Structure of British Industry volume 2 (Cambridge: Cambridge University Press, 1958): 331-75.

³ E. M. Tansey, "Pills, Profits and Propriety: the Early Pharmaceutical Industry in Britain" Medical History 25.3 (1994): 151-57; Jonathan Liebenau, "The Rise of the British Pharmaceutical Industry" British Medical Journal (3 October 1990): 724-28; Gold on the Green: 50 Years of Glaxo at Greenford (London: Glaxo, 1985); D. Chapman- Huston and E. C. Cripps, Through a City Archway, the Story of Allen & Hanbury's 1715-1954 (London: John Murray, 1954); S. Chapman, Jesse Boot of Boots the Chemist (London: Hodder & Stoughton, 1974); Boots Pure Drug Co. Ltd. (Nottingham: Boots, 1938); R. P.

major natural drugs such as insulin and penicillin, rather than drugs invented by the pharmaceutical industry. These histories therefore give no insight into how British companies developed products of their own research, or the strategies they followed.⁴

This introduction outlines the previous work done in this field and identifies some of the gaps. Chapter 2 develops the details of how the pharmaceutical industry evolved, so the framework is described only briefly here. A common theme is that historians have tried to categorise the British industry as successful or not by measuring how it compared with Germany in terms of synthetic drugs, or with America in terms of external collaborations, often simplifying a complex issue by the choice of unrepresentative case studies. Economic historians have described how the general growth of the pharmaceutical industry was achieved by discovering new drugs, without giving an insight into how this was achieved.⁵ In some cases, they measured success by simply counting the number of patents filed or sales figures, which may be very misleading, especially if the firm had interests other than just pharmaceuticals, as many did, or if there were a series of similar products, some of which never made it to market.⁶ Company policies on patenting certainly varied greatly.

T. Davenport-Hines, J. Slinn, Glaxo, A History to 1962 (Cambridge: Cambridge University Press, 1992); Geoffrey Tweedale, At the Sign of the Plough: 275 Years of Allen & Hanbury's and the British Pharmaceutical Industry (London: John Murray, 1990); Judy Slinn, A History of May & Baker 1834 – 1984 (Cambridge: Hobson's, 1984).

⁴ Gladys Hobby, Penicillin: Meeting the Challenge (New Haven: Yale University Press, 1985); H. F. Dowling, Fighting Infection: Conquests of the Twentieth Century (Cambridge, Mass: Harvard University Press, 1977); R. Hare, The Birth of Penicillin, and the Disarming of Microbes (London: George Allen & Unwin, 1978); R. Hare, "New Light on the History of Penicillin" Medical History 26 (1982) 1.

⁵ W. Duncan Reekie, M. H. Weber, Profits, Politics and Drugs (London: MacMillan, 1975); Michael H. Cooper, Prices and Profits in the Pharmaceutical Industry (Oxford: Pergamon Press, 1966); W. Duncan Reekie, The Economics of the Pharmaceutical Industry (London: MacMillan Press, 1975); Bjorn Lundgren (ed.), Pharmaceutical Economics (Stockholm: The Swedish Institute of Health Economics, 1984); D. Schwartzman, Innovation in the Pharmaceutical Industry (Baltimore: Johns Hopkins, 1977); Sainsbury Report: Committee of Enquiry into the Relationship of the Pharmaceutical Industry with the N.H.S. 1965-7 (London: HMSO, Cmnd. 3410, 1967).

⁶ J. Kemp, "Pharmaceutical Patents: In Britain, India, Italy, Japan and the US" in G. Teeling-Smith (ed.), Innovation and the Balance of Payments: the Experience in the Pharmaceutical Industry (London: Office of Health Economics, 1967): 23; J. Liebenau,

The politics and marketing of drugs have dominated more recent investigations. The Office of Health Economics⁷ has supported the industry, while many authors have been critical of drug safety,⁸ pricing⁹, promotion, animal testing, or more recently, policies in developing and marketing drugs for the Third World,¹⁰ often from pre-conceived positions.¹¹

Haber, in his otherwise exhaustive discussion of the chemical industries in 1971 concluded: “There is not enough material on the growth of proprietary medicines and, during the early part of the present (twentieth) century, of the pharmaceutical industry.” He went on: “Although it would encounter great obstacles, a study of the early years of the pharmaceutical industry in the principal countries would make a rewarding contribution to modern economic history”.¹² In his earlier volume Haber had stated:

“Economic historians have frequently described the development of technology in industries in which change was simple and have neglected the

“Patents and the Chemical Industry: Tools of Business Strategy” in J. Liebenau (ed.), The Challenge of New Technology: Innovation in British Business (Aldershot: Gower, 1988).

⁷ G. Teeling-Smith, The Pharmaceutical Industry and Society: A Study of the Changing Environment and Economics of the International Industry (London: Office of Health Economics, 1972).

⁸ A. Chetley, Problem Drugs (London: Atlantic Highlands, N. J. Zed Books, 1995).

⁹ L. Marsa, Prescription for Profits: How the Pharmaceutical Industry Bankrolled the Unholy Marriage between Science and Business (New York: Scribner, 1997).

¹⁰ G. Gereffi, The Pharmaceutical Industry and Dependency in the Third World (Princeton: Princeton University Press, 1983); T. Heller, Poor Health, Rich Profits: Multinational Drug Companies and the Third World (Nottingham: Spokesman Books, 1977); M. Silverman, M. Lydecker, P. R. Lee, Bad Medicine: the Prescription Drug Industry in the Third World (Stanford: Stanford University Press, 1992).

¹¹ Richard Harris, The Real Voice (New York: MacMillan, 1964); C. Medawar, “Failings of the Pharmaceutical Industry” Pharmaceutical Medicine 2 (1987): 259- 263; Milton Silverman, Philip R. Lee, Pills, Profits and Politics (Berkeley: University of California Press, 1974); James S. Turner, The Chemical Feast (New York: Grossman, 1970); Brian S. Inglis, Drugs, Doctors and Disease (London: Andre Deutsch, 1965); M. Silverman, The Drugging of the Americas (Berkeley: University of California Press, 1976); Wyndham Davies, The Pharmaceutical Industry: a Medical, Economic and Political Survey of the Worldwide Pharmaceutical Industry (Oxford: Pergamon Press, 1967).

¹² L. F. Haber, The Chemical Industry 1900- 1930: International Growth and Technological Change (Oxford: Clarendon Press, 1971): 7.

more complex but equally important development of chemical manufacture”.¹³

This quote captures some of the reasons why the pharmaceutical industry has received little attention, as the factors involved are complex and multifactorial, the sources are scattered, and gaining access to pharmaceutical company records is problematic, even if they exist. Although some progress has been made in understanding the development of the pharmaceutical industry, Quirke wrote in 2000 that: “histories of the major national pharmaceutical industries are relatively rare, especially in comparison with the chemical industry. It is a sector that is difficult to apprehend (sic) as a whole because of its complexity due partly to its variety of origins”.¹⁴

For the purpose of this introduction, I refer primarily to the dozen main authors that have provided most of the background: many other contributions will be referred to in the main body of the text. These are Swann, Parascandola and Liebenau for the American industry, and Liebenau, Robson and Quirke for Britain, (and the latter two for France). For clinical trials, although Liebenau set out some of the groundwork, recent theses by Desirée Cox-Maksimov and Helen Valier have developed this theme, with some reference to Harry Marks for America, while for company histories the most exhaustive modern historic accounts have been by Tweedale, Davenport-Hines and Slinn regarding Allen & Hanbury’s, Glaxo and May & Baker. For Burroughs Wellcome there have been numerous contributions, the most important for me being that of Tansey, who explained the background to the development of the Physiological Laboratories and the licensing of the laboratory, allowing me to focus primarily on the chemical developments within the laboratories in which new drugs were created to replace natural extracts.¹⁵ Other histories have focused on Henry Wellcome himself.¹⁶

¹³ L. F. Haber, (1958): ix.

¹⁴ Viviane Quirke, “Experiments in Collaboration: The Changing Relationship Between Scientists and Pharmaceutical Companies in Britain and in France, 1935- 1965” (University of London: PhD thesis, 1999).

¹⁵ E. M. Tansey, “The Wellcome Physiological Research Laboratories 1894 – 1904: the Home Office, Pharmaceutical Firms and Research Experiments” *Medical History* 33 (1989): 1- 41.

¹⁶ Helen Turner, *Henry Wellcome, the Man, his Collection and his Legacy* (London: Heinemann, 1980).

Nineteenth century pharmaceutical manufacturing existed in two main forms in all of the major countries. Ethical drug firms manufactured science-based drugs for physicians, with emphasis on active principles, and differentiated their products from other firms based on the novelty of their tablets or pills, their strength, the level of impurities, their benefits and tolerance, and later pharmacological experiments and clinical ‘experience’. Patent medicines were advertised directly to patients, with fanciful names and extravagant claims. For many years the two systems co-existed but the medical profession became increasingly critical of the unsubstantiated claims of patent medicines. The British Medical Association’s “Secret remedy” campaigns in 1907-09 highlighted the unreliability of patent medicines, and concerns about adulterated medicines in America led to legislative controls on secret remedies and on advertising of drugs.¹⁷ Legislation in Britain curbed only the worst excesses associated with extravagant claims; the heavy use of alcohol, narcotics or tonics – or, at the other extreme, the failure to incorporate any known beneficial substances.

A new form of large-scale pharmaceutical manufacture evolved in Germany in the last two decades of the nineteenth century, based on chemical synthesis from by-products of the dyestuffs industry. Synthetic drugs were developed with assistance from external pharmacologists. A further development around 1891 was diphtheria antitoxin and German firms were well placed to take advantage of this through their close collaboration with the universities. By the end of the century most German firms had developed laboratories for assaying raw materials, for checking the purity of synthesised products, but also for product research, and testing the relationship of chemical structure to physiological function.

Much of the research on German firms focuses on the evolution of chemical manufacture from dyes and state support.¹⁸ In the English literature, an excellent insight into the collaboration of industry with Paul Ehrlich and other academic scientists is given in

¹⁷ J. B. Blake (ed.), Safeguarding the Public: Historical Aspects of Medicinal Drug Control (Baltimore: Johns Hopkins University Press, 1970): 112 - 122, 144 - 157.

¹⁸ T. Lenoir, Revolution from Above: The Role of the State in Creating the German Research System, 1810-1910 *The American Economic Review* (May 1998): 22-27.

Bäumler's account, to which I refer extensively in Chapter 2.¹⁹ Beer gives an excellent account of the development of laboratories in German firms,²⁰ while Fox, Haber and Reader provide background on dyestuffs developments.²¹

For America, historians have concentrated on the ethical manufacturers that characterised their products scientifically, and on the relationship between industry and academia. Liebenau covered the period up to 1914, showing that American firms flourished during and after the American Civil War and were noted for their development of novel dosage forms, particularly tablets. He showed that American firms adopted the German laboratory model later, and also prepared diphtheria antitoxin in 1895. He showed that Parke Davis employed a chemist to measure and standardise active principles within ergot, and both Lilly and Searle employed laboratory staff in the 1880's. Smith Kline & French had an analytical laboratory from 1893 and performed assays as early as 1884. However, Liebenau assumes that these laboratory workers eventually got involved in (unspecified) product development.²² How 'scientific' these laboratories were is open to debate as Swann reported that Edward Kendall left the laboratory at Parke Davis in 1910 because of the "lack of a scholarly atmosphere" and because "he was treated like a factory worker".²³ Swann argued that the foundations for the rise of industrial pharmaceutical research in the interwar period were progress in natural sciences, an institutional framework, which

¹⁹ E. Bäumler, Paul Ehrlich, Scientist for Life (New York: Holmes & Meier, 1984).

²⁰ J. J. Beer, The Origins of the German Chemical Industry (Urbana: University of Illinois Press, 1959); J. J. Beer, "Coal Tar Dye Manufacture and the Origins of the Modern Industrial Research Laboratory" Isis 49 (1958) 123- 131.

²¹ M. R. Fox, Dyemakers of Great Britain 1856-1976: a History of Chemists, Companies, Products and Changes (Manchester: I.C.I. plc, 1987); W. J. Reader, Imperial Chemical Industries Ltd. A History: The Forerunners 1870 – 1926 volume 1 (London: Oxford University Press, 1970); L. F. Haber, (1958) and (1971).

²² Jonathan Liebenau, Medical Science and Medical Industry: The Formation of the American Pharmaceutical Industry (Basingstoke: MacMillan, 1987): 5, 125; Jonathan Liebenau, "Marketing High Technology: Educating Physicians to use Innovative Medicines" in R. P. T. Davenport - Hines (ed.), History, Bagmen and Markets: Studies in the History of Marketing and British Industry (Aldershot: Gower, 1986): 82-101, 183-236.

²³ John P. Swann, Academic Scientists and the Pharmaceutical Industry: Cooperative Research in Twentieth Century America (Baltimore: John Hopkins Press, 1988): 34.

facilitated its application, and the willingness of industrialists to recognise the importance of science and of scientists to work with industrial firms.

Like Liebenau²⁴, Swann²⁵ concluded that in Britain up to 1920, research developed from assays and laboratory controls, assuming again that those performing assays in laboratories later began performing research for new products. Neither Swann nor Liebenau gave any evidence for this. One immediate conclusion is that a more carefully worded definition is required of what constitutes ‘research’ and there must be a clear recognition that laboratories come in different forms. A laboratory worker, skilled in performing assays does not necessarily have the skills to synthesise and develop new drugs. Nor do small studies in laboratories equate to developing a successful manufacturing procedure and transferring this technology to the manufacturing works.

Parascandola examined pharmaceutical developments in America,²⁶ with particular emphasis on pharmacology and the evolving role of structure-activity studies²⁷ and showed the importance of collaborations with external pharmacologists and pharmacists in Wisconsin and Philadelphia.²⁸

²⁴ Jonathan Liebenau, “Scientific Ambitions: the Pharmaceutical Industry, 1900-1920” *Pharmacy in History* 27.1 (1985): 3-11; J. Liebenau, “The Rise of the British Pharmaceutical Industry” *British Medical Journal* (3 October 1990): 724-28.

²⁵ John P. Swann, *Academic Scientists and the Pharmaceutical Industry: Cooperative Research in Twentieth Century America* (Baltimore: John Hopkins Press, 1988): 34.

²⁶ J. Parascandola, “The Pharmaceutical Sciences in America, 1852-1902” *J. Am. Pharm. Assoc.* 40.6 (2000): 733-35; J. Parascandola, “Drug Therapy in Colonial and Revolutionary America” *Am. J. Hosp. Pharm.* 5.1-2 (1976): 69-77.

²⁷ J. Parascandola, “Industrial Research Comes of Age: the American Pharmaceutical Industry 1920-1940” *Pharmacy in History* 27.1 (1985): 12-21; J. Parascandola, “Structure – Activity Relationships – the Early Mirage” *Pharm. Hist.* 13 (1971): 3-10; J. Parascandola, “The Controversy over Structure Activity Relationships in the Early Twentieth Century” *Pharm. Hist.* 16 (1974): 54-63.

²⁸ J. Parascandola, “The Founding of the University of Wisconsin School of Pharmacy” *Pharm. Hist.* 38.2 (1996): 51-61; J. Parascandola, J. Swann, “Developing Pharmacology in American Schools of Pharmacy” *Pharm. Hist.* 25.3 (1983): 95-115; J. Parascandola, “John J. Abel and the Early Development of Pharmacology at the Johns Hopkins University” *Bull. Hist. Med.* 56.4 (1982): 512-27.

For England, Tansey²⁹ gave the background to the development of laboratories at Burroughs Wellcome and the problems of overcoming the antivivisectionist movement in Britain. Even after the formation of laboratories in Britain, and especially after the Dangerous Drugs Act of 1923, when pharmacists had to be in charge, Quirke saw British and French laboratories, as ‘demand- pulled’ rather than ‘research-pushed’, and this conclusion is easy to understand. However, as Tweedale pointed out³⁰, firms such as Allen & Hanbury’s did not see themselves competing directly with German firms, even after they developed laboratories and this is a point that I will develop. Quirke³¹ emphasised the importance of major mergers to form Imperial Chemical Industries (ICI) and Rhône Poulenc in 1926 and 1938 respectively, though I found it hard to follow her argument that ICI developed pharmaceuticals in 1926 and “these firms became trendsetters.” In fact ICI only dedicated a staff of seven to exploratory medicinal chemistry from 1936 after the discovery of sulphonamides, and although they expanded their efforts during and after the Second World War, they did not form a pharmaceutical division until 1954.³²

Swann recognised that some American firms became important pools of scientists, collaborating with pharmacologists in universities and medical schools in the interwar period.³³ The examples given included Eli Lilly, Merck, Parke Davis, Abbott and E. R. Squibb, all of which evolved to be major U.S. pharmaceutical manufacturers. Swann identified three main types of external collaborator: the generalist, the specialist and the project-specific consultant, and they were primarily pharmacologists and chemists. From a

²⁹ E. M. Tansey, “The Wellcome Physiological Research Laboratories 1894 – 1904: the Home Office, Pharmaceutical Firms and Research Experiments” Medical History 33 (1989): 1- 41.

³⁰ Geoffrey Tweedale, At the Sign of the Plough: 275 Years of Allen & Hanbury’s and the British Pharmaceutical Industry (London: John Murray, 1990).

³¹ Viviane Quirke, “Experiments in Collaboration: The Changing Relationship Between Scientists and Pharmaceutical Companies in Britain and in France, 1935- 1965” (University of London: PhD thesis, 1999).

³² Frank L. Rose, “Origin and Rise of the Synthetic Drugs” in F. N. L. Poynter (ed.), Chemistry in the Service of Medicine (London: Pitman, 1963): 179-197. In the Rose account it says 1954 and the main site at Alderley Park did not open until 1957.

³³ John P. Swann, (1988): 3-4, 33-34, 45, 51, 65-83; Richards performed research with Henry Dale at the National Institute of Medical Research in London: C. F. Schmidt, “A .N. Richards” Biographical Memoirs of Fellows of the Royal Society 13 (1967): 327–42.

company perspective the best known are the collaborations of Eli Lilly with Toronto University regarding insulin and the collaboration of Harvard University with several firms with liver therapy for pernicious anaemia. Swann addressed some of the difficulties of collaborative work including proprietary interests, sharing information with outsiders, publications and patenting, but concluded that this was a particular success for the American industry.

Viviane Quirke drew parallels between the systems that evolved in France and England up to 1965. She suggested that Henry Dale at the National Institute of Medical Research and Ernst Fourneau at the Pasteur Institute exhibited many parallels; both coming from academic backgrounds, working in the pharmaceutical industry, then returning to academia, but investing heavily in collaborative research. She argued that collaborative work developed widely in France in the interwar period despite a lack of support, whereas it developed in Britain as a result of government support and largely through Dale.³⁴

Robson described the British drug industry as comprising four distinct types of firm at the end of the nineteenth century³⁵:

1. Traditional traders that imported raw materials, purified and processed them – such firms included Morson's, Whiffen's, May & Baker, Allen & Hanbury's and Howard's.
2. Marketing firms concentrating on the retail trade, exemplified by Boots, Taylor's and the London Drug Company.
3. Edinburgh-based alkaloid manufacturers such as MacFarlan's, T. H. Smith and Duncan Flockhardt.
4. More research oriented firms including Burroughs Wellcome and Evans Sons, Lescher & Webb.

The traditional firms have received little attention, except in individual company histories by Tweedale and Chapman-Huston (Allen & Hanbury's), Slinn (May & Baker)

³⁴ Viviane Quirke, (University of London: PhD thesis, 1999).

³⁵ M. Robson, "The British Pharmaceutical Industry and the First World War" in J. Liebenau (ed.), The Challenge of New Technology: Innovation in British Business Since 1850 (Aldershot: Gower, 1988): 82-105.

and Davenport Hines and Slinn (Glaxo) and although a definitive history of Burroughs Wellcome is awaited, most attention has focussed on physiological standardisation by Tansey as Burroughs Wellcome produced vaccines and antitoxins from 1895.³⁶

Regarding British firms in the period to 1940, Liebenau concluded that: “successful as they were in maintaining their small businesses and a turnover of basic products, and given few incentives to grow, British firms such as Howard’s, Evan’s, Morson’s, Bell’s, even Allen & Hanbury’s, did relatively little to extend their markets”. He did not refer, as I do, to those firms that did grow most significantly, namely Burroughs Wellcome, May & Baker, Boots and British Drug Houses.³⁷ In his thesis, Michael Robson compared the economics of the British pharmaceutical industry with France and Switzerland but again with little emphasis on the development and testing of drugs.³⁸ He expanded previous work to compare the number of patents and publications from industry. However, his in depth analysis shows that firms may have differed greatly in their policy, even from product to product.

The surprising finding therefore is that there is a significant part of the history of the British pharmaceutical industry that has not been examined. Having referred to the rhetoric of “backwardness and decline” in interwar Britain and France, Quirke notes the stronger British pharmaceutical industry that emerged from the Second World War and argues that this was a result of collaboration within the Therapeutic Research Committee, involving several firms, and the ‘victory’ of penicillin. Once more this conclusion arises from the focus on major developments (in this case penicillin) and an acceptance that little was achieved in the interwar period. And yet there is a remarkable contrast between the position of the British industry in 1938, preparing to make drugs that might be required for war, compared to the stark realisation at the outbreak of the First World War that Britain relied so heavily on Germany, not only for drugs but for the chemical intermediates required to

³⁶ D. Chapman- Huston and E. C. Cripps, (1954); R. P. T. Davenport-Hines and J. Slinn, (1992); Geoffrey Tweedale, (1990); Judy Slinn (1984); E. M. Tansey, (1989): 1- 41.

³⁷ M. Robson, (1988): 94.

³⁸ M. Robson, “The Pharmaceutical Industry in Britain and France 1919-1939” (Dept. of Economic History, London School of Economics: PhD. thesis, June 1988); J. Sigvard, “Drug Industry in France: Some Historical Points” Bull. Acad. Natl. Med. 166 (June 1982): 829-34.

make them. Examining the First War in isolation is insufficient as it was an artificial situation with disruption of trade and the absence of a competitive threat from Germany. One of the main challenges was to produce drugs on a large scale and cost-effectively to compete with Germany *after the war*.

Synthetic drugs are the mainstay of the modern pharmaceutical industry, but the molecular manipulation that gave rise to new drugs began in Germany at the end of the nineteenth century, and Germany held a monopoly in synthetic drugs prior to the First World War, with drugs such as Salvarsan, Novocaine and Aspirin. As a result there has been a dearth of interest in this aspect of the development of the pharmaceutical industry outside the Germanic countries and an assumption that America and Britain eventually followed the German model. I will discuss how this was not always the case, at least until after 1939.

Swann made only passing reference to the fact that Eli Lilly established a research team on synthetic drugs in 1912, involving up to 20 researchers; he did not explain where they came from or whether they did evolve from assay work. He described how Abbott first developed synthetic drugs, but as a result of external collaboration, and then by employing a postdoctoral student in 1918. Beyer described how Dilantin (phenytoin) was first synthesised at Parke Davis in 1911, but he did not describe the initial evaluation only pointing out that its hypnotic effects were only found as part of a routine screen in 1926 and its benefits in epilepsy were not described until 10 years later: he stated that Parke Davis did not formally establish a Chemistry department until the 1920s.³⁹

In the Great War, America, like Britain was denied German drugs, initially as a result of naval blockade. The 1916 version of “New and Non-Official Remedies” listed 228 of 592 drugs as coming from Germany. After the USA declared war in April 1917, some German patents were abrogated and America, like Britain, had a “Trading with the Enemy Act”, and yet Swann suggested that: “U.S. pharmaceutical firms soon filled the demand for these (synthetic) drugs.” However, elsewhere in his book Swann demonstrated that it was only after the war in most American firms that internal research facilities were established, initially appointing external scientists, notably at Abbott (1918), Lilly (1919), Parke Davis

³⁹ Karl H. Beyer, Discovery, Development and Delivery of New Drugs (New York: S. P. Medical and Scientific Books, 1978): 43.

(1920), and Merck (1930), although Upjohn and Squibb appointed their first research scientists in 1913 and 1915 respectively. It remains unclear how American pharmaceutical firms first established synthetic drug synthesis and nothing has been written on manufacturing capacity. Certainly several firms continued to depend on external collaborations for discoveries and this seems to be a strong feature of the American industry.⁴⁰

Liebenau addressed the production of Salvarsan by the Dermatological Research Laboratories in Chapter 8 of his book *Medical Science and Medical Industry*. Robson briefly addressed the problems of wartime drug shortages: “It was the First World War that disturbed the status quo and marked the turning point for the standing of science within the pharmaceutical industry”. However, he concluded that there were “no immediate shortages” as a result of the dislocation of trade, without going into detail about how the essential drugs were defined, manufactured or tested.⁴¹ This contrasts with my finding that Britain was heavily reliant on Germany for synthetic drugs and certain alkaloids.

Both Robson and Quirke to a degree refer to some of the staff mobility between the MRC and industry, with Robson making a brief reference to Francis Carr and his departure from Burroughs Wellcome. However, Carr’s role was perhaps not fully understood by Quirke who briefly described him as being taken on by BDH *to produce insulin*, whereas it was his establishment of the manufacturing capacity of BDH in the period 1920-22 that made the insulin development the success that it was. Similarly I did not follow Quirke’s argument that a focus on antisera “prevented” the earlier exploitation of penicillin in Britain. She argued that Fleming was obsessed with demonstrating that penicillin could be used as a selective inhibitor of bacterial growth and specifically a method to isolate *Haemophilus influenzae*, and that this tied in with the influence of Almroth Wright in promoting vaccines, including one for influenza.

A more obvious explanation is that neither Fleming, nor the many others that investigated penicillin in the next 14 years could envisage a method of large-scale production and this separates an interesting laboratory phenomenon from a practical drug.

⁴⁰ John P. Swann, (1988): 35-6.

⁴¹ M. Robson, (1988): 82-105.

It eventually took a massive international effort to develop penicillin and this was only stimulated by the wartime needs and following the success of the sulphonamides. No new drug is useful unless it can be manufactured reliably and part of the challenge for Britain in this interwar period was to encourage the training of chemical engineers and manufacturing chemists to make this possible.

However, details aside Quirke provides a valuable comparison of Britain and France, in which she contrasts the central co-ordinating roles of the Pasteur Institute and the MRC for which she identified the important role of Dale in breaking down the barriers between industry and academia, though as I will show barriers still existed to getting clinical trials performed.

1.3 Clinical Testing of Novel Drugs.

Still less attention has been given to the origins of clinical trials of new drugs from industry. Some authors have charted ancient “trials” or the development of measurement in medicine.⁴² The historiography suggests that numerical methods of assessment in medicine spread from Paris at the start of the nineteenth century and Troehler examined this in a thesis, which focussed on the techniques and the scope of data collected.⁴³ His thesis is an excellent initial source for an understanding of the development of the numerical account in medicine, offering a series of individual examples of well-recorded “properly recorded observations,” starting with James Lind and collections of ‘statistics’ in the Navy on scurvy in 1763, rather than a clear path of influences. He shows that there were many early examples of large well-controlled studies, and yet the methods were intermittently adopted. John Ferriar, a Manchester physician, wrote in 1792 that the tendency “so

⁴² J. P. Bull, “The Historical Development of Clinical Therapeutic Trials” Journal of Chronic Diseases 10 (1959): 218-248; H. J. C. J. L’Etang, “Historical Aspects of Drug Evaluation” in E. L. Harris, J. D. Fitzgerald (eds.), Principles and Practice of Clinical Trials. (Edinburgh: Churchill Livingstone, 1970); Jan P. Vandenbroucke, “A Short Note on the History of the Randomised Controlled Trial” Journal of Chronic Diseases 40 (1987): 985- 987; A. M. Lilienfeld, “Ceteris Paribus: the Evolution of the Clinical Trials” Bulletin of the History of Medicine 56 (1982): 1-18; U. Troehler, “Quantification in British Medicine and Surgery, 1750 – 1830 with Special Reference to its Introduction into Therapeutics” (University of London: PhD thesis, 1978).

⁴³ Erwin Ackerknecht, Medicine at the Paris Hospital 1794- 1848 (Baltimore: Johns Hopkins, 1967); J. P. Vandenbroucke, “Clinical Investigation in the 20th Century: the Ascendancy of Numerical Reasoning” The Lancet (October 1998) Sii: 12-16.

fashionable at present of publishing single cases, appears not well calculated to enlarge our knowledge either of the nature or cure of diseases.” Troehler demonstrated that the numerical method was often adopted to defend new approaches to surgery, or in testing a new method of treatment, with several examples from early debates on vaccination, but his main thesis covered the period 1750 – 1830, so it does not address how the pharmaceutical industry got its drugs tested.

Recognising that the nineteenth century British pharmaceutical industry manufactured drugs required by the medical profession, that were accepted without challenge, a new situation arose in the interwar period when the ethical pharmaceutical industry in Britain produced novel drugs and had to persuade doctors to evaluate and then utilise them. A ‘grey area’ existed between some of the novel drugs and patent medicines that were heavily promoted. How would companies get their new drugs evaluated and which were the drugs that doctors needed? Swann described how the long-standing conflict between laboratory workers and clinicians was gradually overcome by clinician researchers, biochemists, and physiologists returning to America from periods of training in Germany, and establishing University Chairs of Clinical Research, based on the model outlined in Abraham Flexner’s 1910 report; I will describe parallels to the system developed by the MRC in Britain.⁴⁴ Harry Marks examined the establishment of cooperative clinical trials in America, emphasising that other forms of therapeutic trials pre-dated randomised controlled trials.⁴⁵ He examined how therapeutic decisions were made and emphasised the role of the American Medical Association’s Council on Pharmacy and Therapeutics and of academic research centres within the National Research Council’s Division of Medical Science. He cautioned against taking a purely methodological approach, as there was more to changing views on therapeutics than the design of the experiments. Clinicians deferred to more knowledgeable experts and part of the rationale for collaborative trials was to engage

⁴⁴ Abraham Flexner, Medical Education in the United States and Canada (New York: Carnegie Foundation, 1910).

⁴⁵ Harry M. Marks, *Ideas as Social Reforms: The Legacies of Randomized Clinical Trials* (PhD Thesis, Harvard Medical School, 1983); Harry M. Marks, *The Progress of Experiment: Science and Therapeutic Reform in the United States, 1900-1990* (Cambridge: University Press, 2000).

many centres so that there was not an undue influence of one or two physicians in each centre. He examined the major chemotherapeutic agents, including Salvarsan, sulphonamides and penicillin and concluded with some later work on oral hypoglycaemic drugs, but he did not examine how industry got their drugs tested. Like Quirke, I conclude that the system in Britain was more centrally coordinated by the MRC, than the independent system of collaborations that existed in America.

In Britain, even after Burroughs Wellcome demonstrated physiological activity of their drugs, tested them for purity and standardised them in their own laboratories, they still had difficulty in establishing clinical trials. Whereas in Germany the close collaborations between firms and pharmacologists led to early testing of new products in clinical trials, it was difficult to make these arrangements in other countries. Gerald Geison described this in “Divided we stand”⁴⁶ and Swann referred to long-standing conflicts between laboratory workers and clinicians. Most of the historic research on the pharmaceutical industry has focussed on drug discovery, telling us what was discovered and when, and with little on drug development.

The development phase that has evolved since novel drugs were prepared was initially a simple process, but has become increasingly complex it involves turning a newly discovered drug into a medicine that can be prescribed safely to patients. It involves selecting the dose, formulating the drug as an injection, tablet or some other form, and ‘testing’ it first in animals and then in patients, producing data to encourage other doctors to try the drug and ultimately to make it a commercial success. Another part of drug development operates at a strategic level and concerns decisions regarding, which drugs to develop and what resources and facilities are required to support each potential drug. This phase of drug development has received limited attention and I explored this through the internal records of the Burroughs Wellcome Scientific and Technical Committee, and based on my own conclusions of what other companies produced and had tested by the Therapeutic Trials Committee.

⁴⁶ G. L. Geison, “Divided We Stand: Physiologists and Clinicians in the American Context” in M. J. Vogel and C. E. Rosenberg, The Therapeutic Revolution: Essays in the Social History of American Medicine (Philadelphia: University of Pennsylvania Press, 1979).

Liebenau concluded that the MRC studies on insulin formed the model for future collaborative research, and both Quirke and Robson referred to his “seminal” work. Thus, on the basis of a limited appraisal a view has been perpetuated that this was a foundation model upon which the MRC refined study designs and a drug development process culminating in the first ever randomised controlled trial of streptomycin in 1946. To a degree this has been fuelled by the writings of many of the participants in those later trials.⁴⁷

The conclusion that a system of clinical trials was modelled on those for insulin and that the MRC built upon this in an effort to “control” the industry has not been challenged since Liebenau’s account in which he referred mistakenly to insulin as a pituitary hormone.⁴⁸ Booth examined the growth of MRC sponsored clinical research centres, but only by referring to MRC annual reports.⁴⁹ Was the insulin model representative of other studies performed by the MRC in the period up to 1946 or is this model only applicable to the development of products where the MRC held the patent and could control the collaborators? In their recent theses, both Desirée Cox-Maksimov and then Viviane Quirke took insulin as the accepted model. The impression is given in these accounts that drugs simply came into general use, as if it were obvious that drugs that worked in the laboratory would be efficacious and safe in man. This may have been the case for insulin and penicillin, regarding their spectacular activity, but this focus on major successes gives no insight into the routine research for novel drugs that was the ‘bread and butter’ of the pharmaceutical industry. What about those drugs that did not work or caused adverse effects? The forefront of this research was in the clinic. Even at the end of the nineteenth century, Ehrlich recognised that the only true test of a drug was in man and companies used their early experience in patients to modify their products, to evaluate new dosage forms, to

⁴⁷ J. Liebenau, “The MRC and the Pharmaceutical Industry: the Model of Insulin” in Joan Austoker and Linda Bryder (eds.), Historical Perspectives on the Role of the MRC (Oxford University Press, 1989): 163 – 180.

⁴⁸ J. Liebenau, “The MRC and the Pharmaceutical Industry: the Model of Insulin” (1989): 169.

⁴⁹ C. C. Booth, “Clinical Research” in J. Austoker, L. Bryder (eds.) Historical Perspectives on the Role of the MRC. (Oxford: Oxford University Press, 1989): 205-241.

modify the dose or duration of treatment or even to substitute one drug for a better alternative, as indeed Ehrlich did with neosalvarsan.

Quirke⁵⁰ defended the progress of British industry in developing a collaborative network through the work on insulin - but it was not difficult for the MRC to find doctors ready to 'test' insulin, after it had already been shown in Canada and the USA to dramatically lower blood glucose. It was quite another thing for a British firm to test a novel chemical in man for the first time. The more that I looked at this problem, the more surprised I was that it had been ignored. It seemed to me that the research to date had been fitted around the best available source material rather than considering this fundamental question.

Desirée Cox-Maksimov described the Therapeutic Trials Committee (TTC) as the "model" that emerged from the earlier Chemotherapy Committee for randomised controlled trials.⁵¹ Her study was carried out in parallel with my own research and covers my period of interest. Because she also examined the TTC, her thesis bears the closest parallels to mine and therefore deserves close attention. In a series of case studies she contrasted the efforts of patent medicine manufacturers with the scientific approaches of the medical establishment and the State, which supported the more acceptable standardised medicines evaluated by the MRC.⁵² She examined trials of insulin for diabetes, trials of pneumococcal serum, and patulin for the common cold.⁵³

Thus, her approach was very different, ignoring the products arising from pharmaceutical industry research and concentrating on the methodology of the larger trials rather than the principles of testing new agents.⁵⁴ Patulin, like insulin was a natural product

⁵⁰ Viviane Quirke, (University of London: PhD thesis, 1999).

⁵¹ D. Cox-Maksimov, "The Making of the Clinical Trial in Britain, 1910 – 1945. Expertise, the State and the Public" (Cambridge: PhD. Thesis, September 1997): 17- 130.

⁵² D. Cox-Maksimov, "The Making of the Clinical Trial in Britain, 1910 – 1945. Expertise, the State and the Public" (Cambridge: PhD. Thesis, September 1997): 17- 130.

⁵³ D. Cox-Maksimov, (1997): 183 –262.

⁵⁴ Ibid. .

arising from academic research⁵⁵ rather than a drug from industry and the patulin studies were used to describe the mechanisation of trials and the key role of the statistician, Major Greenwood, who had been involved in clinical trial design for many years.⁵⁶ The MRC were becoming arbiters of drug evaluation, determining how medical research was reported, the characterisation and standardisation of medicines, the recognition and authority of experts, how the research was reported - even the centres involved.

According to Cox-Maksimov, the TTC was about promoting a certain type of medical research, but was it really? My argument is that by selecting only the ‘winning drugs’ such as insulin historians may have introduced a bias. Quirke also evaluated the impact of the insulin clinical studies and concluded, like Liebenau, that these formed the model for all future trials and collaborations with industry. Liebenau, Quirke and Cox-Maksimov do not address the issue of manufacturing insulin or who was involved. In not doing so they missed the important link that Francis Carr, who had prepared Salvarsan at Burroughs Wellcome, had moved first to Boots then to British Drug Houses where he established the capacity to manufacture 95% of British requirements for insulin. Carr, among others led the requests from industry for a system of clinical testing of new drugs and the companies at the time clearly did not see insulin trials as a model to meet their needs.

The trial of pneumococcal serum was not at all representative of the main work of the TTC as it was already planned in 1929, two years before the establishment of the TTC in 1931. Furthermore the study addressed questions about the need to vaccinate rather than being a study of new drugs, and furthermore, initial vaccine supplies came from America.

Cox-Maksimov examined in turn how all of the procedural elements of the randomised clinical trial were in place by 1946 and argued that the pneumococcal trial defined procedures. I am not convinced that the pneumococcal study was the major influence that she suggests and without intending to claim an increased validity of a first-

⁵⁵ H. Raistrick (first of several presentations), “Patulin in the Common Cold. Collaborative Research on a Derivative of *Penicillium patulum* Bainier” *Lancet* (20 November 1943): 625-34.

⁵⁶ L. Hogben, “Major Greenwood” *Biographical Memoirs of Fellows of the Royal Society* 7 (1950): 139-54.

hand source, her interpretation conflicts with the account recalled to me by Sir Austin Bradford Hill, the founder of the randomised controlled trial and by his surviving colleagues.⁵⁷ There were quite different objectives and also ethical constraints in vaccinating individuals against the possibility of acquiring a common disease compared with treating them with a novel chemical to treat a disease already present and particularly regarding withholding therapy in the placebo group. Cox-Maksimov made the important point that recent accounts have been “winners’ histories of Clinical Trials”, one in which statisticians such as Peter Armitage⁵⁸, Richard Doll,⁵⁹ Richard Peto and Sir Austin Bradford Hill dominate and claim ownership of clinical trials. Their arguments concern the quality of the design of experiments, the removal of sources of bias, and a certain way of reporting data and in this respect their authority cannot be questioned, but was this later model of relevance in the 1930’s? Cox-Maksimov argued for a natural progression through the TTC pneumococcal study, the MRC streptomycin studies, and patulin studies,⁶⁰ arguing that Armitage had referred to Bradford Hill having a role in the TTC, though she recognised there was no documentary evidence and I found little either- the first reference to him was his attendance at the tenth committee meeting in 1939.⁶¹ Lilienfeld took an almost genealogical approach and tried to trace the controlled trials link back further to studies of the gold therapy, sanocrysin in 1925, and others have also argued that

⁵⁷ Letter to myself from Sir Austin Bradford Hill (6 October 1988); P. D’Arcy Hart, “Early Controlled Trials” British Medical Journal 312 (10 February 1996): 378-79; A. Bradford Hill, “Measurement in Medicine: The Clinical Trial” Brit. Med. Bull. 7.4 (1951): 278-82; A. Bradford Hill, “The Clinical Trial” New England J. Med. 247 (1952): 113; P. Armitage, “Bradford Hill and the Randomised Controlled Trial” Pharmaceutical Medicine 6 (1992): 23- 37; R. Doll, “Sir Austin Bradford Hill and the Progress of Medical Science” British Medical Journal 305 (19-26 December 1992): 1521-26; I. Chalmers, M. Clarke, J. G. Scadding, in I. Chalmers, I. Milne, U. Troehler (eds.), “TheJamesLindLibrary” (www.jameslindlibrary.org) accessed 7 January 2003.

⁵⁸ P. Armitage is Emeritus Professor of Applied Statistics at the University of Oxford: “P. Armitage, (1992): 23-37.

⁵⁹ Richard Doll, (1992): 1521-26.

⁶⁰ J. M. Stansfield, A. E. Francis, C. H. Stuart-Harris, “Laboratory and Clinical Trials of Patulin: Medical Research Council, Clinical Trial of Patulin in the Common Cold” (16 September 1944) Lancet: 373-75.

⁶¹ Bradford Hill was only appointed to the TTC for the tenth and final meeting in 1939: TTC Minutes 10, (28 March 1939), MRC File 1523/15 (TTC).

there were even earlier isolated cases of randomised controlled trials.⁶² In this thesis I show that many of the trials organised by the TTC were of limited scope and statisticians were not involved and the studies were just large enough to satisfy the company need for some data. A subgroup of studies in areas of specific interest to the MRC was larger, not by design but on account of the types of patients selected and the experience of the centres involved. As it was the pharmaceutical firms that requested the establishment of the TTC, we should see how British firms judged its success, or otherwise rather than accepting the account of the TTC Secretary, Frank Green. Hence there remains much scope for an evaluation of the interaction between the British pharmaceutical industry and the MRC in evaluating novel drugs.

Cox-Maksimov did not recognise the strong push from manufacturers to have novel drugs tested by the MRC. She suggested “there was not much difference between pharmaceutical firms and patent medicine manufacturers at the turn of the (nineteenth) century.⁶³ The achievements of the British in purifying and isolating active ingredients and in tableting technology were ignored and achievements were minimised so that rather than emphasising the remarkable technical achievement of the synthesis and production of Salvarsan, she emphasised only that:

“Salvarsan produced by Burroughs Wellcome in the War was toxic and there were problems with its quality during the war and how the Board of Trade forced companies to get official certificates; the embarrassment to legitimate companies like Burroughs Wellcome and May & Baker should not be underestimated”.⁶⁴

I propose that the origins of clinical testing go back to those early days with Salvarsan and that the Therapeutic Trials Committee established by the MRC in 1931 evolved out of a more complex relationship with the firms over a longer time period. It was the pharmaceutical companies that cajoled the MRC into the establishment of the TTC, after

⁶² D. B. E. C. Gill, “Randomised Mental Health Trial Began in 1935...” and M. Clarke. “Quasirandom Allocation of Treatment was Reported in 1930”, both in British Medical Journal 312 (18 May 1996): 1298; A. M. Lilienfeld, “Ceteris paribus”, the Evolution of the Clinical Trial. Bulletin of the History of Medicine 56 (1982): 1-18.

⁶³ D. Cox-Maksimov, (1997): 21.

⁶⁴ D. Cox-Maksimov, (1997): 21.

two previous failed attempts, just as Burroughs Wellcome had led the way on biological standardisation and had requested the testing of Salvarsan.

In summary, there have been limited attempts to review the establishment of the British pharmaceutical industry and in particular to understand how it developed from preparing extracts at doctors requests to synthesising new drugs and there has hardly been any attention given to the problems faced by British manufacturers in getting their own new drugs tested clinically.

1.4 Sources and Thesis Outline.

I have examined information from diverse secondary sources in chemistry, dyestuffs, chemical engineering, pharmacy, medicine, clinical research, therapeutics, pharmacology, physiology, economics, business histories, and biographies.⁶⁵ However, I also concentrated on archive material, particularly the records of the Wellcome Chemical Research Laboratory, the manufacturing works, and personal archives of staff members, physicians and researchers. Some First World War material, discussing the first testing of British-produced synthetic drugs is based on files of the MRC Salvarsan Committee, the laboratory books from Burroughs Wellcome, the Committee and Council Minutes of the MRC, and files of the Association of British Chemical Manufacturers. The original source references are given in the bibliography and reflect the referencing systems in place at the time of my original examination, and although much of the MRC material has been reclassified and is available at the National Archives, formerly the Public Record Office, some was destroyed prior to the move.

The thesis is set out along broadly chronological lines but it includes recurring themes, such as the interactions between the pharmaceutical industry, basic scientific research, medicine, and government. I show how close these relationships were, whereas previous authors such as Moonman stated: “it is only since the end of the second war that

⁶⁵ Pietro Corsi, P. Weindling, Information Sources in the History of Science and Medicine (London: Butterworth, 1983); P. Weindling, “Research Methods and Sources” in E. Clarke (ed.), Modern Methods in the History of Medicine (London: Athlone, 1971): 173.

the idea of Government shaping industry has taken root".⁶⁶ A major emphasis is placed on the role of significant individuals, and particularly Francis Carr.⁶⁷

The early part of the thesis addresses the dominance of German chemistry within a research-oriented industry. Dyestuffs and chemical intermediates were primarily imported from Germany. University-based chemists, many of whom were consultants to industrial firms, had warned before the First World War about the factors leading to the dominance of Germany.⁶⁸ A general theme throughout is the shortage of suitably trained British chemists, particularly those with manufacturing experience. Many of the chemical processes dovetailed into each other and the many complex interdependencies between firms relied on chemical intermediates. Little preparation was made for the outbreak of War and it is interesting to contrast how better prepared Britain was between 1937- 1939 and how much the country depended on the interwar efforts.

The themes that emerge therefore are of sustained efforts to ensure that Britain never again had to rely on a foreign power for key resources. This involved defining what drugs were essential, who made them, what chemical intermediates and solvents were needed, how the drugs could be standardised and how their potency could be measured. Additionally the synthetic arsenical drugs, replacing those hitherto only made in Germany, were potentially toxic and had to be shown to be safe and effective.

The MRC took a central role in the evaluation of Salvarsan but many of their staff came from industry and particularly Burroughs Wellcome. Given the scarcity of chemists, pharmacologists, physician researchers and other key members of staff, it is interesting to chart their careers to see the effect that they had on the development of several British pharmaceutical firms. The MRC and government continued to support the British industry throughout the period under study, and another theme which emerges is the effort made to protect the evolving research-based British pharmaceutical industry, firstly under the

⁶⁶ Eric Moonman, Reluctant Partnerships: a Critical Study of the Relationship Between Government and Industry (London: Victor Gollanez, 1971): 17.

⁶⁷ Joseph Ben-David, The Scientists Role in Society (Englewood Cliffs: Prentice Hill, 1979): 160-68.

⁶⁸ W. M. Gardner, The British Coal Tar Industry, Its Origin, Development and Decline (London: Williams & Norgate, 1915).

artificial situation of War, but then by a series of direct and indirect measures. A distrust of foreign medicines, had been sparked by the increasing imports of patent medicines, with exaggerated or even fraudulent claims, but continued into the twentieth century through the assay of antitoxins and organ extracts in which many foreign drugs were found wanting. Ethical British manufacturers wanted to show the medical profession that their novel drugs were standardised, pure and had a reliable and quantifiable degree of activity- in fact that they were as good or better than German drugs. Assays of impurities in starting materials, measurement of total alkaloid content, amounts of active ingredients, impurities in the final drug, biological standardisation and measurement of clinical activity were all means of showing the benefits of drugs prepared by British firms and of highlighting the problems inherent in foreign drugs. Here it was the interaction between the Government, the MRC, the Pharmaceutical Society, individual firms, the Association of British Chemical Manufacturers and related groups such as the Society of the Chemical Industry that became important. Throughout this work I have tried to take the holistic view of what firms were trying to achieve in their daily challenges. In addition to insulin, the newly discovered vitamins and the many organotherapies arising from academic advances were beneficial to the growth of British industry; British firms were at the forefront of investigating these opportunities, involving complex extraction and manufacturing techniques, but their success with these novel therapies led to increases of manufacturing potential and commercial successes and their close relationship with physiologists and university chemists led to synthetic forms of both vitamins and hormones being developed. Firms such as Allen & Hanbury's and Glaxo expanded significantly as a result of these opportunities.

A major recurrent and previously ignored theme, is the gradually acquired expertise in synthetic drug manufacture, first seen in some of the alkaloids and further exemplified by Salvarsan during the war and other drugs post-war. Synthetic drugs brought together many of the previous intertwined issues such as the lack of chemists, the need to test new drugs in animal models, the understanding gained in relating chemical structure to physiological function, and the clinical studies required to evaluate the safety and efficacy of these agents. Here was a key development of the British pharmaceutical industry, perhaps ignored because it did not turn on a single event or a particular study. For companies this was not an issue of demanding a specific type of clinical trial. The firms evaluated here simply wanted their drugs tested in whatever manner possible as they had

major difficulties in arranging studies directly, at least in Britain. Even if the study was only in a handful of cases, that was enough as long as the MRC ultimately vouched for the drug and gave it a positive appraisal. Even many of the successful drugs mentioned here are long forgotten. They played their part in the therapy of the period as evidenced by their inclusion in the pharmacopoeia of 1948 but many have been replaced since then. The consequence of these studies was the recognition then, as now, that not all drugs would be marketed either because insufficient activity was demonstrated, or there were some safety issues, or there was insufficient data or demand to make the drug commercially viable.

The firms and the MRC had a common interest in collaborating as the studies allowed the MRC to expand the number of centres involved in clinical research. However the TTC and the early tests of biological standardisation probably had as much of an effect by excluding foreign drugs as by helping British drugs to secure a place on the market. A constant frustration for both the MRC and the companies was the slow progress of the TTC's clinical trials and it is not surprising that after the second world war, which brought a further stimulus to the British pharmaceutical industry through penicillin and increased manufacture of synthetic drugs, companies began to employ their own pharmacists and physicians to establish the clinical testing of drugs,⁶⁹ and this trend even began in the late 1930's.

Despite the broad chronology of the thesis, inevitably there are some slight overlaps between sections. For example it seemed sensible to include all of the War activities, including production and testing of Salvarsan in one chapter, so I also included the work that continued on Salvarsan after 1918 as it involved the same individuals.

Following on from this Introduction, Chapter 2 describes the varied origins of the Pharmaceutical industry in the nineteenth century and assesses the position of the small British companies in relation to their larger international rivals, contrasting the ethical manufacturers with producers of patent medicines.

⁶⁹ K. J. Williams, B. Gennery, "The History of the Pharmaceutical Industry" in J. Lloyd, A. Raven (eds.), *Handbook of Clinical Research* (London: Churchill, 1994): 1-22; K. Williams, "A Tenth Anniversary for the Association for Clinical Research in the Pharmaceutical Industry (ACRPi)" *Pharmaceutical Medicine* 3 (1988): 219-224.

Chapter 3 describes the most research- oriented British firm, Burroughs Wellcome, and how they combined the best of German synthetic chemistry with American advances in drug formulation, especially tablets. It was the only British firm initially in a position to rapidly take up the synthesis of the more complex German drugs and to develop the strong links with the newly founded MRC. I introduce individuals who were to play an important role in the development and testing of drugs throughout the inter-war period of 1919-1931.⁷⁰

Chapter 4 examines how the First World War forced the British Government to intervene in pharmaceuticals, first by establishing committees to establish which drugs were essential and then how to resolve their production. I examine how British firms began to collaborate formally for the first time as the Association of British Chemical Manufacturers, how British firm's mastered large-scale chemical synthesis, and how the MRC first got involved in testing Salvarsan as an extension of the standardisation work carried out by its staff when they were at Burroughs Wellcome.

Then follow 3 chapters that broadly cover the same period:

Chapter 5 covers two aspects of post-war Britain. It examines how British pharmaceutical firms sought protection post-war, first by tariffs, then by standardisation of biological and hormonal extracts. The MRC assisted and in doing so established their international reputation for drug standardisation, while extending their interest in clinical outcomes.

Chapter 6 describes how British firms campaigned for clinical testing of drugs from 1922 – 1930 and demonstrates how the MRC was an ideal intermediary between the firms and researchers to establish ground rules for early clinical trials in Britain. The specialised MRC subcommittees and the Chemotherapy Committee did not meet the needs of the pharmaceutical companies and I demonstrate the distinction between MRC research to support industry and their own more academically oriented studies and the utilisation of their emerging network of clinical centres.

⁷⁰ Francis J. Griffin, "Obituary, Francis Carr" Chemistry and Industry (15 February 1969): 196.

Chapter 7 examines the strategy of Burroughs Wellcome post-war and especially the period 1925 to 1931, up to the establishment of the Therapeutic Trials Committee through the strategic debates within their Scientific and Technical Committee.

Chapter 8 examines the actual workings of the Therapeutic Trials Committee, how they initially favoured British drugs and how the studies complemented their own research and interests. This examination of all of the drugs tested gives an insight into the research strategies of British (and some foreign) firms and allows an assessment of the success or otherwise of the TTC giving insights into the testing, both from the MRC perspective and that of Burroughs Wellcome (from STC Minutes 1931-1939) and other firms.

Chapter 9 offers some conclusions, both by reviewing the key topics identified and by comparing the position of British manufacturers at the outbreak of the Second World War with the position that they found themselves in at the outbreak of War in August 1914. Some opportunities for further work are then identified.

A full bibliography of sources is given at the end.

CHAPTER TWO: The Origins of the Pharmaceutical Industry.

2.1 The Growth of the Pharmaceutical Industry in the Nineteenth Century.

Early nineteenth century drug therapy was aimed at alleviating symptoms such as fever and pain.¹ By 1900 two parallel but overlapping systems of drug marketing had evolved in all of the main manufacturing countries. Patent medicines had been available for over two centuries, but their use expanded dramatically during the nineteenth century.² They were preparations whose ingredients were kept secret, and which were sold under brand names for a wide range of illnesses.³ Their success depended upon heavy advertising in the popular press, and the fact that they spared patients the expense of a doctor's consultation fee. Patent medicines were of variable quality, were often laced with opiates or alcohol, or only incorporated minute quantities of what doctors and pharmacists considered active drugs. Doctors were concerned that they were ineffective and even potentially dangerous.⁴

'Ethical' manufacturers took a different approach. The identification, extraction, and purification of morphine in Paris in 1803 stimulated the establishment of several alkaloid-manufacturing firms in France, followed by Boehringer, Merck, and Schering in

¹ A. Burman, "The Heroic Approach to Nineteenth Century Therapeutics" Bulletin of the American Society of Hospital Pharmacists 11 (1954): 320-27; David L. Dykstra, "The Medical Profession and Patent and Proprietary Medicines During the Nineteenth Century" Bulletin for the History of Medicine 29 (1955): 401- 19.

² "Patent Medicine Tax Receipts 1829-1914" Chemist & Druggist 85.1 (8 August 1914): 35-36; T. Hughes, "The Patent Medicine Stamp Duty: its Origin and History" British Medical Journal (9 January 1932): 32-33; "Revenue from Patent Medicine Tax Stamps 1800-1931" Chemist & Druggist 114 (30 May 1931): 639.

³ V. Coleman, The Medicine Men (London: Temple Smith, 1975); B. McNamara, Step Right Up: an Illustrated History of the American Medicine Show (New York: Doubleday & Co., 1976); Roy Porter, Quacks, Fakes and Charlatans in English Medicine (Charleston: Tempus, 2001); William H. Helfand, The Sellers of Nostrums in Prints, Posters, Ephemera and Books (Chicago: Chicago University Press, 2002).

⁴ James H. Young, The Toadstool Millionaires: a Social History of Patent Medicines in America Before Federal Regulation in America 1660-1850 (Princeton: Princeton University Press, 1961); James H. Young, The Medical Messiahs: a Social History of Health Quackery in Twentieth Century America (Princeton: Princeton University Press, 1967); M. Silverman, Magic in a Bottle (New York: McMillan, 1941); M. Silverman, The Drugging of the Americas (Berkeley: University of California Press, 1976).

Germany.⁵ Such manufacturers differentiated themselves further by producing the newly discovered chemical elements bromine and iodine, in rich supply in Germany.⁶ Luke Howard in London produced calcined magnesium, bismuth and mercury salts from 1801.⁷ Morson's and Howard's sold quinine sulphate instead of cinchona from 1821, and firms were able to compare the best sources of quinine. From 1827 firms such as Merck sold purified morphine, instead of opium, as did T. H. Smith in Edinburgh by 1837.⁸ Firms manufactured plant extracts and inorganic remedies according to the demands of physicians.⁹ In other words, doctors decided which drugs were needed and pharmaceutical manufacturers provided them.

Some doctors produced their own medicines, but as extraction of alkaloids became more complex, requiring solvents, distillation and crystallisation, manufacturers saved them the expense of purchasing machinery. As capacity increased, standard packs were prepared and distributed widely for treating standard and specific diseases. Many firms produced the same basic drugs, but individual firms distinguished their drugs from competitors by assaying chemical constituents and impurities in simple laboratory tests.

⁵ M. Weatherall, In Search of a Cure: a History of Pharmaceutical Discovery (Oxford: Oxford University Press, 1990); Walter Sneader, Drug Discovery: the Evolution of Modern Medicines (London: John Wiley, 1985): 6-7, 9-14; C. D. Leake, An Historical Account of Pharmacology to the Twentieth Century (Springfield, Illinois: C. C. Thomas, 1975): 120-1; John Harley Warner, The Therapeutic Perspective: Medical Practice, Knowledge and Identity in America 1820 -1885 (Cambridge, Massachusetts: Harvard University Press, 1986); E. Merck of Darmstadt: a History of Chemical Achievement 1827-1937 (Darmstadt: Merck, 1937).

⁶ Walter Sneader, (1985): 41-42.

⁷ D. L. Howard, Brit. Col. Pharmacist (August 1926): 241.

⁸ W. Bernsmann, "Arzneimittelforschung und Entwicklung in Deutschland in der Zweiten Hälfte des 19 Jahrhunderts" Pharmazeutische Industrie 29 (1967): 6; Mark Honigsbaum, The Fever Trail: The Hunt for the Cure for Malaria (London: MacMillan, 2001).

⁹ E. Kremers, G. Urdang, The History of Pharmacy (Philadelphia: J. B. Lippincott, 4th edition, 1976); R. D. Mann, Modern Drug Use, an Enquiry on Historical Principles (Boston: MTP Press, 1984); F. N. L. Poynter, The Evolution of Pharmacy (London: Pitman Medical, 1965): 131-49; E. H. Ackerknecht, Therapeutics From the Primitives to the Twentieth Century (New York: Hafner, 1973): 88-89; Jonathan Liebenau, "The Rise of the British Pharmaceutical Industry" British Medical Journal (3 October 1990): 724-28, 733.

The purity of drugs produced by reputable firms improved as their pharmacists adopted a more professional role.¹⁰

Jacob Bell of John Bell & Co. was one of the founders of The Pharmaceutical Society of Britain in 1841 and was President 1856-9.¹¹ William Allen of Allen & Hanbury's was the first president.¹² The Society was modelled upon the Philadelphia College of Pharmacy, founded in America in 1821.¹³ Whereas French firms made reference to experiments in animals by physiologists such as Francois Magendie and Claude Bernard, and Germans referred to Emil Fischer, Hermann Kolbe and others, such assays were continuously hampered in Britain by the antivivisection lobby from the 1860's and this inhibited the development of pharmacology and interactions between the pharmaceutical industry and external academics in Britain.¹⁴ By the close of the nineteenth century, the British pharmaceutical industry was struggling to keep up with its counterparts in Germany and in America.¹⁵ Pharmaceuticals evolved on a large scale in Germany, whereas American firms made significant advances in novel means of administering drugs. An appreciation of the competition faced by British firms will enable us to understand much about the ways in which a section of the British pharmaceutical

¹⁰ J. K. Crellin, "The Growth of Professionalisation in Nineteenth Century British Pharmacy" Medical History 11 (1967): 215-227; F. A. Filby, A History of Adulteration and Analysis (London: George Allen & Unwin, 1934); E. W. Stieb, G. A. Sonnedecker, Drug Adulteration, Detection and Control in 19th Century Britain (Madison: University of Wisconsin Press, 1966); J. A. Blake (ed.), (1970).

¹¹ "John Bell- a Coming Centenary" Chemist & Druggist 52 (11 June 1898): 160-5; S. W. F. Holloway, Royal Pharmaceutical Society of Great Britain 1841-1991: A Political and Social History (London: The Pharmaceutical Press, 1991): appendix.

¹² L. G. Matthews, History of Pharmacy in Britain (Edinburgh and London: E. & S. Livingstone, 1962): 118-27; L. G. Matthews, "An Unrecorded William Allen Caricature" Medical History 15 (1971): 305-6.

¹³ J. W. England (ed.), The First Century of the Philadelphia College of Pharmacy 1821-1921 (Philadelphia: Philadelphia College of Pharmacy, 1922).

¹⁴ J. M. D. Olmsted, Francois Magendie (New York: Schumanns, 1944); Claude Bernard, An Introduction to the Study of Experimental Medicine Trans. H. C. Greene, (New York: Dover, 1957); R. D. French, Anti-Vivisection and Medical Science in Victorian Society (Princeton: Princeton University Press, 1975).

¹⁵ J. T. Mahoney, Merchants of Life: An Account of the American Pharmaceutical Industry (New York: Harper, 1959).

industry adapted and made use of laboratory science as a means of developing and marketing competitive new products in the 1880's.¹⁶

2.2 Evolution from Small Pharmacy Firms in America.

In the early nineteenth century most medicines used in the USA were imported from Britain. Philadelphia became the “cradle of pharmacy” for the American nation, famous for the College of Pharmacy founded in 1821, around which an American pharmaceutical industry was established. Early graduates of the College such as Ernst R. Squibb attacked the fraudulence and adulteration associated with patent medicines.¹⁷

Philadelphia- based firms created and effectively controlled a lucrative new sector of the pharmaceutical market, ethical drugs sold solely to medical professionals.¹⁸ The term ‘ethical’ medicine came into use in the USA after the 1847 code of ethics of the American Medical Association forbade doctors from procuring a patent for a remedy, and from selling patent medicines or nostrums, or giving testimonials.¹⁹ As in Britain, there was a huge market for these remedies, often sold with fancy names.²⁰ The 1877 byelaws of the Philadelphia section of the American Medical Association stated:

“Any physician who shall procure a patent for a remedy or for any instrument of surgery, or who sells or is interested in the sale of patent remedies or nostrums, or shall give a certificate in favour of a patent or proprietary remedy or patented instrument, or who shall enter into agreement

¹⁶ The ‘Pharmaceutical Industry’ to varying degrees included ‘the Chemical and Allied Trades’ and ‘the Fine Chemical Industry’: “What is a Fine Chemical” Chemist & Druggist 85.2 (29 August 1914): 51.

¹⁷ L. G. Blochman, Doctor Squibb: The Life and Times of a Rugged Idealist (New York: Simon & Shuster, 1958); J. T. Mahoney, “Philadelphia, Cradle of Pharmacy: Smith, Kline & French, Wyeth and Others” (1959): 30-41.

¹⁸ J. F. Marion, The Fine Old House: Smith, Kline Corporation's First 150 Years (Philadelphia: Smith Kline, 1980).

¹⁹ R. M. Shryock, The Development of Modern Medicine. An Interpretation of the Social and Scientific Factors Involved (New York: Hafner, 1969); M. Fishbein, A History of the AMA 1847-1947 (Philadelphia: W. B. Saunders, 1947): 35-42; Peter Temin, Taking Your Medicine: Drug Regulation in the United States (Cambridge, Mass: Harvard University Press, 1980): 2.

²⁰ B. McNamara, (1976); D. Armstrong, E. M. Armstrong, The Great American Medicine Show (New York: Prentice Hall, 1991).

to receive pecuniary compensation or patronage for sending prescriptions to any apothecary shall be disqualified from becoming a member".²¹

A series of further graduates of the Philadelphia School of Pharmacy gave rise to a new breed of pharmaceutical manufacturers that had the skills to develop novel dosage forms of ethical drugs. The firm of William R. Warner was founded in Philadelphia in 1856 and his future partner in Warner Lambert was a pharmacy graduate of Philadelphia in 1884, as were many other founders of pharmaceutical firms, including Henry Wellcome in 1874 and Silas Burroughs in 1877. Frederick Belding Power, who later joined Burroughs Wellcome as a chemist also trained there.²²

The firm of John Wyeth & Co. originated from a pharmacy opened by Frank and John Wyeth in 1860. John Wyeth graduated from the Philadelphia College of Pharmacy with a thesis on the chemical constituents of various plants and Frank Wyeth, a chemist, also attended the college.²³ John Wyeth & Co. prospered by selling proprietary medicines during the American civil war with a turnover of over \$600,000.²⁴ But they were also an innovative firm that introduced new marketing practices as well as new drug formulations. As early as 1861 they joined the two most like-minded firms, H. K. Mulford and Smith & Kline, to found the Philadelphia Drug Exchange, to campaign for the abolition of stamp duty on patent medicines, because many of the ethical firms still sold these in parallel. The Exchange also established a system for chemically testing imported drugs, particularly patent medicines, which entered America despite a law banning the importation of poor quality materials.²⁵

Wyeth and their colleagues in the Drug Exchange actively distinguished themselves from the manufacturers who made only patent medicines, by also producing purified drugs of known composition sold only to doctors and pharmacists, often using esoteric scientific

²¹ Jonathan Liebenau, Medical Science and Medical Industry: The Formation of the American Pharmaceutical Industry, (Basingstoke: MacMillan, 1987): 26-27.

²² J. W. England (ed.), (1922): 137-8, 200 ff., 216, 410.

²³ J. T. Mahoney, "Philadelphia: Cradle of Pharmacy: Smith Kline & French, Wyeth and Others" (1959): 30-41; L. G. Blochman, (1958); Jonathan Liebenau, (1987): 22-23.

²⁴ J. Wyeth to Burroughs Wellcome, (31 October 1887), WF: 88/47:8.

²⁵ Jonathan Liebenau, (1987): 23; J. W. England (ed.), (1922): 132.

terminology such as 'dialysed' iron.²⁶ They met a ready market among American doctors who wished to minimise the practice of self-prescribing by patients. Other US firms with roots in pharmacy included A. P. Sharp, founded in 1827 in Baltimore, the first in America to produce alkaloids.²⁷ Charles Erhardt and Charles Pfizer established their firm in Brooklyn, New York between 1845-8 after Pfizer had been apprenticed to an apothecary.²⁸ Harvey C. Parke and George S. Davis formed Parke Davis as a small manufacturing business in Detroit in 1866, and W. E. Upjohn founded The Upjohn Pill and Granule Company in Kalamazoo in 1886 to produce friable pills.²⁹

The principal advances by American firms were in creating novel dosage forms such as sugarcoated pills, which were convenient to carry, and sugar masked any bitter tastes.³⁰ Large-scale manufacture of pills developed from 1857, and elixirs (soluble liquid forms) from 1859.³¹ Wyeth prepared compressed hypodermic tablets, and tablet triturates were first made in 1861. These could be readily dissolved for injection or for taking as solutions.³² The first moulded medicines and compressed pills were manufactured in Philadelphia in 1863 and tablets were made commercially from 1869.³³ Wyeth employees designed and patented the first rotary tablet press in America in 1872 to produce opiates, digitalis, strophanthus and quinine tablets. By 1876 patents were secured on the process

²⁶ J. Wyeth to Burroughs Wellcome, (28 June 1881), WF: 88/47:8.

²⁷ J. T. Mahoney, "Merck & Co." (1959): 201-2.

²⁸ S. Miles, Pfizer, an Informal History (New York: Pfizer, 1978); J. G. Lombardino, "A Brief History of Pfizer Central Research" Bull. Hist. Chem. 25.1 (2000): 10-15.

²⁹ Leonard Engel, Medicine Makers of Kalamazoo (New York: McGraw-Hill, 1961); Cecil Roberts, A Century of Caring, Upjohn: Achievement (Kalamazoo: Upjohn, 1938).

³⁰ C. Gunn, "A History of Some Pharmaceutical Formulations" in F. N. L. Poynter (ed.), (1965): 131-50.

³¹ L. F. Kebler, "The Tablet Industry - its Evolution and Present Status: Composition of Tablets and Methods of Analysis" Journal of the American Pharmaceutical Association 3 (1914): 820-48, 937, 958, 1062-99.

³² J. T. Mahoney, "Philadelphia: Cradle of Pharmacy: Smith Kline & French, Wyeth and Others" (1959): 31-2.

³³ "Note about Brockedon's Patent" Pharmaceutical Journal 3 (1844): 554; T. H. Bishop, "Inventor of the Compressed Tablet, William Brockedon" Chemist & Druggist 162 (28 August 1954): 209; F. N. L. Poynter, (1965): 131-49.

and the method of compression of pills.³⁴ In contrast, Britain's pills were made by hand until Allen & Hanbury's bought their first pill-making machine at the Pharmaceutical exhibition in Philadelphia in 1876, but even then no tablets were being made commercially in Britain.³⁵ John Wyeth stated: "Prior to 1877 the formula's (sic) that were sold in tablet form were very few. They consisted of simple chemicals such as potassium chlorate, ammonium chloride etc. and after 1877 combinations followed".³⁶ Wyeth also stated: "we do claim and we know that the preparations we manufacture are unsurpassed by any in the world".³⁷ Parke Davis formulated some products within gelatine capsules from 1887.³⁸ Dr. Abbott of Chicago prepared dosimetric granules, a type of pill with accurately calibrated doses, from 1888.³⁹

Up to 1880 firms such as G. D. Searle of Chicago offered hundreds of elixirs, syrups, powdered extracts and tinctures. Smith Kline & French had a catalogue of about 15,000 items.⁴⁰ However the incorporation of existing products, as tablets required special testing in a laboratory to develop the most suitable methods, meant that firms began to focus upon a smaller range of higher value products. The first American firms to introduce a chemical quality control laboratory to assay raw materials purchased were Mulford and Parke Davis in 1879. A chemist was hired by Parke Davis in 1880 to devise a method to standardise the amount of extracted ergot in tablets. By 1883 Parke Davis offered twenty "normal liquids," and recognising the variability of batches they introduced Lot numbers in April 1886 so that any problems arising could be tracked back to particular materials and

³⁴ J. W. England (ed.), (1922): 154-56; Heritage: a Brief History of Warner Lambert and the Entrepreneurs Who Shaped It (New Jersey: Warner Lambert, 1987).

³⁵ G. Tweedale, At the Sign of the Plough: 275 Years of Allen & Hanbury's and the British Pharmaceutical Industry (London: John Murray, 1990): 67-69, 81, 120.

³⁶ J. W. England (ed.), (1922): 156.

³⁷ J. Wyeth to Burroughs Wellcome, (28 June 1881), WF: 88/47:8.

³⁸ F. N. L. Poynter, (1965): 142.

³⁹ H. Kogan, The Long White Line: the Story of Abbott Laboratories (New York: Random House, 1963); William D. Pratt, The Abbott Almanac: 100 Years of Commitment to Quality Health (Elmsford, New York: Benjamin, 1987).

⁴⁰ J. T. Mahoney, "G. D. Searle" (1959): 144-55; J. F. Marion, (1980): 103.

conditions of preparation.⁴¹ An 1884 price list of Eli Lilly Co. of Indianapolis stated: “Each lot of drug is examined by assay before manufacture. We make no extra charge on this account and we consider it our highest duty to know our preparations to be of uniform and full strength”.⁴² Lilly hired a chemist and botanist for control work from 1893 and Smith Kline & French analysed everything made and organised a research laboratory in 1900 and a physiology laboratory from 1911.⁴³

At the end of the nineteenth century biological drugs, so-called because antisera or antitoxins were raised in animals by the injection of bacteria, were recognised as important, but the response produced in the blood was highly variable. The same problem applied to hormonal extracts prepared from animal organs. These could not be assayed chemically and a biological test of activity in animals was required. Parke Davis was the first to hire a pharmacologist, in their case from the University of Chicago in 1894, to produce standardised diphtheria antitoxin and adrenaline.⁴⁴ Liebenau explained how standardised products could be differentiated on strength and purity, reliability and consistency, rather than having to compete largely on price with many firms producing the same drugs.⁴⁵

Thus in America the main developments were in the technology of presenting different forms of medicines and in standardising these. In selecting the best medicines to incorporate into tablets, firms reacted to changes of medical practice and increasing knowledge of physiology.⁴⁶ The ethical pharmaceutical firms established links with universities such as Wisconsin, where influential clinicians such as John J. Abel offered

⁴¹ Parke Davis at 100, Progress in the Past, Promise in the Future, 1866 - 1966 (Detroit: Parke Davis, 1966); John P. Swann, Academic Scientists and the Pharmaceutical Industry: Cooperative Research in Twentieth Century America (Baltimore: Johns Hopkins, 1988): 20-1; M. L. Hoefle, “The Early History of Parke-Davis and Company” Bull. Hist. Chem. 25.1 (2000): 28-34.

⁴² Jonathan Liebenau, (1987): 43.

⁴³ Jonathan Liebenau, (1987): 104-5.

⁴⁴ J. W. England, (1922): 6.

⁴⁵ Jonathan Liebenau, (1987): 5, 20, 25.

⁴⁶ P. Starr, The Social Transformation of American Medicine: the Rise of a Sovereign Profession and the Making of a Vast Industry (New York: Basic Books, 1982).

advice.⁴⁷ Some US firms such as American Cyanamid had origins in chemical manufacture, but not on the German scale and there was a very limited indigenous dye industry, although in 1913 Monsanto Chemical made vanillin, caffeine, phenacetin and phenolphthalein. America's industry was probably midway between Britain and Germany in size at the end of the nineteenth century.⁴⁸ The US firms were protected by tariffs on finished goods, but like Britain relied heavily on Germany for synthetic drugs and dyes.

2.3 Germany and the Synthetic Model from the 1860's.

The historiography of the German chemical industry is captured under the history of dyestuffs, of individual pharmaceutical firms and more general reviews.⁴⁹ While older German firms such as Merck (1668)⁵⁰ and Schering (1851)⁵¹ with pharmacy roots became justly renowned for the quality of their alkaloids: a further wave of new pharmaceutical firms evolved from dyestuffs manufacturers. Although the synthetic dyestuffs industry had originated in England with the discovery of mauve by William Perkin, British firms faced a shortage of chemists and employed many German trained chemists, and were overtaken by the rapid rise of German firms from the 1860's.⁵² In 1862 the dye firm, Meister, Lucius & Co. was founded at Hoechst, near Frankfurt.⁵³ The Farbwerke Friedrich Bayer was

⁴⁷ J. Parascandola, (1982): 512-27; John P. Swann, (1988); E. R. Brown, Rockefeller Medicine Men: Capitalism in America (Berkeley: University of California Press, 1979): 8, 24, 56, 63, 71, 121; John P. Swann, "Arthur Tatum, Parke-Davis, and the Discovery of Mapharsen as an Antisyphilitic Agent" J. Hist. Med. and Allied Sciences 40.2 (April 1985): 167-87.

⁴⁸ L. F. Haber, The Chemical Industry During the Nineteenth Century: a Study of the Economic Aspect of Applied Chemistry in Europe and North America (Oxford: Clarendon Press, 1958): 173, 176-81.

⁴⁹ J. J. Beer, "Coal Tar Dye Manufacturers and the Origins of the Modern Research Laboratory" Isis 49 (1958): 123-31.

⁵⁰ From Merck's Angel Pharmacy to the Worldwide Merck Group 1668-1968 (Darmstadt: Merck, 1968).

⁵¹ Schering: From a Chemists Shop to a Multinational Enterprise, a Curriculum Vitae / Design Concept (Berlin: Schering Aktiengesellschaft, 4th edition 1997).

⁵² A. Arora, R. Landau, N. Rosenberg (eds.), Chemicals and Long-Term Economic Growth: Insights from the Chemical Industry (New York: John Wiley, 1998); M. R. Fox, Dye-Makers of Great Britain. A History of Chemists, Companies, Products and Changes 1856 – 1976 (Manchester: I.C.I. plc, 1987).

⁵³ F. Aftalion, A History of the International Chemical Industry transl. O. Theodor, (Philadelphia: University of Pennsylvania Press, 1991): 41; D. Gericke, "100 Years

established in 1863.⁵⁴ Leopold Cassella, founded in 1812 as a dye importer, made aniline colours from 1867, and by 1870 had a staff of 18 men including first rank chemists.⁵⁵ The chemists systematically studied the relationships between chemical structures and the properties of the dyes and produced synthetic variants of existing dyes leading to novel colours that exploited expanding markets. Justus von Liebig, the son of a druggist in Darmstadt, studied alkaloids in Paris, but he also developed a special interest in how chemicals reacted quantitatively, and he applied this knowledge to drugs. After he discovered chloroform in 1851, he trained chemists and encouraged them to work closely with biologists in developing new synthetic drugs, based upon the many chemicals contained in the plentiful waste coal tar extracts of the dyestuffs industry.⁵⁶

Chloral hydrate, discovered by Liebig in 1832 was extracted and tested clinically as an anaesthetic in 1869, and the discovery of ether and phenolphthalein in 1871 gave further early indications of the potential benefits of synthetic drugs.⁵⁷ Pasteur and Lister showed that phenol had antiseptic properties and this stimulated German dye firms to develop further synthetic drugs from phenol, which was a major waste product of the dye industry.⁵⁸

The same principles applied to producing synthetic drugs and synthetic dyes, but one key difference was that the drugs had to be evaluated first by pharmacologists and then in the clinic. In order to achieve this Bayer forged links with a school in Würzburg and the

Service to Man: Milestones of the Hoechst Pharmaceutical Company” Fortschr. Med. 102 .20 (24 May 1984): 75-77.

⁵⁴ E. Verg, Milestones (Leverkusen: Bayer AG, 1988); From Germanin to Acylureidopenicillin: Research that Made History (Leverkusen: Bayer AG, 1980).

⁵⁵ E. Bäumlner, Paul Ehrlich: Scientist for Life (New York: Holmes & Meier, 1984): 80.

⁵⁶ J. B. Morrell, “The Chemist Breeders: the Research Schools of Liebig and Thomas Thomson” Ambix 19 (1972): 1-46; H. M. Leicester, “Davis, Davy and Liebig” Journal of Chemical Education (1951): 28.

⁵⁷ F. N. L. Poynter (ed.), Medicine and Science in the 1860's Proceedings of the 6th British Congress of Medicine (London: Wellcome Institute, 1967); M. Weatherall, (1990): 29-30, 35-7.

⁵⁸ R. J. Dubos, “Pasteur and Modern Science” in The Pasteur Fermentation Centennial 1853-1957: a Scientific Symposium (New York: Pfizer, 1988): 17-32; G. T. Wrench, Lord Lister: his Life and Work (London: Unwin, 1913).

University of Göttingen, and AGFA had similar links in Heidelberg.⁵⁹ Meister, Lucius & Brüning collaborated with the Marburg-trained pharmacologist, Hermann Kolbe in Leipzig in 1873-4, resulting in synthetic acetyl salicylic acid, used for treating rheumatism in 1875 and as an antipyretic in 1876.⁶⁰

By 1878, German firms held over 60% of the world dye market and their dominance in manufacturing capacity and production of chemical intermediates allowed them to take an early advantage in the production of synthetic drugs.⁶¹ Thus, “the chief industrialised nation (Britain) and the most practical people in the world” had been “beaten in the endeavour to turn to profitable account the coal tar they possessed”.⁶²

A depression in dyestuffs markets between 1881 and 1885 led German dye firms to diversify further. Meister, Lucius & Brüning used their chemical intermediates as precursors for new industries such as explosives, photographic chemicals and pharmaceuticals and Bayer submitted their first pharmaceutical patent in 1882 for the antipyretic, phenacetin.⁶³ German dye firms already produced their own solvents, acids and chemical intermediates that were essential for drug synthesis: sulphuric acid, chlorine, caustic soda, benzole, toluole, naphthalene, phenol and anthracene.⁶⁴ They subdivided plants, standardised outputs and industrialised the process of invention.⁶⁵ The new health

⁵⁹ T. Lenoir, “A Magic Bullet: Research for Profit and the Growth of Knowledge in Germany Around 1900”: *Minerva* 26 (1988): 66-88.

⁶⁰ M. Tainter, *Aspirin in Modern Therapy* (New York: Sterling Drug Company, 1969); *100 Years of Acetylsalicylic Acid: the Unique Career of the Active Ingredient in Aspirin* (Leverkusen: Bayer, 1997).

⁶¹ G. Muller Thurow, “Industrialisation of Invention: a Case Study from the German Chemical Industry” *Isis* 73 (1982): 363-68.

⁶² E. W. Jenkins, *From Armstrong to Nuffield. Studies in Twentieth Century Science Education in England and Wales* (John Murray: London, 1979): 8.

⁶³ J. C. Ogilvie Will, “On Salicylic Acid” *Lancet* (18 December 1875): 870-72.

⁶⁴ This applied especially to Badische and Hoechst: L. F. Haber, (1958): 16, 130.

⁶⁵ A. J. Levine, *Industrial Retardation in Britain 1880 -1974* (London: Weidenfeld and Nicholson, 1967); J. A. Hobson, *The Evolution of Modern Capitalism* (London: Allen & Unwin, 1949): 126; G. Muller Thurow, (1982): 363-81.

insurance legislation in 1883 directed dye firms further towards pharmaceuticals.⁶⁶ In the 1880's and 1890's Meister, Lucius & Brüning and the Badische Anilin-und Soda-Fabrik (BASF) competed for the advice of the pharmacologist Adolph von Baeyer⁶⁷ and his students, Carl Graebe, Carl Liebermann, Emil and Otto Fischer, and Ludwig Knorr. However, one disadvantage of collaborating with an academic researcher was that if he published his results openly, other firms would be free to take up manufacture of a product. Revision of the patent law in Germany in 1891 extended protection from the process of production to cover the product itself, further encouraging synthetic chemistry as new products created exclusivity and monopoly.⁶⁸

A second strategy was to employ the academic discoverer. In 1883 Meister, Lucius & Brüning hired August Laubenheimer, Professor of Chemistry at Giessen University and he remained with the firm until his death in 1904.⁶⁹ Paul Ehrlich in Frankfurt collaborated with Laubenheimer from 1885.⁷⁰ In 1884 Bayer secured Carl Duisberg, who had trained in Göttingen and Jena, and held a part-time post with von Baeyer, to set up a pharmacology laboratory at Elberfeld at a time when only 40% of German universities, and few elsewhere had such a department.⁷¹ Meister, Lucius & Brüning developed their pharmaceutical department after Ludwig Knorr, a former student of Emil Fischer at Erlangen was persuaded to join them in 1893, and established the first full-time laboratory

⁶⁶ L. F. Haber, (1958) Especially chapter 5:108-134. On Britain see 135-49: for France 150-60: Switzerland 161-172 and other European countries and the U.S.A: 173; J. J. Beer, (1958): 123-31.

⁶⁷ Walter Sneader, (1985): 29, 84, 114, 250.

⁶⁸ J. J. Beer, The Origins of the German Chemical Industry (Urbana: University of Illinois Press, 1959): 371; W. J. U. Woolcock, "Society of Chemical Industry, Leeds" Chemist & Druggist 103.1 (25 July 1925): 137-8.

⁶⁹ E. Bäumlér, (1984): xii, 43, 110-12.

⁷⁰ H. Loewe, Paul Ehrlich, Schoepfer der Chemotherapie (Stuttgart: Wissenschaftlichen Verlagsgesellschaft, 1950): 89-90, 95, 123; T. Lenoir, (1988): 66-88; E. Bäumlér, (1984): xii, 43, 55; Jonathan Liebenau, "Paul Ehrlich as a Commercial Scientist and Research Administrator" Med. Hist. 34.1 (1990): 65-78.

⁷¹ C. C. Mann, M. L. Plummer, The Aspirin Wars (Boston: Harvard Press, 1991): 23-31; L. F. Haber, (1958): 135; M. Silverman, R. Lee, Pills, Profits and Politics (Berkeley: University of California Press, 1974); S. Miall, History of the British Chemical Industry (London: Ernest Benn Ltd., 1931): 124.

in industry.⁷² In 1897 Heinrich Dreser of Darmstadt, Professor of Pharmacology at Göttingen was appointed Director of Research of Bayer.⁷³ The expansion described above encouraged other top German chemists such as Heinrich Caro and August W. Hoffmann,⁷⁴ who had gained experience with English dye firms to return to Germany and establish laboratories at Bayer (1888), Meister, Lucius & Brüning (1891) and BASF.⁷⁵ As a result of the focus on pharmaceuticals, Meister, Lucius & Brüning,⁷⁶ Kalle,⁷⁷ and Merck prepared further synthetic antipyretics, antiseptics and painkillers.⁷⁸

After the Pasteur Institute was established in Paris in 1888, the Koch Institute of Hygiene and Infectious Diseases was established in Berlin in 1890: both had strong support from their respective Governments.⁷⁹ In contrast the British Institute of Preventative Medicine (Lister Institute) received little support from the Government, the British Medical Association or industrialists.⁸⁰ Koch's Institute attracted the attention of many German pharmaceutical firms.⁸¹ One of Koch's assistants was placed in charge of

⁷² E. Bäumlér, (1984): 75; Walter Sneader, (1985): 84.

⁷³ Walter Sneader, (1985): 27, 73, 82.

⁷⁴ M. R. Fox, (1987): 17-18, 20, 23, 98-9, 111, 126 for Caro, and 4, 10, 15, 20, 28, 63, 66, 70, 94-5, 106, 114, 141 for Hoffmann.

⁷⁵ S. Miall, (1931): 66, 74-5; J. J. Beer, (1959): 365-6; From Germanin to Acylureidopenicillin (1980); 50 Years of Bayer Remedies 1888- 1938 (Leverkusen: Bayer, 1938); M. R. Fox, (1987): 13; W. Bernsmann, (1967): 7.

⁷⁶ "Wie die Ersten Heilmittel nach Hoechst Kamen" Dokumentes Hoechster Archiven 8 (Frankfurt: Hoechst, 1965): 8, 15.

⁷⁷ Walter Sneader, (1985): 86.

⁷⁸ K. H. Beyer, Discovery, Development and Delivery of New Drugs (New York: S. P. Medical and Scientific Books, 1978): 24, 178-9; L. F. Haber, (1958): 128; F. Sherwood Taylor, A History of Industrial Chemistry (London: Heinemann, 1957); M. Silverman, (1941): 192-212; C. D. Leake, (1975): 158-65.

⁷⁹ E. Bäumlér, (1984): 49 – 50.

⁸⁰ The British Institute of Preventative Medicine or Lister Institute remained underfunded until a large bequest by Lord Iveagh. The Brown Institute, the Royal Colleges of Physicians and Surgeons and Almroth Wright's laboratory at St Mary's were the only other significant medical laboratories in Britain; Z. Cope, Almroth Wright: Founder of Modern Vaccine Therapy (London: Nelson, 1966): 98-99; H. Chick, "The Lister Institute of Preventative Medicine" Endeavour (July 1949): 106 - 111.

⁸¹ T. D. Brock, Robert Koch: a Life in Medicine and Bacteriology (Madison & Berlin: Springer, 1999).

the tuberculin production plant at Meister, Lucius & Brünig in 1891.⁸² When Ehrlich moved to Berlin, his ongoing collaboration with Meister, Lucius & Brünig placed them in a position to test biological agents such as diphtheria and tetanus antitoxins, discovered there by Emil Behring.⁸³

German firms achieved significant commercial success in the new field of synthetic drugs by exploiting the strengths they had already developed in selling dyes. They had already achieved economies of scale by utilising by-products of the dye industry, both as starting materials and as chemical intermediates. The customers were different, so extensive marketing was combined with close collaboration with physicians to support the introduction of an increasing range of semi-synthetic derivatives that had not previously been administered to patients. From 1894 Bayer marketed derivatives of tannic acid for the treatment of diarrhoea, and the phenacetin derivative Salophen as an antipyretic. In September 1898 Bayer widely advertised Heroin (diaminomorphine) as a cough suppressant and safe alternative to morphine.⁸⁴ E. Merck of Darmstadt evaluated synthetic derivatives of morphine with the Austrian, Josef von Mering and introduced Dionin, the ethyl ether of morphine in 1898.⁸⁵

German firms adopted a hard selling approach, discounting their drugs and promoting them heavily, as they had with dyestuffs, establishing pricing and quota agreements.⁸⁶ Aspirin, discovered by Bayer was promoted from 1899 on an unprecedented

⁸² Arnold Libbertz became the first Director of the bacteriology plant at Hoechst in 1906, E. Bäumlér, (1984): 250-1; G. Muller Thurow, (1982): 363-81; J. D. Bernal, Science and Industry in the Nineteenth Century (London: Routledge & Kegan Paul, 1953): 151.

⁸³ H. J. Parrish, A History of Immunisation (Edinburgh: Livingstone, 1965); E. Bäumlér, (1984): 55-56, 63, 68; T. Lenoir, (1988): 66-69, 73-4; J. Liebenau, "Marketing High Technology" in R. P. T. Davenport - Hines (ed.), History, Bagmen and Markets: Studies in the History of Marketing and British Industry (Aldershot: Gower, 1986): 88-89; A. S. MacNalty, "E. Behring" British Medical Journal (20 March 1954): 668-70.

⁸⁴ Walter Sneader, "The Discovery of Heroin" The Lancet 352 (21 November 1998): 1697-99.

⁸⁵ J. Von Mering, "Physiological and Therapeutic Investigations on the Action of Some Morphia Derivatives" The Merck Report 7 (1898): 5-13.

⁸⁶ W. J. Reader, I.C.I. A History: The Forerunners 1870 – 1926 volume 1 (London: Oxford University Press, 1970): 8, 87.

scale to 30,000 doctors.⁸⁷ To assist the uptake of these complex new drugs, they replaced complicated chemical names with pronounceable Trade names (such as Aspirin) that continued to be referred to long after the patent had expired. They labelled products in foreign languages for export, built an extensive network of agents, and performed sophisticated market research. They convinced doctors of the worth of synthetic drugs compared to natural products, both by reference to pharmacology experiments and to the publication of clinical results. Doctors in Germany had fewer reservations than their counterparts in Britain about supporting commercial products in writing.⁸⁸ Having convinced doctors of the value of synthetic drugs, German firms enhanced their existing products by chemical modification to prepare structural analogues which were evaluated by pharmacologists in animal experiments, so Bayer's successful Trional superseded Sulphonal which was less soluble, and both were overtaken in turn by Bayer's Veronal in 1904.⁸⁹ It became apparent that small changes of chemical structure led to enhanced activity or a better overall profile and that these could be sold as tangible benefits to doctors.

A third strategy for dealing with external consultants was adopted by Meister, Lucius & Brüning. This was the negotiation of exclusive rights to a product such as their local anaesthetic Novocain (procaine hydrochloride), synthesised in 1905 by Professor Alfred Einhorn of Munich.⁹⁰ Meister, Lucius & Brüning and their sister firm Cassella concluded a similar agreement with Ehrlich in which he ceded all products for them to sell uniquely in return for 30% of profits.⁹¹

⁸⁷ F. Sherwood Taylor, (1957): 23; R. Alstädter (ed.), Aspirin: the Medicine of the Century (Leverkusen: Bayer, 1985): 24; Walter Sneader, "The Discovery of Aspirin" Pharmaceutical Journal 259 (1997): 614-7.

⁸⁸ C. D. Leake, (1975): 157, 166-7; C. C. Mann, M. L. Plummer, (1991): 23-31.

⁸⁹ Similarly phenol was replaced by chlorphenol. Salol was replaced by quinoline derivatives that included iodine such as Loretin from Hoechst (1893) and Vioform from Bindstedtler (1899), and Urotropine in 1904. Bindschedler is now part of Sandoz. "Sandoz 1882-1961: 75 Years of Research and Enterprise (Basle: Sandoz, 1961): 136; B. Holmstedt, G. Liljestrand, Readings in Pharmacology (Oxford: Pergamon Press, 1963): 128-34.

⁹⁰ Walter Sneader, (1985): 55, 98; C. C. Mann, M. L. Plummer, (1991): 23-31; J. J. Beer, (1959): 366; C. D. Leake, (1975): 166-7; T. Lenoir, (1988): 66-88.

⁹¹ E. Bäumlner, (1984): 125.

Thus by the turn of the century, German firms had developed an efficient means of transforming waste products of the dye industry into extremely profitable new lines of drugs. They held a monopoly in the production of chemical intermediates and created a scientific aura around the products by collaborating closely, and even employing well-known pharmacologists. They extended sales techniques to provide free samples to doctors and performed ‘clinical trials,’ but they also continued to use their old techniques of cartels and price-fixing and patent protection to create monopolies, which were difficult to challenge.

In 1899 Britain was feeling the full force of German marketing. N. H. Martin of the Newcastle branch of the Society for the Chemical Industry wrote:

“Hardly a month passes but some new substitution compound with a trivial name to indicate its alleged medicinal properties and a scientific name to suggest profound research. They come with laboratory and medicinal reports in a language calculated to deceive”.⁹²

Such was the flow of German synthetic drugs that a cartoon in the *National Druggist* stated “a few of the latest specimens of the increasing flow of foreign synthetics” and asked, “Will they never stop?”⁹³

2.4 Ehrlich: Collaboration, Structure-activity Tests, Biological Standardisation, and Clinical Trials.

Instead of each firm producing the same extracts, the dye manufacturers prepared unique synthetic products that could be protected by process and product patents and by trade names. These were then tested with pharmacologists and their mechanism of action was well understood. The relationship between Meister, Lucius & Brüning (and other firms) and Paul Ehrlich of Berlin typified this new approach. Ehrlich made several major contributions to understanding drug actions. He developed animal models of infections to demonstrate the efficacy of synthetic drugs, so encouraging Meister, Lucius & Brüning to

⁹² N. H. Martin, “Synthetic Medicinal Chemicals” *British Medical Journal* (23 January 1915): 168-69.

⁹³ The advertisement included Resorlin (made in Germany), AntiKol (carries testimonials), Solantol (a scientific compound -literature on application), Pixol (send for report on 100 cases). “Pyrogallopyrine” *Chemist & Druggist* 46 (26 January 1895): 141.

prepare many new chemicals.⁹⁴ He recommended to: “examine all preparations whose potency can be measured only with the aid of physiological experiments,” and in May 1901 he tested a dye from Cassella, which was the first man-made drug to cure an infection without killing the animals; this was developed by the Därmstädter Chemische Werke.⁹⁵

When pharmaceutical manufacturers first prepared biological sera, it was Ehrlich who argued that it was essential to use sera of precisely determined concentration and he provided this service for them.⁹⁶ Ehrlich related chemical structure to activity:

“I have tried to introduce amido groups, sulpho radicals, etc. into trypan red in certain positions and thereby improve its efficacy.... I think the field of experimental chemical therapy will expand increasingly in the future”.⁹⁷

This structure-activity based chemical approach to drug selection for development was unique to Germany, even though some British academics used this approach on a small-scale to study pharmacological effects.⁹⁸ However, this rational therapeutic approach still left problems. Carl Browning performed research with Ehrlich and continued to examine acridine and the neutral non-methylated proflavine when he returned to Britain.⁹⁹ Ehrlich and his colleague Ludwig Benda¹⁰⁰ examined hundreds of acridine dyes on trypanosomes,

⁹⁴ The Vereingte Chemische Werke of Charlottenburg marketed a modified version of arsenious acid, Atoxyl: E. Bäumlér, (1984): 109, 187, 249.

⁹⁵ L. F. Haber, (1958): 116-7, 130.

⁹⁶ E. Bäumlér, (1984): 59-62, 71-75; H. Loewe, (1950): 137.

⁹⁷ E. Bäumlér, (1984): 117.

⁹⁸ A. Crum Brown, T. R. Fraser, “On the Physiological Action of the Salts of the Ammonium Bases Derived from Strichnia, Brucia, Thebeia, Codeia, Morphia and Nicotia” Trans. Roy. Soc. Edin. 25 (1868): 151 – 204; D. B. Dott, R. Stockman, “The Chemistry and Pharmacology of Morphine and its Derivatives” Year Book of Pharmacy (London: Churchill, 1888) 349-55; J. M. Fortescue-Brickdale, “Recent Advances in the Relation Between Chemical Structure and Pharmacological Action” British Medical Journal (16 January 1915): 106; W. D. M. Paton, “The Early Days of Pharmacology with Special Reference to the Nineteenth Century” in Chemistry in the Service of Medicine (London: Pitman, 1963): 78-9.

⁹⁹ C. Browning, Journal of Pathology and Biology 18 (1913): 144; C. H. Browning, “Proflavine and Acriflavine” British Medical Journal (8 April 1967): 111.

¹⁰⁰ E. Bäumlér, (1984): 142-6, 171, 192, 216, 229.

which were parasites that caused sleeping sickness in tropical countries where Germany had colonial aspirations, and he related their activity to their chemical structure.¹⁰¹ Alfred Bertheim,¹⁰² Director of Meister, Lucius & Brüning turned the whole staff onto preparatory work for Ehrlich, and Benda eventually joined their partner Cassella, before the firms merged to form Hoechst.¹⁰³ Optochin, (ethylhydroxycuppreine), a derivative of quinine, and Trypaflavin (acriflavine) were found to be active in animals, but neither was successful in humans and the former was toxic.¹⁰⁴ This raised the question that although animals were useful for preliminary testing, the ultimate tests could only be performed in man. Ehrlich re-emphasised the importance of clinical trials as the only accurate way to finally evaluate a new drug and stressed the need for clinicians and chemists to collaborate closely.

“A combination like that suggested here meets a real requirement of medical research, and do not doubt that this could achieve much for the benefit and well being of the sick and would certainly lead to an expansion of our therapeutic expertise, and the discovery of genuine curative agents”.¹⁰⁵

If chemicals such as Atoxyl and Trypan Red were transformed from the administered substance to active principles in the human body, then their effect would only be seen in studies in patients as opposed to animal studies. Thus with the phenylarsonic acid, 'Arsacetin', from the end of 1906 Ehrlich arranged clinical trials.¹⁰⁶

The continued support from Bayer, Hoechst and the Vereinigte Chemical Company was essential to Ehrlich.¹⁰⁷ His work on the antisyphilitic Salvarsan highlights the

¹⁰¹ H. Loewe, (1950): 87, 91, 124-25; M. Wainwright, “Acridine – a Neglected Anti Bacterial Chromophore” *J. Antimicrobial Chemotherapy* (2001) 47: 1-13.

¹⁰² E. Bäumlér, (1984): 121-3, 142, 144, 147, 161, 165-6, 171, 192, 204, 216-7, 244.

¹⁰³ T. S. Moore, J. C. Phillips, *The Chemical Society 1841 - 1941. A Historical Review* (London: The Chemical Society, 1947): 618; E. Bäumlér, (1984): 244; L. F. Haber, (1958): 131.

¹⁰⁴ E. Bäumlér, (1984): 251; M. Weatherall, (1990): 148.

¹⁰⁵ E. Bäumlér, (1984): 118.

¹⁰⁶ E. Bäumlér, (1984): 127.

¹⁰⁷ E. Bäumlér, (1984): 123, 126, 143-145; H. Loewe, (1950): 100, 192-3, 200-1; K. H. Beyer, (1978): 24.

practical issues involved in preparing and testing this drug; these would have to be faced by British manufacturers when Salvarsan became unavailable as a result of the war, as described in Chapter 4. When he discovered Salvarsan, Ehrlich requested of Hoechst a large supply of a chemical intermediate in June 1909, which enabled him to arrange clinical trials in September 1909, which gave promising therapeutic results.¹⁰⁸ Ehrlich was wise to the needs of industry:

“The most important thing in the first instance is to cover the field by immediate and exhaustive patenting, possibly even of superfluous substances. It will be of especial importance for us to obtain protection for our products here in the developed countries”.¹⁰⁹

By November 1910 there were 25 people working on Salvarsan at Hoechst and almost 400,000 ampoules were made in the last quarter of 1910. The rapidity and the scale of its clinical testing of Salvarsan before general release of the drug at the end of November 1910 were impressive. Ehrlich recalled that:

“In the past drugs were usually tested in only a few hospitals, and often on fewer than a hundred patients. In the future, however, such a procedure would no longer be adequate to reveal any potential defects or harmful properties of a compound prior to its introduction”.¹¹⁰

Hoechst supplied 60,000 free samples to doctors to treat 10,000 patients, and yet Ehrlich was still criticised in some quarters for introducing Salvarsan too early, and by others for delaying the introduction.¹¹¹ By 1911 Hoechst's pharmaceutical business accounted for about an eighth of its massive turnover. Salvarsan became Hoechst's and the world's best selling drug, as sales grew from £50,000 in the first year to £150,000 in 1911. Normally other firms would immediately copy such a successful drug, and although Hoechst felt it was unlikely that other firms would achieve the complex production of Salvarsan, they

¹⁰⁸ Hoechst produced '606' on 2 June 1909 and it was patented on 10 June in Germany and in other countries by October. Results were announced on 18 April 1910 at the Congress of Internal Medicine in Wiesbaden. Ehrlich's compound log ended with 696 or sodium Salvarsan on 11 January 1912; E. Bäumlér, (1984): 144, 155, 161-2, 264.

¹⁰⁹ E. Bäumlér, (1984): 128.

¹¹⁰ E. Bäumlér, (1984): 169.

¹¹¹ E. Bäumlér, (1984): 180, 186.

nevertheless kept details of the synthesis of Salvarsan secret until 1912.¹¹² Despite the unsurpassed activity of Salvarsan, problems of production meant that it was easily contaminated, so the plant had to work under conditions not previously encountered in large-scale operations, and special machines had to be designed for filling the preparation into vacuum sealed ampoules. Much of the apparatus had to be made of silver and the whole production had to be run very quickly.¹¹³

The complexity of the synthesis of Salvarsan meant potentially dangerous consequences if impurities were not removed and if toxic by-products were administered to patients. Ehrlich sought a less toxic and more soluble preparation, and found '914' or Neosalvarsan, which was then also developed by Hoechst, so maintaining their pre-war dominance.¹¹⁴ Ehrlich was conscious of the potential side-effects and he believed that the "development of a treatment with completely harmless substances would remain an unfulfilled dream".¹¹⁵ Thus, Ehrlich can be seen developing animal models of infection, systematically testing compounds and selecting the best and in collaboration with industry suggesting alternative chemical structures. He was involved in both standardising biologicals and arranging the clinical testing of Salvarsan and played his part in promoting its use.

The model developed by Ehrlich of screening many hundreds of chemicals was taken up not only by other German dye firms but also pharmacy-based German firms such as J. D. Riedel, Schering AG and E. Merck that began to use chemistry to modify natural alkaloidal preparations, and they were joined later by C. F. Boehringer, Gehe & Co., Schimmel and Co. and the fine chemicals manufacturers E. de Haen of Seeke, von Heyden, Th. Schuchardt and Knoll & Co.¹¹⁶ The attraction of this method of research was that it provided preparations unique to the company and these could be manufactured on a large scale, standardised and protected by patents and trade-marks. These were drugs that British manufacturers in particular could not copy.

¹¹² L. F. Haber, The Chemical Industry 1900 – 1930: International Growth and Technological Change (Oxford: Clarendon Press, 1971).

¹¹³ E. Bäumlér, (1984): 207-9.

¹¹⁴ E. Bäumlér, (1984): 181, 265.

¹¹⁵ E. Bäumlér, (1984): 169.

2.5 The Scope of Chemical Research in German Pharmaceutical Firms.

In the previous section I demonstrated how German dye firms were able to develop synthetic drugs and how firms such as Hoechst engaged a significant number of chemists to optimise a product, culminating in Salvarsan and Neosalvarsan. The German dye firms had vast resources of chemists who were able to turn their skills to manufacture of pharmaceuticals from waste products of dye manufacture.

Carl Duisberg of Bayer, in a lecture in 1896, explained how his firm had 100 chemists with university education, 65 % with PhDs and 25 engineers from Technical high schools to think of all possible reactions and to make products more cheaply.¹¹⁷ In 1897 Emil Fischer claimed there were 4,000 chemists (excluding University staff) in the German Reich, of which 3,000 worked in industry. In 1900 BASF at Ludwigshafen had a total staff of 6,000 including 148 chemists, 75 engineers and technical experts and 303 mercantile staff. Meister, Lucius & Brüning and Bayer produced ten times as many patents as British firms.¹¹⁸ A British Consular report described 4,500 German chemists in 1901, of which 69% were Ph.D.'s, 10% had a Technical Diploma and a further 5% had both. This compared with less than half of the total in England, where only 21% were even graduates and only 10% had a Diploma.¹¹⁹ Bayer's staff doubled every five years from 119 in 1875 to 5,000 in May 1902, including 160 chemists and 260 engineers plus 680 clerks. By 1913 they had grown to 10,600. Badische had 2,500 men and Hoechst had 1,600 including 54 chemists.¹²⁰ At the end of 1913 Hoechst employed 8,100 including a commercial and scientific staff of 871 and Cassella employed 3,000 men by 1913.¹²¹

¹¹⁶ W. Bernsmann, (1967): 76-81.

¹¹⁷ C. Duisberg, "The Education of Chemists" Chemist & Druggist 48 (13 June 1896): 831-32.

¹¹⁸ A. G. Green, "The Relative Progress of the Coal Tar Industry in England and Germany During the Past Fifteen Years" in W. M. Gardner, The British Coal Tar Industry, its Origin, Development and Decline (London: Williams & Norgate, 1915): 198.

¹¹⁹ Sir J. Dewar, "Applied Chemistry, English and Foreign" Presidential Address to the British Association in Belfast, 1902 in W. M. Gardner, (1915): 222-6; J. J. Beer, Isis (1987): 363-81; L. F. Haber, (1971): 40-1, 48, 133, 865.

¹²⁰ R. Meldola, "The Scientific Development of the Coal Tar Industry" in W. M. Gardner, (1915): 136.

¹²¹ L. F. Haber, (1971): 128.

Merck had the largest factory of the pharmaceutical manufacturers and even in 1905 employed 800 workers, 50 pharmacologists and doctors, and a total staff of 1,500. Thirteen years later this had grown to 2,000. Schering had 935 workers and a permanent staff of about 300 in 1913.¹²² German firms not only had overall staff levels around ten times higher than British pharmaceutical firms but also were increasing at a faster rate.¹²³ In their semi-annual report of April 1903, Schimmel & Co., a maker of essential oils stated:

“There are no grounds for fearing that it (the German Chemical Industry) will be outstripped by competition from abroad, so long as German universities possess such eminent representatives of chemical sciences”.¹²⁴

Despite their already massive scale compared to British firms, Bayer, Badische and the Aktiengesellschaft für Anilinfabrikation of Berlin (AGFA) merged creating the Interessengemeinschaft (later known as 'Little IG') on 1 January 1906 to remain competitive with the firm of Hoechst, formed by the merger of the Frankfurt firms Meister, Lucius & Brüning and Cassella in August 1904, to which Kalle was added between 1907-8.¹²⁵ They pooled processes and patents and agreed not to compete in pharmaceuticals.¹²⁶ Duisberg of Bayer wanted pharmaceutical manufacturers to merge, but instead they formed the informal Pharma IG in 1905, with Merck, Gehe, J. D. Riedel, Knoll and C. F. Boehringer.¹²⁷ The only important pharmaceutical firm outside of the Pharma IG was Schering and its subsidiary C. A. F. Kahlbaum. Pharma IG firms agreed to pool processes,

¹²² L. F. Haber, (1971): 133.

¹²³ T. I. Williams (ed.), A History of Technology: Twentieth Century 1900-50 volume V1 (Oxford: Clarendon Press, 1978): 479.

¹²⁴ Sir William A. Tilden, “The Supply of Chemicals to Britain and her Dependencies” in W. M. Gardner, (1915): 325.

¹²⁵ German firms had collaborated (Verein Chemischer Fabriken) since the early nineteenth century, H. Hollander, (1955); G. C. Allen, Monopoly and Restrictive Practices (London: Allen & Unwins, 1968).

¹²⁶ The Hoechst agreement was on 15-19 October 1904. Duisberg arranged cross-licensing with AGFA and Cassella and urged the move into pharmaceuticals. Bayer; Badische; AGFA were in the ratio of 43: 43: 14 signed on 1 January 1906: L. F. Haber, (1971): 47, 124.

¹²⁷ L. F. Haber, (1971): 132-134; J. Slinn, A History of May & Baker 1834 - 1984 (Cambridge: Hobson's Ltd., 1984): 78 - 79.

and experience and uphold each other's patents and kept close relations with the dye firms. Bayer and Merck also came to an agreement concerning production of sedatives.¹²⁸ British firms relied on participating in German-run cartels to give them access to at least some modern German drugs.¹²⁹ Many of these are detailed in Slinn's account of May & Baker and included cartels for camphor, bismuth, chloroform and mercurial preparations.¹³⁰ Output of German dye firms trebled from 1881 to 1900, and their market share rose from 50% to between 80-90%. By 1914 the German firms represented an overwhelming dominant force.¹³¹

A brief mention however must be given about Swiss firms, which operated as if an extension of the German industry. Several Swiss firms situated around Basel evolved from dye manufacturers in a similar way to German firms.¹³² The Gesellschaft für Chemische Industrie Basel or the Society for the Chemical Industry in Basel (abbreviated CIBA only since 1945) was founded in 1884 from a group of earlier Basel manufacturers including one that had traded in drugs from 1758. Bindschedler & Busch and Edouard Sandoz also opened their own factory in 1886 (becoming Sandoz & Co. in 1893) and they merged with A. Gerber & Co in 1898. The former can be traced back to a dye firm founded in Basel in 1859.¹³³ Hoffmann-la-Roche was founded in 1896 specifically to produce pharmaceuticals and unlike other Swiss firms did not have dyestuffs roots. In order to gain patent protection its original site was within Germany.¹³⁴ The five Swiss firms centred in Basel

¹²⁸ L. F. Haber, (1971): 134.

¹²⁹ Jonathan Liebenau, "The Rise of the British Pharmaceutical Industry" British Medical Journal (3 October 1990) 301: 726.

¹³⁰ Judy Slinn, (1984): 80.

¹³¹ David S. Landers, The Unbound Prometheus (Cambridge: Cambridge University Press, 1969): 276. Paul M. Hohenberg, Chemicals in Western Europe 1850-1914 (Chicago: Rand McNally and Co. 1967); J. J. Beer, (1958): 123- 131.

¹³² CIBA Ltd. The Story of Chemical Industry in Basle (Lausanne: Graf, 1959); Paul Erni, The Basel Marriage: History of the Ciba-Geigy Merger (Zurich: Neue Zurichische Zeitung, 1979); Hans Conrad Peyer with foreword by Paul Sacher, Roche: a Company History 1896-1996 (Basel: Editions- Roche, 1996); Sandoz 1882-1961(1961); P. Bousell, H. Bonnemain, F. Bove, Sandoz: History of Pharmacy and the Pharmaceutical Industry (Lausanne: Asklepios Press, 1983); "The 50 Years of Sandoz Pharmaceutical Products (1917-1967)" J. Med. Lyon (January 1968) 49 (135): 137-8.

¹³³ J. T. Mahoney, (1959): 232-3.

¹³⁴ Hans Conrad Peyer, (1996); J. T. Mahoney, (1959): 216-236.

(‘CIBA’, Sandoz, J. R. Geigy, L. Durand, Huguenin, and the Basler Chemische Fabrik) employed 1,326 people in 1901 and operated profit sharing pools between them.¹³⁵ ‘CIBA’ had 1,600 staff in 1913, Hoffman la Roche had 550, Geigy 400, Sandoz 340 and Durand and Huguenin 100. CIBA began manufacturing pharmaceuticals in the early 1900's and soon a separate section was created.¹³⁶ Switzerland thus had a strong industry, but was still heavily dependent on Germany and bought all the process chemicals and up to 80% of all intermediates from Germany.¹³⁷

2.6 Failure of Britain and Other Countries to Develop Synthetic Drugs.

France, like Britain relied heavily on Germany and did not produce synthetic drugs. Both Quirke and Robson have compared the origins and comparative scale of French firms with Britain. Quirke demonstrated that much of the pharmaceutical innovation came from collaborations with the Pasteur Institute.¹³⁸ The largest firm, the Société des Usines de Rhône, employed 700 staff, including 27 chemists in 1900. By 1913 they specialised in organic chemicals, especially pharmaceuticals, photochemicals, and essences and were the first in France to produce phenol. The much smaller Poulenc Brothers firm is also relevant to this account as they collaborated with Britain's May & Baker before merging with Usines de Rhône in 1928 to form Rhône Poulenc.¹³⁹ The French dyestuffs industry was based on natural alkaloids and minerals and France did not recognise medical patents.

Most British firms were small in comparison with German dye-based firms even before the latter began to merge pre-war. In 1884 there were 800 – 1,000 manufacturers making up to 5,000 medicines with 19,000 employed in manufacture and distribution.¹⁴⁰ Several small

¹³⁵ L. F. Haber, (1971): 20, 113 and 169, F. A. Sherwood Taylor, (1957): 384.

¹³⁶ A. Buergin, *Geschichte der Geigy Unternutze 1758-1939* (1958); L. F. Haber, (1971): 163-4; *Sandoz 1886-1961* (1961): 136; J. T. Mahoney, (1959): 216- 236.

¹³⁷ L. F. Haber, (1971): 19, 163.

¹³⁸ Michael Robson, (University of London: PhD, June 1989) “The Pharmaceutical Industry in Britain and France 1919-1939”; V. Quirke, “Experiments in Collaboration”. *The Changing Relationship Between Scientists and Pharmaceutical Companies in Britain and in France, 1935-1965* (University of Oxford: PhD thesis, 1999).

¹³⁹ Judy Slinn, (1984): 92, 95- 101.

¹⁴⁰ *Chemist & Druggist* 36 (1890): 367; *Chemist & Druggist* 50 (23 January 1897): 125.

local firms with pharmacy roots have long since disappeared, but some did well such as James Woolley Sons & Co., Manchester (founded 1796), Thomas Kerfoot, Ashton-under-Lyne, (1797), Arthur Cox & Co. in Brighton (1839)¹⁴¹, Stafford Allen & Co. London, (1833)¹⁴² and William Ransom & Sons, Hitchin (1846).¹⁴³ The fine chemical manufacturer, Thomas Morson & Sons Ltd., originated from a business established by Thomas Newborn Robert Morson as an apothecary in Fleet Street, London in 1821, having learnt about alkaloid manufacture in France for the previous 3 years. He produced the first quinine and morphine in Britain.¹⁴⁴ Thomas N. R. Morson was President of the Pharmaceutical Society 1848-9 and again 1859-61.¹⁴⁵ Thomas Whiffen's was founded in 1819 and concentrated on fine chemicals.¹⁴⁶ Evans, Lescher & Webb originated from a firm established in Wood Street in London in 1828 by John Sidney Lescher, a founder of the Pharmaceutical Society and John Evans.¹⁴⁷ May & Baker founded in Battersea in 1834, produced bismuth, mercurials, ether and spirits but most novel drugs were bought in under license. They prepared phenacetin and Sulphonal under an 1887 contract with Bayer.¹⁴⁸ By 1900 May & Baker employed about 100 people. From 1903 they manufactured salts of lithium having secured the rights by taking on a chemist who had patented the process. It was their search for a source of mineral from which to extract the lithium that led to a relationship with Poulenc Frères. By 1910 May & Baker had sales of £250,000 but gross profits of less than £22,000 and net profits of just over £7,000.¹⁴⁹

¹⁴¹ C. Fearon, "The History of A. H. Cox & Co. (Arthur Hawker Fox 1813-1903)" Pharmaceutical Historian 23.2 (June 1993): 4-6.

¹⁴² S. Miall, (1931): 133.

¹⁴³ Allan Duckworth, Chemist & Druggist (10 November 1959): 127-139; John Richards Co. claimed to have the largest pill factory in the world having registered 22,000 types of pill. Their stocks of Blaud's pills were usually ¾ ton: F. N. L. Poynter, (1965): 133; K. Holland, "William Ransom & Sons Plc" The Pharmaceutical Journal (14 November 1987): 578-9.

¹⁴⁴ L. G. Matthews, (1962): 227, 231-2; S. Miall, (1931): 133.

¹⁴⁵ S. W. F. Holloway, Royal Pharmaceutical Society of Great Britain 1841-1991. A Political and Social History (London: The Pharmaceutical Press, 1991) appendix.

¹⁴⁶ "Thomas Whiffen 1819-1904" in D. J. Jeremy, C. J. Shaw (eds.), Dictionary of National Biography V (London: Butterworth, 1956): 84-6; S. Miall, (1931): 139-40.

¹⁴⁷ "The late T. E. Lescher", Pharmaceutical Journal 140 (30 April 1938): 460.

¹⁴⁸ Judy Slinn, (1984): 44-45.

¹⁴⁹ S. Miall, (1931): 141; Judy Slinn, (1984): 79.

Duncan Flockhardt, founded in 1806 in Edinburgh, produced nitrous oxide and then chloroform anaesthetics from 1848 and J. F. MacFarlan was founded in 1864.¹⁵⁰ T. H. Smith was founded in Edinburgh in 1827; Stafford Allen & Sons founded in 1833 prepared drugs and essential oils. William John Bush founded the firm known as W. J. Bush in Hackney in 1851, initially making flavouring essences by the steam distillation of herbs and spices before developing drugs.¹⁵¹ Beecham's began in 1848 as a patent medicine manufacturer, and did not produce ethical pharmaceuticals until after the Second World War.¹⁵² In 1851 the patent medicine market had a turnover of £250,000 and the largest company was Thomas Holloway of London, who in that year produced £25,000 worth of pills.¹⁵³ T. & J. Smith (later Smith & Nephew, when H. N. Smith joined in 1896) was established in Hull in 1856, but remained small until the War.¹⁵⁴ A. Boake Roberts was founded in 1865 initially produced brewing chemicals, flavourings and essential oils.¹⁵⁵ Glaxo had origins in New Zealand as J. Nathan & Co., importing dairy produce into Britain and only became established as a baby food manufacturer at the start of the twentieth century.¹⁵⁶ The London Drug Company, and Taylor's¹⁵⁷ concentrated on the retail trade rather than producing their own drugs. Boots, established in 1877 were retailers and expanded to a chain of 200 shops by the end of the nineteenth century.¹⁵⁸

¹⁵⁰ C. G. Drummond, "Pharmacy & Medicine in Georgian Edinburgh" Pharmaceutical Journal 192 (1964): 287- 293; "Pharmacy in Scotland" Chemist & Druggist 81 (27 July 1912): 146.

¹⁵¹ S. Miall, (1931): 141; "W. J. Bush & Co. Ltd: A Centenary" J. Soc. Chemical Industry (3 March 1951): 168.

¹⁵² T. A .B. Corley, "The Beecham Group in the World's Pharmaceutical Industry 1914-70" Gesellschaft für Unternehmensgeschichte (1994) (1): 18-30.

¹⁵³ "Pharmacy in Scotland" Chemist & Druggist (27 July 1912): 146.

¹⁵⁴ R. Bennett, J. A. Leavey, A History of Smith & Nephew (London: Smith & Nephew, 1981).

¹⁵⁵ W. J. Bush, Stafford Allen and A. Boake Roberts no longer exist and were merged as part of a group called International Flavouring and Fragrances Inc., www.iff.co.us

¹⁵⁶ R. P. T. Davenport-Hines, Judy Slinn, Glaxo, A History to 1962 (Cambridge: Cambridge University Press, 1992): 17-45.

¹⁵⁷ Geoffrey Tweedale, (1990): 50, 78, 83.

¹⁵⁸ Chemistry & Industry (23 February 1963): 303; S. Chapman, Jesse Boot of Boots the Chemist (London: Hodder & Stoughton, 1974); C. Weir, Jesse Boot of Nottingham, Boots 1994); A Record of Fifty Years Progress of Boots Pure Drug Co. Ltd: Jubilee 1888-1938 (Nottingham: Boots, 1938).

Even two of the largest British firms, Burroughs Wellcome and Allen & Hanbury's, employed less than 200 staff in the 1890's.¹⁵⁹ Allen & Hanbury's was founded in 1715 and expanded gradually, moving to Bethnal Green in 1874 and to Vere Street in 1880, adopting limited liability status in 1893. By then the firm was producing their own soluble coated pills, disintegrating tabellae and hypodermic injections, but they sold tuberculin that had been developed in Germany, and thyroid extracts. At the end of the nineteenth century, Allen & Hanbury's remained a family run business, with shares owned by Cornelius Hanbury and his son Frederick Janson Hanbury.¹⁶⁰ A technical chemist, John Fordred was employed from 1878, but for more complex tests they turned to the Pharmaceutical Society.¹⁶¹ They employed a pharmaceutical analyst, William Ralph Dodd (1856-1917), to perform assays and he became head of a small manufacturing laboratory after he found the new site at Ware in Hertfordshire and he was elected to the board in 1904.¹⁶² Frederick William Gamble (1872-1948) was appointed as manager of the Vere Street pharmacy in 1900. He had joined at Plough Court in 1896 and transferred to Vere Street the following year, having qualified from the Pharmaceutical Society. He had a "genius for friendly relations with the medical consultants of the neighbourhood" and we will encounter him further.¹⁶³ A rapid expansion at Ware involved the building of pastille and capsule departments in 1900 to complement the jujube and lozenge departments at Bethnal Green, which housed administration and printing works for advertising. In 1903 Allen & Hanbury developed and began using the prototype of the modern rotary tablet machine.¹⁶⁴ At Ware boilers and new moulding machinery were installed, milk evaporation units, rollers, electric motors and stills, and the chemist William Radford, a trained builder, eventually became works manager. Between 1900 and 1914, £16,500 was

¹⁵⁹ A. G. Green in W. M. Gardner, (1915): 132 - 136; L. F. Haber, (1971): 16.

¹⁶⁰ Geoffrey Tweedale, (1990): 86.

¹⁶¹ Geoffrey Tweedale, (1990): 73-74, 79; W. R. Dunstan, A. F. Dimmock, "Estimation of Diastase" *Pharmaceutical Journal* 38 (1879): 773-775; "A Visit to Messrs. A. & H. Works" *Chemist & Druggist* 22 (1880): 14.

¹⁶² Geoffrey Tweedale, (1990): 73, 87, 89, 108, 115.

¹⁶³ Frederick William Gamble was a pharmacist trained at Kensington and the Pharmaceutical Society (1872-1948). He joined the pharmacy of Allen & Hanbury's in 1896. Geoffrey Tweedale, (1990): 99.

¹⁶⁴ C. Gunn, in F. N. L. Poynter, (1965).

spent on expansions at Ware. Although the emphasis was on milk and food products, they made bulk galenicals such as cascara and liquorice as well as castor oil, liquid paraffin and cod liver oil and a significant line in surgical instruments.

2.7 Factors Inhibiting the Development of British Firms.

2.7.1 Introduction.

A number of factors have been explored to explain the reliance upon Germany for novel drugs and chemicals.¹⁶⁵ Britain had many small independent family-owned firms. The only significant merger in Britain was of several small firms in 1908 to form British Drug Houses.¹⁶⁶ They produced highly purified drugs and had laboratories for quality control, advertising that they were the first to offer a warranty of not only compliance with the U.S. Food and Drugs Act and British Pharmacopoeia but even more stringent standards.¹⁶⁷

British dyestuffs firms failed to produce innovative dyes and so could not adapt to manufacture fine chemicals and drugs. There was a lack of available chemists, specifically those with manufacturing-scale experience, a lack of available chemical intermediates, limited marketing capacity, and resistance to testing drugs in animal experiments. British pharmaceutical firms made standard drugs for doctors, who were even slow to adopt pure

¹⁶⁵ Sir W. A. Tilden, "The Supply of Chemicals to Britain and her Dependencies" Journal of the Royal Society of Arts (27 November 1914): 26; Sir William A. Tilden in W. M. Gardner, (1915): 315 - 334; I. Singer, "The Coal Tar Colour Industry of England: Causes of its Progress and Retardation" in W. M. Gardner, (1915): 280- 297.

¹⁶⁶ The grandfather of BDH chairman Charles A. Hill was Arthur Stephen Hill who had entered the pharmaceutical trade in the second decade of the nineteenth century. His firm amalgamated to become Davy, Yates and Hill then merged with Hodgkinson's, Clarke and Ward to form Davy, Hill, Hodgkinson and then in 1908 became BDH incorporating Barron Harvey's & Co. and Hearon, Squire & Francis Ltd; British & Colonial Pharmacist (October 1943): 254 in 2130 B.CARR/IV Press Cuttings. Charles Alex Hill, BSc, FIC, PhD, was Chairman of British Drug Houses from its inception on 1 January 1909. Hill was an Associate of the Institute of Chemistry from 1895.

¹⁶⁷ C. A. Hill, H. S. Collins, "An Effective Method of Applying the Gutzeit Test for Arsenic" Chemist & Druggist 67 (30 September 1905): 548; C. A. Hill, "The Purity of Pharmaceutical Chemicals with Suggestions for Commercially Obtainable Standards" Chemist & Druggist 72 (23 May 1908): 792-97; C. A. Hill, "Quantitative Colorimetric Tests for Lead" Chemist & Druggist 66 (11 March 1905): 388; T. Tusting Cooking, (Davy, Hill, Hodgkinsons) "The Contamination of Zinc and its Compounds with Lead" Chemist & Druggist 69 (29 September 1906): 507;

alkaloids, preferring for many years to use total plant extracts.¹⁶⁸ Few doctors in Britain applied numerical methods to evaluate new treatments and yet they were persuaded by the scientific rationale and marketing of German synthetic drugs, tested pharmacologically, patented, sold under Trade names and promoted heavily. British firms, partly by virtue of their lack of innovation, failed to collaborate with university scientists, pharmacologists and clinicians.¹⁶⁹

An eminent group of British University professors gave early warnings of the dominance of Germany and the need to address this. These included Sir William Tilden, former Professor of Chemistry in Birmingham 1880-4, then Professor of the Royal College of Science in London, who was a member of the Council of the Institute of Chemistry and the Society of Public Analysts;¹⁷⁰ Frederick M. Perkin, a son of the dye founder William Perkin, and head of Perkins & Sons, who became head of chemistry at the Borough Polytechnic Institution in 1897;¹⁷¹ Raphael Meldola (1849-1915)¹⁷² who studied at the Royal College of Chemistry in 1866 before working at the Brooke, Simpson & Spiller dye works in Hackney Wick. He took the chair of chemistry at Finsbury College in 1885 and was Professor of Organic Chemistry at London University from 1912. Meldola and others gave evidence to the 1904 enquiry into the decline of the dyestuffs industry and he was in turn President of the Society of Dyes and Colourists, the Society of the Chemical industry and the Institute of Chemistry. William Ramsay (1852-1916) was Professor of Chemistry at University College, Bristol 1880-7 and then at University College London until his death in 1916;¹⁷³ Arthur Green succeeded Meldola at the works of Brooke, Simpson & Spiller

¹⁶⁸ D. McKie, "Woehler's 'Synthetic' Urea and the Rejection of Vitalism: a Chemical Legend" *Nature* 153 (1944): 608-610; F. G. Hopkins, "The Centenary of Woehler's Synthesis of Urea (1828-1928)" *Biochemical Journal* 22 (1928): 1341-8.

¹⁶⁹ M. J. Allen, *The Statistical Movement in Early Victorian Britain: The Foundation of Empirical Social Research* (New York: Barnes & Noble, 1973): 135-146; A. M. Lilienfeld, "'Ceteris paribus': the Evolution of Clinical Trials" *Bulletin of the History of Medicine* 56 (1982): 1-18; L. Lasagna, "Historic Viewpoint of Clinical Trials" *Drug Information Journal* (1982): 8.

¹⁷⁰ For a series of articles on this see W. M. Gardner, (1915).

¹⁷¹ M. R. Fox, (1987): 100.

¹⁷² Alexander Findlay, William Hobson Mills (eds.), *British Chemists* (London: The Chemical Society, 1947): 96- 110.

¹⁷³ Alexander Findlay, William Hobson Mills (eds.), (1947): 219-246; *J. Chemical Society* (1917) 111: 369-76.

and was then works manager at Clayton Aniline until 1901, when for 2 years he was a consultant, then Professor of tinctorial chemistry at Leeds University.¹⁷⁴ These British chemists complained of a negative attitude to research within Britain, defective patent laws, and general Government apathy. In contrast German firms had extensive financial support from their government and there was more central planning of railways and waterways to stimulate exports.¹⁷⁵ It was not going to be possible to rebuild the dye industry overnight but there were some factors, which were brought to the attention of government as areas that could be addressed. All of the above expressed their concerns within the Society of the Chemical Industry (SCI), which had introduced the first journal devoted to the chemical industry in 1882.¹⁷⁶ The Society had 1,140 members by 1882 climbing to 2,697 in 1891.¹⁷⁷

2.7. 2 The Lack of Practically Trained British Chemists and Chemical Engineers.

Chemists in Britain were in short supply at the end of the nineteenth century, especially those with practical experience in pharmaceuticals.¹⁷⁸ When William Perkin junior inherited his father's dye works in the 1850s, he had only 4 chemists.¹⁷⁹ In 1867 the Chemical Society in Britain (founded 1841) had only 192 members.¹⁸⁰ One of the few sources was Owens College in Manchester where Edward Frankland¹⁸¹ was Professor from 1851, until he moved to South Kensington in 1856, with Henry Roscoe taking up the chair in Manchester. Another was the laboratory of Theophilus Redwood, Professor of

¹⁷⁴ J. Baddiley, "Arthur George Green" Obituary Notices of Fellows of the Royal Society 4 (1943): 251- 270.

¹⁷⁵ W. H. Perkin, "The Aniline or Coal Tar Colours" (1868) in W. M. Gardner, (1915): 1 - 45.

¹⁷⁶ S. Miall, (1931): vii

¹⁷⁷ "Society of Chemical Industry" Chemist & Druggist (11 July 1891): 41-5.

¹⁷⁸ "Academic Chemistry" in L. F. Haber, (1971): 34-67; W. F. Furter, (ed.) History of Chemical Engineering (Washington: American Chemical Society, 1980).

¹⁷⁹ Journal of the Society of the Chemical Industry (1885) 4: 437.

¹⁸⁰ D. S. L. Cardwell, The Organisation of Science in England, A Retrospect (London: Heinemann, 2nd edition 1972): 99-100; C. S. Gibson, Endeavour (1947): 63-8; T. S. Moore, J. C. Phillip, (1947).

¹⁸¹ C. S. Gibson and T. B. Hilditch, "Edward Frankland Armstrong" Obituary Notices of Fellows of the Royal Society 5 (1945-8): 618-29.

Chemistry at the School of Pharmacy at the Pharmaceutical Society in London.¹⁸² A series of eminent German chemists including A. W. Hoffmann performed research and taught at the Royal College of Chemistry founded in 1845.¹⁸³ Frankland worked alongside him since the opening and succeeded Hoffmann in 1865, and he led the early campaigns for better education of chemists. South Kensington became an important source of industrial chemists.¹⁸⁴ Just before Hoffmann left for Berlin, Henry Edward Armstrong joined the laboratory, first as a student, then as an assistant.¹⁸⁵ Armstrong had studied at the Royal College of Mines, founded in 1851, and from 1867 under Kolbe in Leipzig, and Bunsen in Marburg. Armstrong returned as Professor of Chemistry at the London Institution, Finsbury Circus in 1870. The Royal College of Chemistry and the School of Mines were amalgamated in Kensington in 1872. In 1874 Armstrong published his "Introduction to Organic Chemistry". He was a founder member of the Institute of Chemistry in 1877, which aimed to increase the academic status of industrial chemistry. Entrants required 3 years training plus 3 years teaching or industrial experience. In October 1879 he became the first Professor of Applied Chemistry at the City and Guilds Institute founded in November 1878.¹⁸⁶ Armstrong and other senior chemists, many of whom had trained in Germany, were behind the formation of the SCI in 1881, which lobbied for patent reform and technical and practical training of chemists.¹⁸⁷

¹⁸² "Theophilus Redwood, Obituary" Journal of the Society of the Chemical Industry 11 (1892): 228-9.

¹⁸³ D. S. L. Cardwell, (1972): 86-7.

¹⁸⁴ E. Frankland, "Chemical Research in England" Nature 3 (1871): 445; D. Layton, Interpreters of Science: a History of the Association for Science Education (Bath: John Murray, 1984); P. Mathias, The First Industrial Nation: an Economic History of Britain 1700-1914 (London: Methuen, second edition, 1983): 221, 419; R. M. Macleod, "The Support of Victorian Science. The Endowment of Research Movement in Great Britain in 1868-1900" Minerva iv (27), (1971): 197- 230; D. S. L. Cardwell, (1972): 87.

¹⁸⁵ G. Van Praagh, "H. E. Armstrong and Science Education" (London: John Murray, 1973); Sir Frederick Keeble, "H. E. Armstrong" Obituary Notices of Fellows of the Royal Society 3 (1941): 238; "H. E. Armstrong" in E. F. Armstrong, Chemistry in the Twentieth Century: An Account of the Achievement and the Present State of Knowledge of Chemical Science (London: Ernest Benn, 1924): 122; "H. E. Armstrong (6 May 1848 to 13 July 1937)" in Alexander Findlay, William Hobson Mills (eds.), (1947): 58-95.

¹⁸⁶ D. S. L. Cardwell, (1972): 127-132.

¹⁸⁷ W. H. Perkin in W. M. Gardner, (1915): 1; Sir William A. Tilden in W. M. Gardner, (1915): 332, 377; S. Miall, (1931): 86; A. J. Levine, (1967).

The City and Guilds Institute moved to the Finsbury Technical College in 1883 and from 1884 it became the more advanced Central Technical College at South Kensington. Henry Armstrong was by then Professor of Chemistry at the greatest chemical engineering school in Britain.¹⁸⁸ Armstrong taught chemistry that was largely analytical with synthetic chemistry on a small scale to examine theoretical chemical structures of alkaloids and coal tar products. His learning in Germany influenced his controversial campaigns for practical 'heuristic' methods of teaching. He had considerable influence as a Fellow of the Royal Society and as Secretary, President and Vice-President of the Chemical Society almost continuously from 1875 until his death in 1937; and as President of the Chemical Section of the British Association.

Armstrong's lectures with George Davis formed the basis of a three-year diploma of chemical engineering launched in 1885.¹⁸⁹ George Davis published the first British text on chemical engineering in 1901, based on his own lectures in Manchester from 1887.¹⁹⁰ He participated in the 1902–3 Technical Education Board with many famous chemists including Leivenstein, Roscoe, Dewar, W. H. Perkin, Ramsay, and Green along with Thomas Tyrer representing drugs, who recognised that the shortfall was in practical chemists and particularly chemical engineers.¹⁹¹ Henry Armstrong recognised that in order to compete with foreigners, sound scientific education was needed and he noted that America promised to become a major competitor.¹⁹²

T. H. Huxley wrote to *The Times* in 1886 that "the last years of this century promise to see us embarked in an industrial war of far more serious importance than the military wars of its opening years".¹⁹³ The limited resources of British pharmaceutical firms were described in 1889:

¹⁸⁸ G. Van Praagh, (1973): 21, 60; P. E. Richmond, A. R. Quarishi, "Armstrong's Heuristic Method" *School Science Review* 45 (1964): 517; J. V. Eyre, *H. E. Armstrong 1848 – 1937* (London: Butterworth, 1958).

¹⁸⁹ F. W. Keeble, (1941): 240.

¹⁹⁰ G. Van Praagh, (1973): 56.

¹⁹¹ D. S. L. Cardwell, (1972): 195-201; "Thomas Tyrer, Obituary" *J. Society of the Chemical Industry* (1918): 91.

¹⁹² L. F. Haber, (1971): 63.

¹⁹³ G. Van Praagh, (1933): 52.

“Our historic drug houses, who have always acted more or less as manufacturers, have much to their detriment neglected research. Each establishment should have its chemist engaged in the chemical examination of new remedies for the discovery of active principles, etc. which must have tended to have kept us out of the arms of foreigners for most of our alkaloids and other organic substances now in such increasing demand in medicine”.¹⁹⁴

Given the lack of chemical engineers, it is important to introduce one that trained with Henry Armstrong and later entered industry with Burroughs Wellcome and played a major part in the development of chemical engineering in the pharmaceutical industry.

Francis Howard Carr, a student of Armstrong at Finsbury became one of the most important chemical engineers in the pharmaceutical industry in the interwar period.¹⁹⁵ Carr plays a central part in this thesis, establishing manufacturing synthetic chemistry at Burroughs Wellcome, Boots and British Drug Houses, a forerunner of Glaxo. He was born in Croydon, the seventh of 12 children of strict Baptist parents. After leaving school at 15 years he was to have entered a City Merchant’s office, but on the day he was due to start he pulled out; fortunately his father recognised that his love of chemistry would be rewarded by attending Finsbury Technical College, where he was to study with Henry Armstrong between 1889-92. Although he had to leave after two years either through ill health or for financial reasons, he completed his Diploma and Armstrong introduced him to W. R. Dunstan, who had run the Pharmaceutical Society laboratory since 1879.¹⁹⁶ Francis Carr then became research assistant to Dunstan at the Pharmaceutical Society from 1892-6, where he was awarded the first Salter’s scholarship, and then followed him to the Imperial Institute as his assistant, when Dunstan became Scientific Director in 1896. Armstrong further supported his protégée and encouraged Carr to take up membership of the Institute of Chemistry in 1895 and to join his own London club, the Athenaeum, to introduce him to influential businessmen.¹⁹⁷

Carr explained that there had been insufficient trained chemists in Britain:

¹⁹⁴ C. Umney, “Presidential Address”, *British Pharmaceutical Congress, Pharmaceutical Journal* 49 (14 September 1889): 214-18.

¹⁹⁵ T. A. Henry, “Wyndham Rowland Dunstan (1861-1949)” *Obituary Notices of Fellows of the Royal Society* 7 (1950): 65.

¹⁹⁶ T. A. Henry, (1950): 62 – 81.

“ It is not so much more colleges and more students as it is better methods of training which need to be considered in connection with the educational question which is only one of the many important sides of the problem of the chemical industry in this country. The technical college should go beyond the process of developing the mind to that of the application of mental processes to the problem of industry”.¹⁹⁸

Carr became active in promoting practical training of chemists at Finsbury, but he also had a significant direct effect himself in training others on the job as he moved from firm to firm. He joined Burroughs Wellcome at Dartford in January 1898 as Chief Manufacturing Chemist, and his influence there will be discussed in Chapter 3.

2.7.3. Patent Protection.

SCI members were behind changes in the patent laws with Ivan Levinstein on behalf of Levinstein's and other dye firms, and Thomas Tyrer leading the campaigns.¹⁹⁹ Ivan Levinstein's firm had been founded a generation earlier, but he expanded the business to Blackley, north of Manchester in 1865 and employed 20 men by the end of the nineteenth century. Levinstein was President of the Chamber of Commerce in 1903, but resigned his post to take part in Joseph Chamberlain's Tariff Commission and he was Vice-President of the Tariff league.²⁰⁰ Thomas Tyrer had been a partner at May & Baker and when the original partnership was dissolved he had set up his own company in 1898 by acquiring the Stratford Chemical Works in East London.²⁰¹

As a result of the drive of Tyrer and Levinstein, the 1907 Patent Law Amendment, came into force in January 1908, compelling German companies to transfer part of their production to Britain in order for patents to remain valid. This was an attempt to stimulate the chemical industry in Britain, to provide potential jobs, and stimulate the study of chemistry. Following the Act, the group of BASF, Agfa and Bayer bought a site at

¹⁹⁷ F. H. Carr archives at Imperial College Transcripts by A. E. Guenther B.CARR FH 6.

¹⁹⁸ F. H. Carr, Press cuttings - letter "Opinions on Education Pre-1914", Carr 2130 B/CARR IV.3

¹⁹⁹ M. R. Fox, (1987): 51- 52; W. J. Reader, I.C.I. A History: The Forerunners 1870 – 1926 volume 1: 265.

²⁰⁰ M. R. Fox, (1987): 2-16.

²⁰¹ Judy Slinn, (1984): 54. He was awarded the medal of the Society of the Chemical Industry in 1910 and remained its treasurer for the 10 years before he died in 1918.

Bromborough on the River Mersey, while a second group comprising mainly Hoechst bought a site at Ellesmere Port, Cheshire.²⁰²

Whereas the original intention of the 1907 Act was to force the production of dyes needed for the British market, a court ruling two years later emasculated the Act by allowing firms to import many intermediates and semi-finished goods; they only needed to sell a proportion in Britain and it was impossible to check what was imported.²⁰³

2.7.4 Alcohol Supplies and Duty

British dye firms had campaigned for long periods to have the excise duties on ethanol reduced. Alcohol was needed as a solvent in which to dissolve various chemicals in order to get them to react, and was required in the preparation of salts and as a chemical intermediate itself in a relatively pure state. In addition it was essential to have a supply of cheap acetone, and acetic acid. However, the government believed that if alcohol were not taxed heavily, it would be used for drinking and distillation and in Britain spirits were methylated to prevent this. The government also had concerns over the high amounts of alcohol used in patent medicines and tonics. However, both the excise duty and the purification costs were prohibitive for industry, and as a result certain dyes and chemicals could not be produced cost-effectively in Britain. The government gave no concessions to industry - in contrast to Germany where it was available at special rates to industry.²⁰⁴ The price of ether was threefold higher in England than in Germany, although Britain did prohibit the export of phenol from 1901.²⁰⁵ A departmental committee on alcohol reported on the situation in 1905, but did little to help as the government failed to reduce the duty.²⁰⁶ Absolute alcohol was especially used for the manufacture of chloral hydrate, and in 1913 we imported 28,994 proof gallons from Germany.²⁰⁷

The availability of a cheap source of manufactured alcohol as a starting material for drug production was constantly mentioned as one of the main hurdles to drug development.

²⁰² M. R. Fox, (1987): 51-52.

²⁰³ M. R. Fox, (1987): 32-33.

²⁰⁴ M. R. Fox, (1987): 43

²⁰⁵ L. F. Haber, (1971): 13.

²⁰⁶ Departmental Committee on Alcohol Report Q1378, (ed.) 2477 (London: HMSO, 1905).

²⁰⁷ Chemist & Druggist 85.2 (19 September 1914): 48-9; M. R. Fox, (1987): 43.

At the outbreak of War it was stated that there was further discussion on alcohol supplies and it was stated that:²⁰⁸ “if this country had duty free alcohol Germany will not be in a position for some time after the war, if ever again to export their preparations”.²⁰⁹

2.8 The Extent of Reliance on Germany for Pharmaceuticals and Especially Synthetics.

Although the production of organic chemicals increased in Great Britain between 1880 and 1910, exports of British chemicals rose more slowly than imports between 1900 and 1914.²¹⁰ Later in 1926 when Francis Carr gave his presidential speech he looked back to the period before the war. He recalled that statements to the effect that the British chemical industry was negligible were exaggerated as the number of workers in the chemical industries had doubled between 1900 and 1914.²¹¹ Furthermore the shortages of synthetics were:

“Not solely because they were not made here, for several firms had achieved that already; but antipyrin, aspirin, salicylic acid, phenacetin, chloral hydrate, salol, phenolphthalein, saccharin, veronal, sulphonal, trional, eucaine and novocaine were not manufactured here and these amounted to over £1m worth of synthetic drugs”.²¹²

This apparently misleading quotation meant that although technically many of the chemicals could be made, at least on a small scale, it was not possible for British manufacturers to prepare them in bulk on a competitive basis. Owing to our inferior organisation we thus became in a measure “the shuttlecock of German men of business”. It was stated: “before the war it would have been very difficult to produce the salicylates here”. Even simple synthetics such as the unpatented Aspirin were not produced

²⁰⁸ F. M. Perkin, in W. M. Gardner, (1915): 298-314.

²⁰⁹ Edwin J. Tookey, “Making Fine Chemicals” Chemist & Druggist 85.1 (29 August 1914): 63.

²¹⁰ H. W. Richardson, “Chemicals” in D. H. Aldcroft (ed.), The Development of British Industry and Foreign Competition 1875-1940 (1979); L. F. Haber, (1971): 121, 148.

²¹¹ F. H. Carr, text of his 1926 SCI speech, “Manufacture of Organic Medicinal Chemicals” in his archives at Imperial College. B/CARR/III Lectures 1920-60. He did not give the actual numbers of chemists.

²¹² F. H. Carr, “Synthetic Organic Drugs: Their Manufacture as Affected by the War” Chemist & Druggist 88.4 (29 July 1916): 778-779.

commercially in Britain because it could not be produced “at prices which could compete with those at which Germany was able to offer them”.²¹³

The antifebrile effect of Antipyrin had been described and patented in July 1883, but even though all of the synthetic patents had expired British firms could not prepare it to sell competitively against German firms, and the same was true of Lanolines.²¹⁴ In addition some alkaloids including atropine, cocaine, emetine, hyoscine, morphine, ergometrine were only manufactured in Germany. Carr continued:

“Pre-War Germany’s trade was very much enhanced by selling cartels and the drawing together of large manufacturing concerns. The first achievements were the elimination of competition within Germany and the organisation of concerted effects to undersell rivals in those lines where dangerous competition seemed likely to arise. There was certainly plenty of evidence of these sales cartels and the practice of selling below cost at the least threat of competition”.²¹⁵

In summary, a series of factors conspired against British manufacturing chemists. Firstly there were less university-trained chemists in Britain than in Germany, and many of them were trained on theoretical rather than practical grounds. The size of German firms was much greater than British firms, so there were greater economies of scale and Germany had subsidised transport and cheaper raw materials, particularly ethanol. It was not beyond the wit of British chemists to make the drugs, but they could not manufacture them as cheaply as the Germans could. However, “although prior to the war, the manufacture of organic fine chemical products by synthesis was to a very large extent a continental monopoly there was nevertheless a beginning made within this country”.²¹⁶

As further evidence of the importance of German synthetics, The Royal Commission on vivisection, which reported in 1912, listed the drugs that had recently been introduced as a result of animal studies. These included the soporifics - chloral, sulphonal and veronal; local anaesthetics - cocaine, eucaïne and stovain; the analgesics and antipyretics - antipyrin, antifebrin, phenacetin and exalgin; physostigmine (or eserine) for

²¹³ F. H. Carr, text of his 1926 SCI speech, “Manufacture of Organic Medicinal Chemicals” in his archives at Imperial College. B/CARR/III Lectures 1920-60; “The War and the Scarcity of Some Drugs” British Medical Journal (27 March 1915): 559-561.

²¹⁴ Chemist & Druggist 85.2 (15 August 1914): 37; patent 26429 from 22 July 1883.

²¹⁵ A cartel existed for iodine and other drugs: “The War and the Scarcity of Some Drugs” British Medical Journal (27 March 1915): 559 – 561.

²¹⁶ D. L. Howard, British & Colonial Pharmacist (August 1926): 243.

glaucoma; amyl nitrites for angina; and the diuretics - caffeine, theobromine, diuretin and urotropin.²¹⁷ Out of a total of chemical imports from foreign countries and British possessions of £1.3 m, more than 25% was from Germany in 1913.²¹⁸ Figures, specifically for drugs are not readily available, as drugs were often combined with chemicals, polishes, glasses, gelatine, plastics, and artificial silk.

The Empire also relied on Germany. India took £8.5m of produce from Germany and £3m from Austria while Australia, New Zealand and Canada all relied on Germany for chemical intermediates.²¹⁹ Contemporary accounts show how Britain relied on Germany for “the synthetical and other drugs, which have in some ways revolutionised medical science, and also many of the more important disinfectants”.²²⁰ German synthetics were seen by 1914 as “a serious competition to our trade”.²²¹

British firms manufactured profitable lines such as morphine, strychnine and caffeine while other alkaloids were left to Germany who in turn took their raw materials from British colonies. Smith’s, Morson’s, Howard’s, Whiffen’s, and MacFarlane’s between them made morphine, brucine, strychnine, quinine, caffeine, nicotine and salicin and a number of other alkaloids in Britain. As will be described in the next chapter, Burroughs Wellcome produced pilocarpine salts, hyoscine, atropine, emetine, apomorphine, aconite, colchicines, cotarnum, homatropine, hydrazoline and spaline. Pre-War Burroughs Wellcome prepared several of these synthetically, at least on a small scale in order to estimate the purity of their extracts.²²²

²¹⁷ “Vivisection Vindicated” British Medical Journal (16 March 1912): 626-7.

²¹⁸ W. H. Perkin, “Drugs Unenumerated, including Medicinal Preparations” in “The Aniline and Coal Tar Colours” J. Royal Soc. of Arts (27 November 1916): 76.

²¹⁹ “War and Business” Chemist & Druggist 88.4 (29 July 1916): 798-9.

²²⁰ Prof. W. H. Perkin, “The Position of the Organic Chemical Industry” in W. M. Gardner, (1915): 408.

²²¹ S. Chapman, (1974): 96.

²²² “Malay Fine Chemicals” Chemist & Druggist 85.1 (22 August 1914): 46; D. B. Dott, “Vegetable Alkaloids; How the War has Affected Production” Chemist & Druggist

2.9 Concluding Remarks.

In the latter half of the nineteenth century Britain had come to rely on Germany for many drugs and in particular synthetic drugs. Britain exported coal tars to Germany and then imported finished dyes and as a result failed to develop its dye industry, so becoming reliant on Germany for chemical intermediates. Many of the drugs were needed urgently for the War- painkillers, anaesthetics and antiseptics plus antitoxins and vaccines. The focus of British firms was more towards extraction of oils, alkaloids, glucosides, than the preparation of synthetic chemicals. British firms were small in comparison to their German counterparts and could not compete on efficiency of production or price, and if they tried to the Germans had many cartels and pricing arrangements that it was best not to compete head to head. British firms therefore produced different alkaloids and extracts. Whereas Germany led the way on synthetic chemistry, it was in America that most novel dosing forms were invented and this brings us to an examination of how an American importer of medicines created a niche, by establishing his own firm of Burroughs Wellcome. The success of this firm and its adoption of chemical synthetic work is the subject of the next chapter.

88.4 (29 July 1916): 777; T. A. Henry, The Plant Alkaloids (London: J. and A. Churchill, 4th edition 1949): xi, 4; R. Robinson, Journal of the Chemical Society 111 (1917): 876.

CHAPTER THREE:

Burroughs Wellcome: British Origins of Collaborative Research.

3.1 Introduction.

In this chapter I examine how the first research- based British pharmaceutical firm, Burroughs Wellcome, restructured the pharmaceutical market in Britain by incorporating novel alkaloids and German synthetic drugs into American style tablets, and by taking the best of both countries' marketing techniques: the use of Trade names and scientific advertising from Germany, and the use of travelling representatives selling directly to doctors as in America. With the creation of scientific laboratories employing prominent physiologists and chemists, Burroughs Wellcome changed the relationships between industry, academia and government in Britain, and between laboratory science and medical practice. Burroughs Wellcome was the first British firm to recognise the commercial advantages of adopting scientific methods and basing new products on laboratory investigations- the aim throughout was to differentiate their products from those of other firms.¹ When the government threatened taxing them as patent medicine producers, because of their advertising and importation of medicines from America, the firm responded by producing 'ethical drugs', characterised chemically and standardised by biological testing in animals.

I will show how Burroughs Wellcome utilised synthetic chemistry on a small scale to confirm the structure of physiologically active principles isolated from plants, and how they investigated the activity of synthetic chemical derivatives to gain an understanding of the relationship of chemical structure to physiological function. This has not been previously recognised as a characteristic of the British pharmaceutical industry at the end of the nineteenth century, and it was these chemical skills that enabled the firm to eventually produce its own synthetic drugs. Even Burroughs Wellcome, the British firm with the most advanced chemistry, only rarely manufactured synthetic drugs on a commercial scale. In 1908 Francis Carr cited that production of suprarenal hormone was performed 'chemically,' while codeine and out of patent drugs such as Atoxyl and isoquinoline

¹ M. Weatherall, "Research in the Pharmaceutical Industry: 19th Century" *Pharmaceutical Journal* 242 (1989): 543-545.

derivatives of adrenaline (Suprarenin synthetic) were made in small quantities.² However, Burroughs Wellcome chose not to compete directly with German firms in producing synthetic drugs; they sold different alkaloids, incorporated German drugs into their own unique Tabloids and differentiated their products by purifying and standardising them in animal tests against pure synthetic chemical standards. In doing so they created a framework for establishing a new type of drug development in Britain.

This chapter also introduces the many individuals from Burroughs Wellcome that played a major role in the establishment of laboratories at the MRC, the Pharmaceutical Society and in other pharmaceutical firms, and helped to develop the regulatory framework for drug development in the interwar period.

The historiography of the firm of Burroughs Wellcome has previously concentrated on the firm's pharmacy origins.³ Tansey has examined the origins of physiological research in detail.⁴ Others have focused on the partners themselves, particularly Wellcome, because of his lasting legacy.⁵ The chemistry and manufacturing side has received little attention, but was equally important to the development of Burroughs Wellcome and to the rest of the British pharmaceutical industry; I therefore limit examination of the physiology laboratories to their relation to the chemical laboratories, the growth of the firm's manufacturing capacity, and their dealings with external collaborators, particularly relating to clinical trials.

Liebenau concluded that 'product development' and 'research' evolved out of early laboratories that performed assays, but he gave no examples other than serum therapies.⁶

² D. L. Howard, British & Colonial Pharmacist (August 1926): 243.

³ J. Liebenau, "The Rise of the British Pharmaceutical Industry" British Medical Journal 301 (1990): 724-728; G. MacDonald, In Pursuit of Excellence: One Hundred Years of Wellcome (London: Wellcome Foundation Ltd., 1980).

⁴ E. M. Tansey, "The Wellcome Physiological Research Laboratories 1894-1904: the Home Office, Pharmaceutical Firms and Research Experiments" Medical History 33 (1989): 1- 41.

⁵ J. R. Vane, "The Wellcome Centenary. Henry S. Wellcome, his Research Philosophy and Current Excitements" Trans. Med. Soc. London 97 (1980-1): 41-50.

⁶ J. Liebenau, Medical Science and Medical Industry: The Formation of the American Pharmaceutical Industry (Basingstoke: MacMillan, 1987): 4-10.

Here I show that the situation was more complex. I argue that the chemistry performed in Britain has previously been very much underestimated: techniques and expertise developed before the Great War explain how Burroughs Wellcome were able to rapidly produce synthetic drugs when they became unavailable from Germany.

3.2 The Establishment of Burroughs Wellcome (1880).

In order to understand the strategies adopted by Burroughs Wellcome it is essential to understand the firm's origins as an importer of American medicines. Although several authors have examined parts of the Burroughs Wellcome story there is no comprehensive overview. The following account is based mostly on primary sources at the Wellcome Foundation and shows that both Burroughs and Wellcome built upon their contacts in Philadelphia, London and Cambridge to establish their firm. Silas Mainville Burroughs (1846-1895) had worked in pharmacies in Lockport and Buffalo in America before graduating from the Philadelphia College of Pharmacy in 1877. He had an early interest in tablets and his thesis was on "The Compression of Medicinal Powders".⁷ He first came to Britain in 1878 to establish a London office for the Philadelphia pharmacy-based ethical manufacturing firm of John Wyeth & Co.⁸ Burroughs initially intended to only spend 6-12 months in England, but seeing an opportunity to sell novel tablets, he set up his own business from April 1878 in Great Russell Street, London, as sole importing agent on behalf of Wyeth.⁹ The novelty of their drugs was emphasised in Wyeth's British advertisements: "Purity, activity and beauty. Elegant pharmaceutical preparations, compressed powders or pills and medicinal fluid extracts".¹⁰

⁷ J. W. England (ed.), The First Century of the Philadelphia College of Pharmacy 1821 - 1921 (Philadelphia: College of Pharmacy and Science, 1922): 494; He also successfully applied for a patent, number 20269 for 'Compressed Peptonic Tablets', dated 8 September 1879: "Trade Marks." WF: 85/16.

⁸ G. MacDonald, (1980): 5-7, 19-21; "Obituary of Silas Burroughs" Chemist & Druggist 47 (9 & 16 February 1895): 213-214, 254-258.

⁹ Miss Hunt, "A Recollection of Early Days at Burroughs Wellcome 1880-7" WF: 86/98:19. "A Century of Wyeth Products in the UK" Slough, Eton Chronicle and Windsor Observer (1 December 1978) in WF: Box 38J.

¹⁰ J. Wyeth to Burroughs Wellcome, (31 October 1887): Correspondence between Burroughs Wellcome and John Wyeth WF: 88/47:8. Burroughs advertised Wyeth products on his first price list, (28 May 1878), WF: Box 112.

Burroughs' business expanded rapidly, partly because of his personal dynamism and sales flair, partly because of the novel products he was selling. In 1879 he purchased the rights to Kepler's malt extract business, took on Robert Clay Sudlow, and in May he moved the business headquarters of the firm to Snow Hill, near Holborn viaduct in central London.¹¹ In 1880 Burroughs began to import the sugarcoated pills of Lanman and Kemp, a firm based in New York since 1858.¹² To consolidate this expansion, Burroughs offered a partnership to Henry Wellcome, who had also graduated from the Philadelphia College of Pharmacy in 1874.¹³ Wellcome had been a pharmacist with Poole & Geisinger from 1866 to 1870 in Rochester, then in Chicago before joining the New York firm of Caswell, Hazard & Co. as a sales representative. From 1876 he had travelled extensively in South America for another New York firm, McKesson & Robbins whose business in capsuled pills he brought to England with him as the sole importing agent.¹⁴ In the *Lancet* on 31 March 1880, Burroughs produced a 27-page advert of their wide range of products.¹⁵

Burroughs Wellcome Co. was founded on 25 September 1880.¹⁶ In October 1880 the firm expanded into the adjacent site, which they used as a warehouse and Sudlow

¹¹ This remained the headquarters until burnt down following bomb damage in the Second World War. G. MacDonald, (1980): 24-30.

¹² H. Wellcome to S. Burroughs, Letterbooks 1881 - 20 May 1897, (27 July 1883), WF: S/G/148-2: 76; Lanman & Kemp dated from 1858: H. W. Holcombe, Patent Medicine Tax Stamps: a History of the Firms Using United States Private Die Proprietary Medicine Tax Stamps (Lawrence, Mass: Quartermann, 1979): 8-16, 321-3.

¹³ C. M. Wenyon, "Henry Wellcome" Obituary Notices of Fellows of the Royal Society 2 (1938): 229-238; A. R. Hall, B. A. Bembridge, Physic and Philanthropy: a History of the Wellcome Trust 1936-1986 (Cambridge: Cambridge University Press, 1986): 3; H. Turner, Henry Wellcome, the Man, his Collection and his Legacy (1980): 5-8; Sir Henry Dale, "Obituary of Henry Wellcome (1853-1936)" The Times (1 August 1936); James R. Rhodes, Henry Wellcome (London: Hodder & Stoughton, 1994).

¹⁴ H. Turner, (1980): 5-7; Articles of Agreement, WF 88/47:8; H. J. Parish, The Wellcome Research Laboratories and Immunisation: The History of Inoculation and Vaccination (London: Burroughs Wellcome, 1913): 1, WF: 85/17.

¹⁵ Letterbooks 1881-1897, H. Wellcome to S. Burroughs, (30 March 1883), WF: S/G/148-2: 110-12; *Lancet* advertisement, WF: 85/20:2.

¹⁶ Articles of Agreement, WF 88/47:8; G. MacDonald, (1980): 5.

became General Manager.¹⁷ By 1881 Burroughs Wellcome imported drugs for several firms.¹⁸ However, tensions developed between Burroughs Wellcome and Wyeth, because of the expanding collaborations with other firms, issues about quality and pricing, and Burroughs' exploitation of the novelty of Wyeth's products by registering the trademarks of their ethical drugs under his own name.¹⁹ John Wyeth felt Burroughs "always had what we might style patent medicine impulses." As a travelling representative for Wyeth in America, although "active and energetic" he had often "caused more trouble than all the other travellers put together, by making too hasty arrangements with customers, often prejudicing the firm's interests by making statements not possible to fulfil".²⁰ Wyeth claimed that Burroughs took too much profit in Britain and failed to reach sales targets despite spending too much on advertising, though as a counter-argument Burroughs complained that the royalty levied by Wyeth added to his prices. John Wyeth felt that they should obtain premium prices by emphasising the ethical nature of his products:

"There is no possible similarity" with patent medicines, he stressed: "[We] gave you standard preparations, [including] our compressed pills... [which]...no one else can manufacture, a trade [which] once established cannot be taken from you; compared with proprietary medicines, which require continued advertising".²¹

Wyeth argued that their ethical values were compromised when Burroughs sold sub-standard versions of Wyeth's 'Beef, Wine and Iron'.²² On the other hand Wyeth prepared some drugs to the standards of the American rather than the British Pharmacopoeia, "due

¹⁷ G. Pearson, A Chronology of the History of Burroughs Wellcome & Co. 1878-1936 (typescript, 1936), WF: 88/24:41d: 1; "Origins of the Chemical Works" volume I, WF: 89/57:8; Miss Hunt, "A Recollection of Early Days at Burroughs Wellcome 1880-7", WF: 86/98:19; Articles of Agreement, WF: 88/47:1.

¹⁸ H. Wellcome to S. Burroughs, (27 July 1883), WF: S/G/148-2.

¹⁹ After Wellcomes' arrival he added the 'Tally Ho' range of perfumes, and McKesson and Robbins capsuled pills: "Trade Marks 1879-86", WF: 85/16.

²⁰ J. Wyeth to Burroughs Wellcome, (28 June 1881), WF: 88/47:8.

²¹ J. Wyeth to Burroughs Wellcome, (28 June 1881), WF: 88/47:8.

²² For a full account of the relationship between Burroughs Wellcome and Wyeth see Fairchild Brothers and Foster to Burroughs, (5 November 1895), WF: 88/47:8.

to our ignorance that the British had a standard”.²³ This led Burroughs Wellcome to appoint A. Searl from Howard’s and Sons, as the works manager with the responsibility for maintaining standards, and so defining their commitment to the ethical approach.²⁴ In the period between October 1881 and February 1884, Burroughs was away almost continually, establishing the business throughout the Empire.²⁵

Meanwhile, Henry Wellcome took over the daily running of the British business and adopted the Wyeth ethical strategies and marketing techniques.²⁶ Products were advertised only in the medical press as “Medicinal Formulae of new and improved chemical and pharmaceutical preparations,” being of high quality, and were presented using the latest Wyeth tableting and packaging techniques.²⁷ Henry Wellcome absolutely refused to advertise in newspapers like the patent medicine manufacturers, as he believed this created prejudices, which the medical profession had to such a course.²⁸ Wellcome introduced American-style travelling representatives in 1881, selling only to pharmacists and doctors.²⁹ He also adopted the policy of sending out around 200,000 American style circulars and

²³ J. Wyeth to Burroughs Wellcome, (28 June 1881), WF: 88/47.

²⁴ Letters to G. E. Pearson, WF: E2 PF Box 23.

²⁵ Burroughs travels are documented, S. Burroughs to H. Wellcome, (30 March 1883): 110, 114, Letterbooks 1881- 20 May 1887, WF: S/G/148-2; Burroughs Wellcome to J. Wyeth, (22 August 1882), WF: 87/33 (1882-3); and Letters to Pearson, WF: E2; G. MacDonald, (1980): 23.

²⁶ Radford & Frankland to H. Wellcome (7 January 1885), WF: E2 PF; H. Wellcome to S. Burroughs, (25 August 1882), Letterbooks 1881-1897, WF: S/G/148-2.

²⁷ G. Pearson, (1936): 2.

²⁸ A. W. Haggis, Typescript History of the Works: 5- 6.

²⁹ H. Wellcome to S. Burroughs, (9 July 1885): 381, Letterbooks 1881-1897, WF: S/G/148-2; For an account of an American style detailman see P. Temin, Taking Your Medicine: Drug Regulation in the United States (Cambridge, Mass: Harvard University Press, 1980): 84 ff.; J. Liebenau, “Marketing High Technology: Educating Physicians to use High Technology Medicines” in R. P. T. Davenport- Hines (ed.), History, Bagmen and Markets: Studies in the History of Marketing and British Industry (Aldershot: Gower, 1986): 82-101; J. Liebenau (ed.), The Challenge of New Technology. Innovation in British Business Since 1850 (Aldershot: Gower, 1988).

15,000 samples of their proprietary beef juice to doctors.³⁰ Doctors were provided with reminders of the firm and its products in the form of medical diaries, pocket pens, pencil cases and paper knives bearing the company logo and drug names. Pamphlets were sent from head office and advertisements were placed in the medical press.³¹ Further advertising to doctors took place at meetings of the British Medical Association or the Pharmaceutical Society and Burroughs Wellcome received independent prizes awarded for novel drugs and standards of excellence.³² Burroughs Wellcome had a stand at the International Medical and Sanitary Exhibition in London in the summer of 1881.³³ In the following years Wellcome extended these influences significantly, inviting editors of scientific journals and influential physicians to elaborate social events.³⁴ Some of these such as J. Fletcher Moulton, initially a distinguished mathematician and brilliant lawyer and later Lord Chief Justice, then first chairman of the MRC were important in supporting Burroughs Wellcome.³⁵

Previously I have described the two forms of marketing - patent medicines advertised directly to the public and ethical medicines advertised to doctors. Since the eighteenth century doctors and editors of medical journals had campaigned against patent

³⁰ Burroughs Wellcome to J. Wyeth, (22 August 1882) and (1 February 1893), WF: 88/47:8.

³¹ G. MacDonald, (1980): 11, 23; Wellcome Chemists Diary 1906, WF 90/19; H. J. Parish, "History of the Firm" chapters 5- 6, WF: 85/20:2:105.

³² H. Wellcome to S. Burroughs, (8 April 1884): 303, WF: S/G/148-2; These were advertised in two Burroughs Wellcome handouts American and European Newsletter (1896): 161-162, Chronicle and District Times (24 April 1894).

³³ Exhibitors certificates, WF: 130: 973/1-12.

³⁴ G. Pearson (1936) WF: 88/ 24: 41d: 4-8; G. MacDonald, (1980): 11; H. Turner, (1980): 8-10; H. J. Parish, History of the Firm: 5- 6, WF: 85/20:2: 105; H. M. Stanley was a guest speaker visited on 21 April 1884 with Dr. Manson. Chronicle and District Times (24 April 1884). He also visited on 14 July 1900; H. M. Stanley, British Medical Journal (12 January 1890): 325-7; A dinner for Power was held in July 1886, WF: YL Box 18BB/86; "Dr. Frederick B. Power" Chemist & Druggist 49 (25 July 1896); Letterbooks, Wellcome to Burroughs (9 July 1885): 381, WF: S/G/148-2; A large commemoration for Balfour took place on 8 December, 1902, WF: 90:14:2; R. C. Sudlow's retirement dinner was on 14 September 1903, WF: 90/14:3 Box 158.

³⁵ Wellcome often consulted J. Fletcher Moulton. "Lord Moulton of Bank, Obituary" British Medical Journal (19 March 1921) (1): 433; F. B. Power Files, WF 88/94:79a.

medicines and the unsubstantiated yet extensive claims made on their behalf, but the Government had done little to regulate sales except for imposing taxes.³⁶ There were concerns about lack of beneficial effect and the possibility of adverse effects. The increasing flow of foreign patent medicines into Britain, especially from America, led the Government to try to restrict imports with the passage of the Revenue Stamp and Infringement of Trade Marks Act of September 1882, which imposed stamp duty of 12-15% of the retail prices on imported patent medicines.³⁷ Though this tax was not aimed at ethical drugs, the boundaries between ethical and patent medicines were somewhat confused. Burroughs' extensive advertising, and in particular the American origin of their medicines caused the Government to initially class Burroughs Wellcome as a patent medicine vendor despite their plea that they sold only 'known' drugs; Wellcome remarked that "The Government solicitor prosecuted and fined us for selling foreign medicines unstamped" and "our enemies [are] campaigning against us".³⁸ If imposed upon them, the tax would have affected Burroughs Wellcome in three ways: in the first place, they would have had to pay duty as well as the large royalty already paid to Wyeth making them unprofitable.³⁹ Secondly, they would have been obliged to stamp their products as patent medicines, and lose the advantage of marketing them as 'ethical' drugs. Thirdly the Act would also have required them to destroy many of their existing labels and circulars.⁴⁰ The proposed stamp duty came at a particularly difficult time for the company; they had already overextended

³⁶ R. Porter, Quacks, Fakers & Charlatans in English Medicine (Tempus: Stroud, 2001).

³⁷ William Wyatt, "The Acts of Parliament Relating to Stamped Medicines" Chemist and Druggist 106.1 (12 February 1927): 201; Wellcome fought against the Revenue Stamp and Infringement of Trade Marks Act of September 1882: Burroughs Wellcome to John Wyeth, (22 August 1882), WF: 88/47:8; Wellcome to Burroughs, (6 September 1882), (4 December 1883) and (14 December 1883), Letterbooks 1881-7, WF: S/G/148-2.

³⁸ H. Wellcome to S. Burroughs, (6 September 1882), Letterbooks 1881-7, WF: S/G/148-2.

³⁹ Burroughs Wellcome paid 15% on initial sales and 20% on the majority. In return Burroughs claimed travel expenses, postage, rent, advertising and salaries: Burroughs Wellcome to J. Wyeth, (15 August 1887), WF: 88/47:8.

⁴⁰ H. Wellcome to S. Burroughs, (14 December 1883), Letterbooks 1881-7, WF: S/G/148-2.

themselves by establishing the business in France and Spain; the profits for the last quarter were only £600 against the previous £1,800.⁴¹

As a result Wellcome had to delay payment of an outstanding bill of \$5,000 to J. Wyeth and he cautioned Burroughs: “I hope you will not arrange any business matters in America that will draw upon us for funds during the coming year”.⁴² Burroughs Wellcome also faced growing competition for the ethical market, including the initiation of tablet manufacture by other British and foreign firms.⁴³ Wellcome wrote to Burroughs: “our competitors have never been so aggressive in pushing business, especially in Extract of Malt; Allen & Hanbury’s, Savory & Moore and others [were] striking out very boldly”.⁴⁴ Secondly, Burroughs Wellcome had to challenge a number of infringements of their own trademarks.⁴⁵ In order to meet the crisis they had to extend their existing loans and decrease advertising.⁴⁶

The only way that Burroughs Wellcome could convince the Government that all of their medicines were ethical and not patent medicines, was to begin manufacture of the Wyeth drugs in Britain and to emphasise their standards. After several fines had been imposed on them, Wellcome suggested the purchase of Wyeth trade names, the details of

⁴¹ H. Wellcome to S. Burroughs, (30 March 1883), (15 October 1883) and (19 October 1883), Letterbooks 1881-7, WF: S/G/148-2.

⁴² H. Wellcome to S. Burroughs, (26 October 1883) and (5 November 1883), Letterbooks 1881-7, WF: S/G/148-2.

⁴³ H. Wellcome to S. Burroughs, (6 September 1882), Letterbooks 1881-7, WF: S/G/148-2; Burroughs Wellcome to John Wyeth, (27 September 1882), WF: 88/47:8.

⁴⁴ H. Wellcome to S. Burroughs, (6 September 1882), WF: S/G/148-2: 27; (27 January 1883), WF: 86/98.

⁴⁵ Lundberg preparations and their 'Hazeline' brand were copied by a firm called Haseline (sic.). The Manchester firm of Thomas Kerfoot used the same tableting machinery and packaging as Wyeth to prepare their 'Pure chlorate of potash pearls', and a German firm began exporting compressed tablets at half of the Burroughs Wellcome price: Wellcome to Burroughs, (6, 27 September 1882 and 30 March 1883), WF: S/G/148-2; Burroughs Wellcome to J. Wyeth, (27 July 1883), WF: 88/47:8. German firms were even accused of spying and impersonating Burroughs Wellcome representatives in what became known as the Graves case, WF: E2; J. Wyeth to Burroughs Wellcome, (14 September 1882), WF: 88/47:8.

⁴⁶ H. Wellcome to S. Burroughs, (22 and 26 October 1882), WF: S/G/148-2.

their drug constitutions and their tableting machinery.⁴⁷ Wyeth agreed only to lend rather than sell some of their tableting machines to Burroughs Wellcome, subject to a 20% royalty on the sale of Wyeth drugs, and payment of the transport costs.⁴⁸ Nevertheless, the Government agreed to suspend stamping of imported Wyeth products, conditional upon manufacturing starting in Britain. “It was a narrow escape for the young firm,” Henry Wellcome explained to Burroughs: “had they [the Government] rigidly enforced the law our penalties would have been something enormous, to say nothing of the great inconvenience and loss incurred.” The crisis over, Wellcome commented: “we may thank our lucky stars we got off so easy”.⁴⁹

Burroughs suggested the company should buy the rights to further Wyeth lines. Wellcome was not so keen as he felt a better option was to seek independence from Wyeth. As the main novelty of Wyeth’s drugs lay in their presentation as tablets, he realised they could prepare the same drugs from cheaper raw materials purchased in Britain, and hence avoid paying royalties to Wyeth; tea to produce quercital, for example, was half the price in London.⁵⁰ Wellcome therefore crucially persuaded Burroughs to begin manufacturing and he informed Burroughs in September 1882 that: “erection of machinery proceeds rapidly”.⁵¹ Three tableting machines were purchased from Wyeth, who suggested it would take three months to install them.⁵² Although Wellcome regretted separating the office

⁴⁷ Burroughs Wellcome to J. Wyeth, (22 August 1882) and J. Wyeth to Burroughs Wellcome, (14 September 1882), WF: 88/47:8. Burroughs Wellcome were fined for selling unstamped Hazeline and were asked to remove 'Burroughs' from the labels: Wellcome to Burroughs, (24 November, 4 December 1883), WF: S/G/148-2: 200- 24.

⁴⁸ Letterbooks 1881-1897, (27 July 1883), WF: S/G/148-2.

⁴⁹ H. Wellcome to S. Burroughs, (4 December 1883), WF: S/G/148-2: 224.

⁵⁰ Other drugs were on average 20% more expensive in Philadelphia. Burroughs Wellcome to J. Wyeth, (27 September 1882), WF: 88/47:8; H. Wellcome to S. Burroughs, (27 July 1883), WF: S/G/148-2; John Henry Evans, (SCI) analytical chemist to Burroughs Wellcome re. Tea supplies – quercitannic acid: Costs- memo to Jowett re. Tabloid manufacture, (2 March 1895), WF: 89/ 29:2.

⁵¹ H. Wellcome to S. Burroughs, (19 September 1882), WF: S/G/148-2: 23-34.

⁵² H. Wellcome to S. Burroughs, (6 September 1882), WF: S/G/148-2: 23-34; J. Wyeth to Burroughs Wellcome, (14 September 1882), WF: 88/47:8.

and works, a much-expanded manufacturing site in a clean country atmosphere was chosen at Bell House Wharf, Wandsworth in 1883.⁵³

The financial situation remained precarious as Wellcome spent more on equipping it than he originally estimated.⁵⁴ Furthermore, he had been unable to sell the original Snow Hill premises.⁵⁵ Wellcome travelled to America in March 1883 to negotiate the purchase of further equipment from Wyeth for the new factory and in April the first pill machines were provided.⁵⁶ However during 1883 the tension between Burroughs Wellcome and Wyeth grew to animosity. After his visit to America, Wellcome described how the two companies were “getting further apart”. He found the Wyeth people “gushing and kind” and “full of soft soaps” when he was with them but still greedy, with “every disposition to bleed us,” and he condemned the “haughty and overbearing spirit with which [Wyeth] have dealt with us”.⁵⁷

Wellcome realised that German alkaloids and synthetic drugs offered additional advantages over the Wyeth drugs, as they were chemicals with a well understood mechanism of action, which could be sold to doctors with a scientific message as ‘ethical drugs’ Furthermore, Burroughs Wellcome could combine German scientific advances into their American-style tablets. He suggested that Burroughs Wellcome make a one-off payment to secure the permanent rights to all Wyeth lines in which they currently dealt.

⁵³ The lease ran from 9 February 1883 until 29 September 1889 though the firm stayed until the end of 1889 because of a fire just before the end of the lease. G. Pearson, (1936) WF: 88/24:41d: 2; H. Wellcome to S. Burroughs, (27 July 1883), WF: S/G/148-2; H. J. Parish unpublished memoirs, WF: 85/17.

⁵⁴ Wellcome supervised the choice of site and the movement of the works to Bell Lane, Wandsworth on 9 February 1883: H. Wellcome to S. Burroughs, (27 July 1883), WF: S/G/148-2; G. Pearson, (1936), WF: 88/24:41d: 2.

⁵⁵ H. Wellcome to S. Burroughs, (12 June 1883 and 27 August 1883), WF: S/G/148-2.

⁵⁶ Two pill machines, a lathe and portable furnace were to be sent to Burroughs Wellcome during April, J. Wyeth to Burroughs Wellcome, (10 April 1883), WF: 84/7:8.

⁵⁷ Wellcome to Burroughs, (13 March 1883, 27 July 1883), WF: S/G/148-2.

Wyeth demanded £50,000 for this privilege and, when agreement could not be reached, they asked for the return of their tableting machines.⁵⁸

In response, Burroughs Wellcome decided to build their own tableting machines, taking advantage, as German firms had recently done, of the fact that Wyeth had not patented their advanced designs in Europe. In order to create their own tablet-manufacturing facility, specialised engineering staff had to be brought into Burroughs Wellcome, principally from German firms. One of the fitters described how he was “the only English chap among the engineers; there were two Germans and they used German machines, lathes etc.”⁵⁹ Wellcome even arranged for the works to be run by a German, Dr. Witte: “a man in whom I have full confidence regarding management”. Witte was sent to visit the Wyeth site to evaluate their methods. After three tableting machines were installed at the Wandsworth site, Burroughs Wellcome produced their own tablets, but still relied on Wyeth for their main bulk drug supplies.⁶⁰ However they resisted preparing too many ‘specials’ at the request of physicians and began to concentrate on large-scale production of a smaller number of lines.⁶¹

Wyeth continued to criticise Burroughs expenses as excessive.⁶² Nevertheless during the first 3 years of business, sales grew from £17,811 in 1881 to £57,156 in 1883.⁶³ By 1884, £10,000 had been invested in the continental business.⁶⁴ Burroughs meanwhile

⁵⁸ An account of the relationship with Wyeth appears in Burroughs to Horton (an agent of Wyeth), (12 July 1893), WF: 88/47:8; J. Wyeth to Burroughs Wellcome, (19 April 1893), WF: 88/47:8. At the same time they ended their five year arrangement with Fellows & Co., Letterbooks, (6 September 1882), WF: S/G/148-2: 227.

⁵⁹ Mr. C. Bargate to H. A. D. Jowett, “History of the Works”, (26 November 1930), WF: YL Box 15; WF 84/7.

⁶⁰ Dr Witte joined in summer 1882 and was placed in charge of developing the Wandsworth site in 1883, Letterbooks, (27 July 1883), WF: S/G/148-2: 98.

⁶¹ Letterbooks, H. Wellcome to S. Burroughs, (26 October 1883), S/G/148-2.

⁶² J. Wyeth to Burroughs Wellcome, (28 June 1881), WF: 88/47.

⁶³ Radford & Frankland to H. Wellcome, (7 January 1885), WF: 88/47(E2).

⁶⁴ H. Wellcome to S. Burroughs, (4 December 1883), WF: S/G/148-2: 218.

became increasingly critical of Wellcome towards the end of 1883.⁶⁵ Wellcome, in turn was aggrieved that initial promises of an equal partnership had been unfulfilled and that Burroughs made major decisions without him. Wellcome criticised his “hasty flashes of judgment” and “impulsive and all too hasty disposition”.⁶⁶ The rift simmered then settled temporarily while a new partnership agreement was drawn up.⁶⁷

The new chemical works at Wandsworth, including Burroughs Wellcome’s own tableting machinery, formally opened on 6 October 1884, establishing the company for the first time with its own large-scale manufacturing capacity. In addition to the old Wyeth lines, the Works produced other firms licensed products and various inorganic preparations, enabling Burroughs Wellcome to establish their own identity, distinct from Wyeth, in the British marketplace.⁶⁸

Central to their strategy was the adoption of the trade- mark ‘Tabloid’ proposed by Wellcome for their special tablets registered first in Britain in March 1884 and then in various overseas countries.⁶⁹ ‘Tabloid’ was initially derived from a contraction of the terms tablet and alkaloid but it was also a strong ‘Brand’ representing a quality product, easily recognised as being only from Burroughs Wellcome. The idea probably came from the increasing use of German trade names, which were short and easily remembered and replaced complex chemical names. Burroughs Wellcome adopted ‘Tabloid’ having earlier sought to monopolise the term ‘tablet’ until challenged by an American firm.⁷⁰ They wrote

⁶⁵ Burroughs criticised the time spent by Wellcome in literary circles, and the failure of the McKesson part of the business, suggesting all that Wellcome brought to the firm was “useless paper and £40”: S. Burroughs to H. Wellcome, (8 March 1888), WF: S/G/148-2; Wellcome expressed his “chagrin” as early as August 1882 when Burroughs suggested delaying the full partnership until four years later. H. Wellcome to S. Burroughs, (25 August 1882) and (6 September 1882), Letterbooks 1881-87, WF: S/G/148-2.

⁶⁶ H. Wellcome to S. Burroughs, (6 September 1882), WF: S/G/148-2: 23

⁶⁷ H. Wellcome to F. B. Power, (9 April 1884), WF: 86/98.

⁶⁸ H. Wellcome to S. Burroughs, (6 February 1884), WF: S/G/148-2.

⁶⁹ Tabloid was registered by Henry Wellcome as a trademark in Britain on 14th March 1884 and in various other countries by 1885: “Trade Marks, 1879-86”, WF: 85/16; H. Wellcome to S. Burroughs, (26 October 1883), WF: S/G/148-2: 164.

⁷⁰ “Tabloids and Tablets” Chemist & Druggist 40 (28 May 1892): 785; “Tabloids and Tablets” Chemist & Druggist 40 (4 June 1892): 817; Burroughs Wellcome, “Tablets and

to the *Chemist & Druggist*, “the word ‘Tablets’ was applied by us to this class of (compressed) drugs at the commencement of our business in 1878. This form of medication had hitherto been known in this country as compressed pills”.⁷¹ ‘Tabloids’, however were further distinguished by emphasising that the tablets contained standardised doses of purified active drug, measured with great accuracy.⁷² This became the central defining concept of Burroughs Wellcome drugs, emphasising that there was greater activity and less variability than other firms’ preparations. Tabloids were promoted in this manner at the annual British Medical Association meeting with “great sales as a result”.⁷³ By the end of 1884 Henry Wellcome reported: “Our business is prospering handsomely and the outlook more encouraging than ever”.⁷⁴ Burroughs Wellcome continued to license in new products; in 1885 acted as agents for Fairchild’s Digestive Ferments.⁷⁵

The new partnership between Burroughs and Wellcome was finally agreed on 29 May 1885.⁷⁶ But the rift between them soon widened again, and in July 1886 Burroughs sued for breach of partnership.⁷⁷ He claimed that Wellcome had not diligently applied himself,

Tabloids” *Chemist & Druggist* 40 (11 June 1892): 849; Burroughs Wellcome, “What is a Tablet” *Chemist & Druggist* 40 (11 June 1892): 881; Armour & Co. “Tablets” *Chemist & Druggist* 40 (25 June 1892): 913; “Evolution and Present Status: Composition of Tablets and Methods of Analysis” *Journal of the American Pharmaceutical Association* 3 (1914): 820-848, 937-958, 1062-99; A. W. Haggis, History of the Firm: 5- 6; WF: 85/20:2: 278-279.

⁷¹ F. N. L. Poynter, *Evolution of Pharmacy* (London: Pitman, 1965): 137.

⁷² Doses of 1/1,000 to 60 grains were prepared: G. MacDonald, (1980): 23.

⁷³ Wellcome to Burroughs, (9 July 1885), WF: S/G/148-2.

⁷⁴ Wellcome to Burroughs, (1 December 1884), WF: S/G/148-2.

⁷⁵ Wellcome to Fairchild’s, (16 June 1885), WF: E2. By the end of October 1885 the firm held a balance of £3,300, Letterbooks, (26 October 1885), WF: S/G/148-2.

⁷⁶ Radford & Frankland (solicitors) to Wellcome, (7 January 1885), WF E2.

⁷⁷ For a full account of events leading up to the end of the partnership see Burroughs to Fairchild Brothers & Foster, New York, (11 April 1891), WF E2; Burroughs Wellcome to J. Wyeth, (26 June 1888), WF: 88/47.

that he had unpaid debts and that he had withdrawn excess profits.⁷⁸ In contrast, all of the evidence points to extensive day-to-day involvement of Wellcome in managing and reorganising the business, while Burroughs played out an equally important, but quite different role in opening up new overseas markets and licensing new products.⁷⁹

Burroughs was “the most widely known personality in the ranks of pharmacy,” and “well known throughout the world”.⁸⁰ Wellcome retorted that the firm had been an “entangled snarl” when he took over operations, which “if it had been left would have been ruined”. He indignantly told Burroughs “you no longer know the business”.⁸¹ Wellcome echoed Wyeth who had also complained of Burroughs’ “want of a system”.⁸² Nevertheless, Wellcome himself had been absent from work for much of 1885-6, but only because he had almost died while heroically saving a lady from drowning.⁸³

In 1886 Wellcome wrote: “Business is in the most wretchedly depressed state throughout Europe and the Colonies, we are holding our own, simplified by giving up the McKesson Robbins pills, the long list of which has been something of an encumbrance”.⁸⁴ This was the first significant step to curtailing the product range. By now the Tabloid range was successful and Burroughs Wellcome extended their trade name strategy to include other novel dosage forms such as ‘Valoids’ (valeriates or creams), ‘Piloids’ as small round pills in 1886, ‘Ovoids’, an easy to swallow shape and ‘Elixoids’, which were palatable

⁷⁸ In the quarter up to July 1885 the trade balance was £1,456 when it should have been £3,000 but this was due to a depression in trade. Wellcome to Burroughs, (9 July 1885), WF: S/G/148-2.

⁷⁹ An overseas office was established in Sydney in 1886 and others followed. West Kent Advertiser (21 March 1924), WF: Box 25.

⁸⁰ Chemist & Druggist 46 “Silas Burroughs Obituary” (9 February 1895): 213; (18 May 1895): 675.

⁸¹ H. Wellcome to S. Burroughs, (25 August 1882), Letterbooks 1881-1887, WF: S/G/148-2.

⁸² J. Wyeth to H. Wellcome, (28 June 1881): 213, WF: 88/47:8.

⁸³ He was awarded a medal from the Royal Humane Society, Letterbooks, Burroughs to Wellcome, (27 July 1886), Letterbooks 1881-1887, WF: S/G/148-2; G. MacDonald, (1980): 17.

⁸⁴ H. Wellcome to J. Wyeth, (8 January 1886), Letterbooks 1881-1887, WF: S/G/148-2: 438.

forms of nauseous drugs such as potassium iodide.⁸⁵ They also incorporated the latest fashionable trends for cod liver oil and malt preparations, and ‘Saxin’ atomisers for antiseptics, inhalers for ammonium chloride, and even produced artificial ear -drums. Rarely a month went by without the introduction of a new line, branded as part of the Burroughs Wellcome range.⁸⁶ Nevertheless, their main US competitor, Parke Davis “made such inroads into our business we decided to undercut” and Wellcome described a “very active fight with other makers of compressed drugs, Merck, Warner and other American, German and English firms who employ steam power, and we think, some American machines”.⁸⁷ Merck had a monopoly in the production of certain alkaloids based upon supplies of raw materials of certain plants.

By 1880 Parke Davis of Philadelphia was probably the most sophisticated American manufacturer of tablets, having overtaken Wyeth. Success in business was determined by differentiation against other firm’s products. While producing better tablets was one possibility, Parke Davis identified a new method by introducing a laboratory in 1879 as a major commitment to purity and standards. Unlike German laboratories, which focussed on new products, the Parke Davis approach was to produce pure standardised drugs from complex extracts. In 1880 they hired the chemist Albert Lyons who devised a method to standardise ergot, an alkaloid-containing product of a fungus that grew on rye. For centuries ergot extracts were known to prevent bleeding after childbirth, but the downside was that contaminated rye when eaten could also cause epidemics of gangrene and convulsions, so it was important to know the potency.⁸⁸ By 1883 Parke Davis had assigned pharmacological activity to a particular component within ergot and began to

⁸⁵ “Trade Marks, 1879-86” WF: 85/16. It was followed by registration of ‘Valoids’ in 1884, ‘Elixoids’ in 1884, ‘Piloids’ in 1886, Soloids (antiseptic solutions) and ‘Ovoids’: Wellcome to Burroughs, (26 October 1883): 164, WF: S/G/148-2.

⁸⁶ Cuttings from adverts. *Chemist & Druggist* 36 (28 January 1888); G. MacDonald (1980): 12, 25; “Successful Pharmacy” (1882) “Progress in Pharmacy” (1888): cuttings – page numbers unknown in WF: 89/29b: 7.

⁸⁷ H. Wellcome to J. Wyeth, (8 January 1886 and 18 May 1886), WF: 88/47:8.

⁸⁸ C. De Costa, “St. Anthony’s Fire and Living Ligatures: a Short History of Ergometrine” *Lancet* (18 May 2002): 1768-70.

standardise their products.⁸⁹ From 1886 the successful policy of incorporating highly active standardised preparations in their tablets was extended to other drugs.

In order to remain competitive Burroughs Wellcome had to extricate themselves from the arrangements with Wyeth and they finally achieved this on 5 November 1888.⁹⁰ By this time Burroughs Wellcome had perfected their tableting and could make all of the original Wyeth lines, as well as some tablets that Wyeth could only prepare on hand-machines. Henry Wellcome declared that their newly- patented tableting machines produced “better finished goods than Wyeth, more accurately, at 400 to 500 per minute, with the capacity to rise to 600 per minute”.⁹¹ This level of efficiency was important as other companies entered the market, forcing prices down.

In summary, Burroughs Wellcome developed a diverse product range, and led the British industry in tableting technology. Furthermore they had adopted patenting of machinery and the use of German-like trade names. Burroughs Wellcome licensed novel synthetic chemical drugs from German firms and incorporated them into their own unique Tabloid form. Examples were Diuretin (theobromine) from Knoll, Phenacetin and Sulphonal from Bayer, and Antipyrin (Hoechst), Lanolin was also imported from Germany; to make the ointment bases that did not go rancid.⁹² Burroughs Wellcome was at last creating a niche market within the growing pharmaceutical industry: though they still did not manufacture chemicals on a large scale, as in Germany, they did incorporate

⁸⁹ Parke Davis at 100: Progress in the Past, Promise in the Future 1866 – 1966; Milton L. Hoefle, “The Early History of Parke-Davis and Company” Bull. Hist. Chem. 25.1 (2000): 28-34: by 1883 the firm was assaying over 20 biological drugs. John P. Swann, Academic Scientists and the Pharmaceutical Industry: Cooperative Research in Twentieth Century America (Baltimore: Johns Hopkins Press, 1988): 20-21.

⁹⁰ Legal negotiations continued until June 1885: Fairchild Bros. and Foster (solicitors) to Silas Burroughs, (5 November 1888), WF: 88/47:8. Burroughs agreed to sell some Wyeth lines through a new agent, William F. Horton: Burroughs Wellcome to Fairchild Bros. & Foster (New York), (11 April 1895), WF: 88/47:8. Wyeth arranged to sell their remaining lines in Britain through Roberts & Co. Burroughs Wellcome to J. Wyeth, (1 February 1893), WF: 88/47:8.

⁹¹ H. Wellcome to J. Wyeth, (5 November 1885), WF: 88/47:8.

⁹² Lanolin was imported from Benro Jaffe and Därmstaedter from July 1886, WF: 86/98/16; Ichthyol from Cordes Hermanii & Co. from 1888, G. Pearson, (1936) WF: 88/24:41d: 3; Instructions/ Memo’s re Dartford Works 1893-1950, WF: 89/29:1.

manufactured chemicals into their tablets. Burroughs Wellcome was still small by German standards even though their staff increased six-fold in the 7 years up to 1891.⁹³

In summary, by this time Burroughs Wellcome had their own independent supplies of drugs and their own manufacturing facilities in which they prepared tablets with defined dosage strength medicines and also incorporated the latest medical advances, selling their products under the ‘Tabloid’ name, which signified quality and reliability.

However their success with Tabloids encouraged the opening of further new works in Dartford on 3 July 1889 on the site of the former Phoenix paper mills.⁹⁴ During the period 1889 to 1893 the firm established their first contracts with British dye manufacturers such as Clayton, Read Holliday and Levinstein’s for the purchase of nitrites, toluidine, benzol, phenol, nitric acid, naphthol, aniline and other fine chemicals to be used as solvents and as intermediates for simple chemical reactions.⁹⁵ As manufacturing output expanded, and drug production became more efficient, drug prices were sometimes lowered, but Burroughs Wellcome Tabloids commanded higher prices than other less sophisticated tablets.

The techniques that Burroughs Wellcome used to develop new formulations were increasingly innovative. In 1891 they introduced sugar coated Cascara tablets as purgatives and in 1892 they licensed a process for making tabloids of tea.⁹⁶ In the same year they introduced concentric coated tablets with a peptonic inner kernel surrounded by pepsin, and film-coated with sugar to make them palatable. The rationale was that this double coat could resist breakdown of the tablets in the stomach so that they could exert their effect on

⁹³ Balance sheet (30 November 1887), WF: E2 (Box 23). By 1900 they employed 115 girls for packing in contrast to only 23 in 1884; “History of the Works of Burroughs Wellcome and Co.” West Kent Advertiser (21 March 1924), WF: Box 25. By 1891 there were 400 staff i.e. six times the 1884 figure and there were 500 in 1892. By 1900 there was a staff of 4,300: Staff Records, WF: 90/14: 3.

⁹⁴ Chemist & Druggist 37 (14 September 1889): 392.

⁹⁵ Purchase of chemicals and dyes (1 October 1889 to 31 October 1893), WF: 84/7 10-11.

⁹⁶ G. E. Pearson, (1936), WF: 88/24:41d: 4.

the intestine.⁹⁷ In 1892 their competitors Allen & Hanbury's introduced soluble coated pills, disintegrating tabellae of compressed drugs, and easily soluble tabellae for the preparation of hypodermic injections.⁹⁸

Henry Wellcome continued to adopt novel marketing techniques and specialities were sold to prestige customers in convenient medicine chests.⁹⁹ He proudly boasted that they: "have equipped every commercial, military, mining, exploring and other expedition of importance which has left these shores for many years past".¹⁰⁰ By August 1893, four years after the move from Wandsworth: "the new works were considerably enlarged and fitted up in a most elaborate scale, on a level with any similar factory in the World." It was a "well ventilated factory with a constant atmosphere of 60 degrees".¹⁰¹

With Tabloids and the emphasis on purity and reliability Burroughs Wellcome had hit upon a successful formula, but in the rapidly developing field of pharmaceuticals there was no room for complacency. A major issue constantly faced by Burroughs Wellcome was that, due to the success of Tabloids, with every innovation, no sooner did they release new tablets and formulations, several companies copied them: "Perhaps there is no English specialty which has been so persistently imitated on the continent as the Burroughs Wellcome Tabloids".¹⁰² Although Wellcome fought threats of copied drugs with court actions, this was costly and time-consuming.¹⁰³

By the 1890s many firms were able to perform alkaloidal extractions and to prepare tablets but that did not mean they were all of the same quality. Henry Wellcome and his staff recognised that extraction of mixtures of alkaloids from plants could result in drugs with variable effects in the clinic. Drugs often came from unreliable sources where different

⁹⁷ An external physician suggested this technique, "Trade Notes" Messrs. Burroughs Wellcome & Co. Chemist & Druggist 40 (11 June 1892): 847.

⁹⁸ Geoffrey Tweedale, At the Sign of the Plough: 275 Years of Allen & Hanbury's and the British Pharmaceutical Industry 1715 – 1990 (London: Murray, 1990): 102-103.

⁹⁹ G. MacDonald, (1980): 29, 43.

¹⁰⁰ "Annual Museum" British Medical Journal (3 August 1895) ii: 294-5.

¹⁰¹ West Kent Advertiser (5 August 1893) WF: E2 Cuttings from newspapers.

¹⁰² Chemist & Druggist (1891) 39: 516, 554, 585, 608. Cuttings found in WF: 89/29:7.

¹⁰³ G. MacDonald, (1980): 12.

species of plant, grown under different conditions and harvested at different times were mixed together. The strength could only be compared by measuring the total alkaloid content, as the active ingredients were unknown but even to measure the total alkaloidal strength required laboratory expertise.

Henry Wellcome established the WPRL in 1894 to standardise the preparation of diphtheria antitoxin. He sought a means by which he could show that his firm's extracts were the most potent and he applied the same thinking to ergot. He was impressed with Parke Davis claims of standardising ergot by a biological reaction, recognising that doctors would also be impressed in being provided with a 'reliable' product free of the side-effects caused by other alkaloids present. Wellcome determined to follow their lead and employed further chemists and physiologists in establishing the Wellcome Physiological Research Laboratories (WPRL) in 1894.¹⁰⁴ This major commitment would set Burroughs Wellcome apart from competitors in Britain as it had for Parke Davis in America in creating market exclusivity; others would only be able to compete if they also developed laboratories.

Wellcome was gradually asserting his influence on the running of the business, while Burroughs continued to travel extensively up to his death on the Riviera on 6 February 1895.¹⁰⁵ In March 1895 it was announced that the business would continue to trade under the direction of Henry Wellcome but would retain the Burroughs Wellcome name. Wellcome now had his unhindered chance to stamp his strategy of purified standardised medicines on the firm, but there were several challenges ahead.

Wellcome strengthened the commercial side of the firm following the loss of Burroughs. On 10th June 1895, Edgar Linstead joined as the head of the Advertising Department, and on 8 July 1895 Wellcome secured the experienced George E Pearson, who had been a senior assistant with the London pharmacy firm of John Bell & Co. since 1889. He joined Burroughs Wellcome as a travelling salesman, initially in West London,

¹⁰⁴ C. M. Wenyon, "Henry Solomon Wellcome" Obituary Notices of Fellows of the Royal Society 2 (1938): 230-231.

¹⁰⁵ "Burroughs Wellcome & Co.'s Trip" Chemist & Druggist (18 July 1891): 70-71; "Mr. Burroughs in the East" Chemist & Druggist 39 (24 October 1891): 625; Burroughs will WF: E2; "Silas Burroughs Obituary" American J. of Pharmacy (1895): 433-4.

but then he travelled extensively as Burroughs had and established the business in Australia, South Africa, Italy, Canada and the USA.¹⁰⁶

Burroughs Wellcome wanted to incorporate laboratory techniques that others would not readily be able to copy. Initially analysis of extracts in the Parke Davis manner was achieved by collaborating with William Rowland Dunstan, who was the recognised expert at analysing alkaloids in Britain.¹⁰⁷ In 1886 Dunstan had become Professor of Chemistry at the School of Pharmacy of the Pharmaceutical Society, and in 1887 he became the Director of the Society's new research laboratories, where his assistants were H. A. D. Jowett and Francis Carr. Dunstan was an active member of the Chemical Society and he standardised preparations for the British Pharmacopoeia and analysed the very variable content of commercial preparations derived from various botanical species and different sources.¹⁰⁸ The collaboration with Dunstan's laboratory was useful to help to identify weaknesses in rival products. Wellcome therefore established the firm on a research footing, taking the best approaches of German and American firms and combining them to produce their own unique range of drugs.

3.3 Chemical Laboratories for Research and Chemical Works for Manufacturing.

In their first decade at Russell Street and Snow Hill in London, Burroughs Wellcome had only limited laboratory facilities at Wandsworth, and later Dartford.¹⁰⁹ They relied on Wyeth for basic tests on chemicals, drugs and plants purchased externally.¹¹⁰ Initial manufacturing in Britain involved only incorporation of drugs provided by Wyeth, though

¹⁰⁶ G. E. Pearson, (1936) WF: 88/24:41d: 5; G. Pearson, WF: YL Box 23; E2 PF.

¹⁰⁷ T. A. Henry, (1950): 63-80; D. Read, Journal of the Chemical Society 77 (1900): 49. Dunstan also examined salicin derivatives of phenol: W. R. Dunstan, Pharmaceutical Journal 40 (1880-1): 809; W. R. Dunstan, F. H. Carr, "The Detection of Aconite" Chemist & Druggist 48 (1896) 248-50.

¹⁰⁸ H. King, "F. L. Pyman" Biographical Memoirs of Fellows of the Royal Society 4 (1944): 681-697, on p. 682; Dunstan collected samples from the colonies for analysis: T. A. Henry, "W. Dunstan" (1950): 64, 74.

¹⁰⁹ "Progress in Pharmacy" Chemist & Druggist 36 (28 January 1888) page unknown – found in WF: 89/29:7.

¹¹⁰ For example they tested *Extractum pancreatitis* of Savory and Moore. H. Wellcome to Fairchild's, (16 June 1885), WF: 88/47:8.

from 1886 limited research on tablet production was performed.¹¹¹ Unlike pills, which were simply rolled in an outer coating, tablets were more complex and had to be prepared as chemical salts which would resist breakdown in the stomach, retain an acceptable taste and dissolve readily. This section shows how Henry Wellcome attracted key staff with the required chemical skills to establish the Wellcome Chemical Research Laboratories (WCRL).¹¹² As described previously, little attention has been given to this side of the business.

Wellcome wrote to Frederick Belding Power within days of Burroughs's death and his establishment in the key post as Director of Chemical Research on 30 May 1896 was a key appointment in developing chemical research at Burroughs Wellcome.¹¹³ Power was a long-time friend of Wellcome and had accompanied him on his first visit to Britain in 1880. Power had a childhood interest in drugs and worked in a local drug firm in Hudson, New York, from the age of 13 years, and then at a pharmacy in Chicago where he performed his first experiments. Wellcome took over from him in 1872, and followed him to the Philadelphia College of Pharmacy where Power made an instant impression on his Professors who supported his application to the American Pharmaceutical Association in 1872. He graduated in the same year as Wellcome and with the highest prize in Chemistry (1874) he was described as "the best student in the college, bound to excel all others... a natural chemist". His first publications were on chinchona alkaloids in 1875.¹¹⁴ Power's professors introduced him to the influential works of Daniel Hanbury and to Professor F. L. Flückiger's famous '*Pharmacographia*,' which prompted him to seek a research post in the pharmacognosy laboratory of Flückiger in Berne in 1876. Flückiger later described him as a

¹¹¹ "Trade reports" British Medical Journal (3 August 1895): 294-295.

¹¹² E. M. Tansey and R. C. E. Milligan "The Early History of the Wellcome Research Laboratories, 1894-1914" in *Pill Peddlers, Essays on the History of the Pharmaceutical Industry*. (Monograph 13) J. Liebenau, Elaine C. Stroud, Greg J. Higby, (eds.) (Madison, Wisconsin: American Institute of Pharmacy, 1990): 91-106.

¹¹³ "History of the WCRL", Power to Johnson, 22 January 1907 and 27 December 1912, WF: 88/94; Pharmaceutical Journal (24 May 1913): 721; "Obituary" Chemistry & Industry (8 April 1927): 324. A dinner for 50 was held to celebrate his arrival. "Dr. Frederick B. Power" Chemist & Druggist 49 (25 July 1896): 163.

¹¹⁴ Power Archives, WF: 88/94:59.

“genius in research”.¹¹⁵ Power then worked with eminent German scientists including Baeyer in Chemistry, and Schmiedeberg in Pharmacology, and his thesis on the resins of *Podophyllum* gained him a D. Phil. In 1880 Power returned to America and directed the pharmacy of Fritzsche Brothers of New Jersey, becoming Professor of Analytical Chemistry at Philadelphia College of Pharmacy, and from 1883, Professor of Pharmacy at Wisconsin University. Power participated in the Commission appointed in 1890 for the 7th revision of the U.S. Pharmacopoeia.¹¹⁶ By the time of his appointment to Burroughs Wellcome, Power had a reputation as a world authority on plant alkaloids. Wellcome had kept in touch with his friend Power and visited his research laboratory in Strasburg and knew he was the ideal man to lead Burroughs Wellcome into new avenues of research.¹¹⁷ Powers’ appointment opened up new possibilities for preparing extracts and organic chemical derivatives of plant alkaloids and attracting new staff. His knowledge of botany was important when the firm established its own materia medica farm so that plants of a uniform species could be grown under standard conditions so that the firm did not have to depend on the vagaries of the market places.¹¹⁸

With Power in place, the WCRL, occupying three floors and independent of the Works was formally established in 1896 to manufacture series of chemicals to assist in the identification of extracted plant alkaloids. Power described how: “the materials available for therapeutic use consisted for the most part of simple chemicals and galenicals preparations, with a few active principles of natural drugs. Little was known regarding the composition of many of the natural drugs in common use, the production of synthetic drugs was just beginning and few chemists had the temerity to work at such biological

¹¹⁵ Geoffrey Tweedale, (1990): 61-65.

¹¹⁶ G. MacDonald, (1980): 7.

¹¹⁷ F. B. Power, F. Hoffmann, Examination of Medicinal Chemicals (Philadelphia: H. C. Leas Sons, 1873); H. Wellcome to S. B. Power, (9 August 1883), WF: 88/47:8.

¹¹⁸ A. W. Haggis, History of the Works: 5- 6, WF: 85/20: 2: 123-127; Power’s role in the standardisation of medicines was recognised in 1902 at the International Conference for Unit of Formulae of potent medicaments in Brussels, when the U.S. Secretary of State appointed him as a delegate: International Conference for the Unification of formulae of potent medicaments in Brussels on 15 September 1902, WF: 88/94: 26 and 84; G. Pearson, (1936), WF: 88/24: 41d: 7.

problems”.¹¹⁹ On 1 September 1896 Wellcome secured the employment of Dunstan’s assistant H. A. D. Jowett from the Pharmaceutical Society laboratory. Jowett had recently gained his D.Sc. from London University after working on the small- scale extraction and characterisation of alkaloids.¹²⁰ He had carried out “noteworthy investigations of natural products of medicinal interest under Professor W. R. Dunstan”.¹²¹ Under Power he sought to achieve better means of extraction, purification and standardisation of existing and novel alkaloids. These were then patented as inventions using the German-style trade names that others could not copy. Power recruited additional staff until he was “assisted by a large staff of well trained young chemists”.¹²² One of the first chemists, Dr. S. B. Schryver joined on 4 April 1898, though he only stayed until the end of the year.¹²³

“The firm had difficulty obtaining young pharmacists and chemists who are thoroughly qualified to work independently and to organise. Burroughs Wellcome are extending their manufacture in such directions that they constantly require more men possessing pharmaceutical and technical skills and knowledge such are necessary for supervising processes and devising methods – among applicants are few 100% men”.¹²⁴

The analytical laboratory was established as an independent section within the WCRL in February 1897, headed by Dr. F. H. Lees.¹²⁵ E. F. Harrison, who had also trained under

¹¹⁹ F. B. Power, “WCRL” WF: 88/94.

¹²⁰ “H. A. D. Jowett, Obituary” Chemist & Druggist 125.1 (15 August 1936): 177; The Times (14 August 1936), WF: Box 22; F. B. Power. “History of the W.C.R.L.” (1907 and 1912), WF: 90/14:1; G. Pearson, “A Local Industry, History of the Works and Burroughs Wellcome” West Kent Advertiser (21 March 1924), WF: YL Box 25 D3DW.

¹²¹ H. King, “Frank Lee Pyman” (1944): 682; T. A. Henry, “Wyndham Rowland Dunstan” (1950): 63 – 81.

¹²² Wellcome Research Labs – Dinner to F. B. Power, (21 July 1896), WF: 88/94: 79a.

¹²³ Dr. S. B. Schryver became Professor of Biochemistry at Imperial College of Science and Technology, WCRL Staff, WF: YL Box 25; F. B. Power, “History of the WCRL” (1907 and 1912), WF: YL Box 25.

¹²⁴ “A Day in Dover” Chemist & Druggist 52 (25 June 1898): 954.

¹²⁵ Lees moved to the WCRL in July 1899, and then in August 1905 he became Head of the Analytical Department at Dartford. He resigned from Burroughs Wellcome after prolonged illness in October 1915, Works Records WF: 90/15: 2; F. H. Carr, Harrison Memorial Lecture, Pharmaceutical Journal 103 (26 July 1919): 93-99.

Dunstan at the Pharmaceutical Society, and like his good friend Francis Carr, performed research on alkaloids of aconite, assisted Lees. Harrison remained at Burroughs Wellcome for six years before taking on a consultancy role and achieving fame for his exposé of the contents of patent medicines in the BMA campaigns against Secret Remedies and then as a consultant to the War Office regarding protection against poisonous gases.¹²⁶ On the one hand the analytical laboratory formalised the important task of checking the purity and composition of purchased raw materials, chemical products, intermediates and competitor drugs; on the other hand it assessed the quality of each batch of material produced by their own chemical research laboratory, checking the purity and the yields of chemical reactions.¹²⁷ Thus it had both analytical and research functions.¹²⁸ Henry Wellcome emphasised to the analysts that: "The securing of chemicals of the finest quality and of the highest purity is the prime raison d'être, but the question of profit must never be lost sight of".¹²⁹

Wellcome was meticulous in his instructions to laboratory staff. Branded products had to be sealed by a responsible person and signed for when supplied, and all broken seals had to be reported to head office. Company labels had to be removed from returned vials. Precautions were taken against intermixing drug preparations, and arsenicals were banned from the quinine production section. Wellcome prepared a series of standing orders covering such aspects as avoidance of glass splinters in vials, performing tablet tally checks

¹²⁶ J. K. Irvine, "The Part the Chemist Plays in National Health Insurance" Pharmaceutical Journal (1 February 1930): 101-102; Pharmaceutical Journal (8 February 1930): 129-30; E. F. Harrison. Laboratory Book, WF: 88/94: 26; Metallic Impurities: Tests of Bland's Pills, WF: 89/29/1 (1887); L. G. Matthews, History of Pharmacy in Britain (Edinburgh: E. & S. Livingstone, 1962). Harrison began as a Jacob Bell scholar in 1890, qualifying the next year and gaining a BSc from London University in 1892 and the Associated exam of the Institute of Chemistry. In 1905 he became a fellow of the Institute of Chemistry, WF: 88/94:26.

¹²⁷ "History of the WCRL, Power to Johnston, (22 January 1907 and 27 December 1912, WF: YL Box 25; Laboratory books WF: 85/9, which are now retained at Glaxo Smith Kline.

¹²⁸ G. Pearson, (1936) WF: 88/24:41d; Mr. Hogg, Organisation of the Wellcome Chemical Research Works, Dartford 1897-1934, WF: 89/57: 1-3.

¹²⁹ H. Wellcome, Chemical Departmental Instruction 18 (29 November 1898) volume ii, in WF: S/G/145 in Hogg, Organisation of the Wellcome Chemical Research Works, WF: 89/57:2.

and not leaving materials unsupervised.¹³⁰ In 1898 Wellcome wrote: "the aim is for improved quality and not to rely on the products of others" and "under no circumstances whatever may drugs etc. purchased outside be used until they have been passed by the analyst".¹³¹ It is clear that the promotion of Burroughs Wellcome products according to standardisation and purity was not only a promotional tool, but was taken very seriously internally.

Henry Wellcome recognised that there were various means by which he could claim his products were better than competitor extracts. The first was by ensuring a reliable source of raw material supply. In this respect Power was important in checking the species, source and quality of purchased alkaloids. Even better was to grow the plants required locally. The second was to standardise chemically the conditions of extraction and to use reliable strengths of solvents for the process. Lees checked these in the analytical department. A third means was to prepare different salts of the alkaloids to improve their physical properties and their compressibility into tablets. This was part of the work of the Chemical laboratory. A further means was to improve the assay of alkaloids. In the past the total amounts of alkaloids extracted had been measured but as chemical constitutions were defined the individual alkaloids could be measured.

Power and Jowett and their staff purified and characterised the chemical structures of the many alkaloids they extracted and worked out how to synthesise them. Subsequent extracts could then be compared against a synthetic standard to show how much active ingredient had been extracted, in a close collaboration between the WPRL and WCRL. From 1898 Schryver, Power and Jowett prepared many alkaloids synthetically so that alkaloidal extracts from plants could be standardised against an absolute standard before incorporation into tablets.¹³² The final step was to scale up these processes so that staff at the Works could perform extractions on a manufacturing scale.¹³³ Once this was in place,

¹³⁰ *Ibid.*

¹³¹ WF: 89/57 I-III; H. Wellcome, "Chemical Departmental Instruction 3" (29 November 1898) volume ii, in WF: S/G/145.

¹³² Staff WCRL, WF: YL Box 25.

¹³³ B. CARR F.H. Laboratory Notebooks. Imperial Institute of Science and Technology; 2132 B/CARR/1 vols. I and II.

it simply became a process that could be repeated time and again to extract, synthesise and standardise a whole series of alkaloids. Jowett produced the first Burroughs Wellcome semi-synthetic gold salts of the alkaloids hyoscine, hyoscyamine and atropine, which were incorporated into tablets and made on a commercial scale from August 1897.¹³⁴ An engineer, Mr. Raisin, prepared the necessary equipment to support him.¹³⁵ Then it was a matter of publicising the science. Power joined the Chemical Society and became closely involved with the SCI. He was on their Council and Publications Committee, where he was a close friend of Sir William Tilden and other influential dye-manufacturing chemists and Professors of Chemistry, already described in chapter 2 such as William Perkin, William Ramsey, Raphael Meldola, and James Dewar.¹³⁶ Many of the Burroughs Wellcome characterisations of natural products were published in the *Journal of the Society of the Chemical Industry*.

Initially, the chemistry at the WCRL involved only simple hydrolysis, condensation or substitution reactions, but over the next decade the complexity of chemistry performed increased dramatically. The WCRL staff characterised natural products such as the bark of *Cascara sagrada*, (*Rhamnus purshianus*), extracts of which had been used as a purgative, and evaluated the chemistry of resins, volatile oils and crystalline extracts to establish what was responsible for the biological action.¹³⁷

As this work increased the WCRL expanded further to occupy an additional floor of the Snow Hill site, which remained the location until the move on 24 May 1899 to completely new premises at 6 King St., Snow Hill. The new laboratories were equipped with pumps, vacuum filters, electric supplies, distillers, analytical balances, a dark room and a dry mill. The library was stocked with the key journals reporting advances in chemistry, such as the *Journal of the Chemical Society*, *Berichte der Deutsche Chemische*

¹³⁴ H. A. D. Jowett, "Some New Gold Salts of Hyoscine, Hyoscyamine, and Atropine" *J. Chemical Society* 71 (1897): 860; Mr. Hogg, "Organisation of the Wellcome Chemical Research Works", WF: 89/57 I-III.

¹³⁵ G. Pearson, (1936), WF: 88/24:41d: 7.

¹³⁶ Wellcome Research Labs – Dinner to F. B. Power, (21 July 1896), WF: 88/94: 79a.

¹³⁷ H. A. D. Jowett, "A New Glucoside From Willow Bark" *J. Chem. Soc.* (1900): 707-12; R. Bentley, *A Textbook of Organic Materia Medica* (London: Longmans, Green & Co., 1887): 99.

Gesellschaft, Chemical News and the *Journal of the Society of the Chemical Industry*.¹³⁸

As the work became more specialised a department was established for the preparation of alkaloids and synthetics, separate from those producing inorganic chemicals and galenicals.¹³⁹ Jowett's work there on the alkaloids of *Jaborandi* from 1899 was described as 'pioneering' and led to the isolation and proposal of the chemical structure of the active ingredient, pilocarpine in 1902 and various further chemical derivatives were isolated and investigated for physiological activity.¹⁴⁰ *Jaborandi* leaves had entered use in medicine in 1874, slowing the heart and increasing salivary secretions, but there had been some confusion over the best species of plant to use to prepare extracts.¹⁴¹ The work of Jowett and subsequently Pyman meant that the pharmacological action could be better understood and preparations could be standardised for the content of each active ingredient, improving existing alkaloids and also newer drugs.

Thus by the close of the nineteenth century the firm had established chemical laboratories where research work of considerable commercial importance was performed but instead of producing synthetic drugs, the techniques were used to improve existing production of alkaloids. In addition to plant extracts the firm began to extract animal tissues such as a dried thyroid extract following the new concepts of organotherapy.¹⁴² Many natural extracts, synthetic derivatives of morphine, new creosote compounds and

¹³⁸ C. L. Oakley, "A. T. Glenny" Biographical Memoirs of Fellows of the Royal Society 12 (1966): 163-180; F. B. Power, "History of the WCRL", (22 January 1907) and supplement (27 December 1912), WF: YL Box 25. D3 DW; A photograph of the King Street laboratories appears in H. Turner, (1980): 19; "The WCRL", WF: 88/94:80.

¹³⁹ G. Pearson, (1936), WF: 88/24:41d: 7.

¹⁴⁰ H. A. D. Jowett, Year Book of Pharmacy 36 (1899): 435; Journal of Chemical Society 77 (1900): 474, 851; Journal of Chemical Society 79 (1901): 581, 1331; H. King, "F. L. Pyman" (1944): 682; H. A. D. Jowett, "Pilocarpine and the Alkaloids of the *Jaborandi* Leaves" J. Chem. Soc. (1900): 473-98; H. A. D. Jowett, "The Assay of Preparations Containing Pilocarpine and the Characteristics of Pilocarpine Nitrate and Hydrochloride" Pharmaceutical Journal (29 July 1899): 91-93.

¹⁴¹ H. A. D. Jowett, J. Chemical Society 83 (1903): 438; H. A. D. Jowett, J. Chemical Society 83 (1903): 442; T. A. Henry, (1939): 549-58.

¹⁴² W. Sneader, Drug Discovery: the Evolution of Modern Medicines (London: J. Wiley, 1985): 192; M. Borell, "Organotherapy, British Physiology, and the Discovery of the Internal Secretions" J. Hist. Biol. (1976) 9: 235-68.

new salts of older agents required biological standardisation in animals at the end of 1900.¹⁴³ This work could not be performed within Burroughs Wellcome until the Home Office licensed the WPRL laboratories in 1901.¹⁴⁴

Large- scale extractions took place at the Chemical Works in Dartford, which were considerably enlarged with a floor space of 100 by 45 feet in July 1896.¹⁴⁵ The Works had a constant temperature and were “crammed with costly machinery” and “on a level with any similar factory in the world,” and the first German inorganic lines were produced in August 1896 with Jowett temporarily in charge, while retaining his research role at the WCRL.¹⁴⁶ In order to relieve the strain on Jowett, an approach was made to Dunstan to recruit Francis Howard Carr as chief manufacturing chemist for the Chemical Works and he took up this role on 3 January 1898.

Carr, like Jowett had a thorough grounding in both analytical chemistry and pharmaceutical science, and particularly in studying the efficiency and yields of chemical reactions. His earlier training with Henry Armstrong, one of the founders of chemical engineering, was described in Chapter 2. Carr was Dunstan’s student from 1892-6, performing research on the alkaloids of aconite, ergot, hyoscyamine, and ipecacuanha. He was the first to make the alkaloids pyracotinine, exotinine, ergotoxine, and norhyosyamine. Dunstan and Carr co-authored several research papers on aconite preparations arising from India and Asia, and then Carr followed Dunstan to the Imperial Institute early in 1896.¹⁴⁷ Carr’s role at Burroughs Wellcome was to improve the manufacturing processes, increase efficiency of production and to collaborate with researchers at the WCRL, to characterise active ingredients by comparing the extracts with synthesised substances. He came with an excellent pedigree, having already established himself as an assistant examiner at the

¹⁴³ H. Wellcome to Rt. Hon. Charles Thompson Ritchie, (25 February 1901), WF: 86/92:1; S. B. Schryver, F. H. Lees, “Researches on Morphine” pt 2 *J. Chem. Soc.* (1901): 563 – 580.

¹⁴⁴ E. M. Tansey, (1989): 1- 41.

¹⁴⁵ G. Pearson, (1936) WF: 88/24: 41d: 7.

¹⁴⁶ “Silas Burroughs Obituary” *Chemist & Druggist* 46 (8 February 1895): 213; A. W. Haggis, *History of the Works*: 5- 6, WF: 85/20:2: 1.

¹⁴⁷ Carr's archives are at Imperial College, B.CARR FH6 including notes of a conversation with by A. E. Guenther; T. A. Henry, “W. Dunstan” (1950): 62-81.

Institute of Chemistry under Percy Faraday Frankland.¹⁴⁸ Carr secured the assistance of further former colleagues from Dunstan's laboratory who had trained at Finsbury College, including W. C. Reynolds and W. E. Thompson.¹⁴⁹ They performed biochemical tests on Soloids, assayed chaulmoogra oils, glycerophosphates, samples from the colonies,¹⁵⁰ plants grown at Dartford, and tested manufactured batches against synthetic standards.¹⁵¹

Five further chemistry assistants joined the Works between November 1897 and October 1899, including one who transferred from the Pharmacy department, but these were unqualified 'boys'.¹⁵² Burroughs Wellcome opened another new Fine chemical building on 6 June 1898 to produce chemical intermediates and inorganic salts and "Burroughs Wellcome had just completed a large building and (were) laying foundations of another 58 feet by 130 feet with 3 storeys".¹⁵³ In December 1898 a malt-brewing plant opened to produce the Kepler range of products, and in January 1899 erection of a new Tabloid building began, which was ready by October 1900. Carr attended International exhibitions of laboratory equipment in Paris and Germany to purchase the latest

¹⁴⁸ A. Findlay, William Hobson Mills (eds.), British Chemists (London: The Chemical Society, 1947): 58-97.

¹⁴⁹ William Colebrook Reynolds joined the works on 1 April 1899 and reported to Carr. He left on 3 November 1911: Mr. Hogg, "Organisation of the Wellcome Chemical Research Works", WF: 89/57 1-III. W. E. Thompson joined 1 August 1899. Previously he had worked as a lab boy at the Pharmaceutical Association before going to the Imperial Institute where he did no formal training except for 3 years under Carr. At Burroughs Wellcome he prepared alkaloids, eserine, and pilocarpine at the Experimental lab and WCRL and departed in January 1916; John Augustus Goodson who joined the Tropical Institute in Khartoum in 1906 and later worked at the WCRL also trained at Finsbury under Raphael Meldola, WF: YL Box 25.

¹⁵⁰ W. Dunstan to Burroughs Wellcome, (17 February 1906), WF Business correspondence 1895-1940, WF: D3 DWE; G. E. Pearson, (1936), WF: 88/24:41d: 7.

¹⁵¹ "Laboratory reports 1889-1893", (10 October 1889), WF: 84/7.

¹⁵² Hogg, "Organisation of the Wellcome Chemical Research Works", WF: 89/57; II (S/G/145) Staff Records. Taylor eventually took over as head of the Works when Carr left in 1914.

¹⁵³ A note referring to the firms outing of 700 staff to Dover explained how 2 years ago the staff was just 500. They had just completed a large building and were laying the foundations of another 3 storeys high, "A Day in Dover" Chemist & Druggist 52 (25 June 1898): 954.

manufacturing equipment.¹⁵⁴ He enhanced the Works equipment and even patented his own furnace design.¹⁵⁵ Between 1901 and 1908 he oversaw the introduction of mains electric power, an electric crane, motor vans, works telephones and a packaging conveyer.¹⁵⁶ A new chemical building was opened in 1901, a further Tabloid building in 1903, a chemical department office in 1904, an engineering shop and a plant to produce chloroform. The laboratories impressed visiting Society of the Chemical Industry members on 15 July 1905 and another plant for arsenicals opened in 1908.¹⁵⁷ In the period from 1896 to the outbreak of the First World War, the WCRL and the manufacturing capacity at the Works were significantly enhanced.

3.4 The Wellcome Physiological Research Laboratories up to 1901.

In this section on the WPRL prior to 1901 I will introduce the key characters and show how the WPRL and WCRL interacted to utilise chemistry to differentiate Burroughs Wellcome products based upon purity and standardisation. I have demonstrated already that Burroughs Wellcome had been pursuing a chemical approach since the inception of ‘Tabloids’ in 1884.

Emil von Behring’s discovery of diphtheria antitoxin in Germany in 1890 was recently described by the historian William Bynum as “probably the single most important catalyst in the creation of the modern pharmaceutical industry,” because it stimulated the search for a better understanding of the relationship between the strength and purity of a preparation and its action.¹⁵⁸ Diphtheria antitoxin could be produced in any laboratory that had the facilities to raise and assay it in animals. Not having a licence, Burroughs Wellcome

¹⁵⁴ In September 1900 Carr and Raisin, by now head of engineering, attended an international meeting in France: B. CARR FH 6; Mr. Hogg, WF: 89/57 I-III; Wellcome himself visited European centres to study the latest equipment: H. Turner, (1980): 12.

¹⁵⁵ B. CARR FH 6; Mr. Hogg, WF: 89/57 I-III.

¹⁵⁶ The dramatic expansion of the works staff between 1884 and 1907, was reflected by the numbers of ‘girls’ employed; only 23 in 1884, with 115 in 1890, 121 in 1894, 278 in 1898, 467 in 1901, 502 during wartime in 1902 and 412 in 1907: Mr. Hogg, WF: 89/57 I-III; WF: YL Box 25; G. Pearson (1936), WF: 88/24:41d: 8-10.

¹⁵⁷ WF Box 77, 51 D3DW and Mr. Hogg, WF: 89/57 I-III.

¹⁵⁸ W. F. Bynum, Science in the Practice of Medicine in the Nineteenth Century, (Cambridge: Cambridge University Press, 1994): 164- 165.

tried to negotiate the rights to distribute diphtheria antitoxin produced by the British Institute of Preventative Medicine (BIPM) but while they prevaricated and Allen & Hanbury's took up that role, Burroughs Wellcome decided to make their own supplies.¹⁵⁹ However, the antitoxin required sophisticated biological standardisation in animals in order to ensure safety and potency, and this made commercial production exclusive to technically oriented firms such as Lederle, Parke Davis, and Mulford and some government laboratories.¹⁶⁰ However, the 1876 Cruelty to Animals Act did not allow commercial firms to perform such work in Britain. Tansey discussed in detail the implications of the Act for Burroughs Wellcome and the determined efforts to overcome the initial rejection of the Burroughs Wellcome application.¹⁶¹

They produced their own diphtheria antitoxin from April 1894.¹⁶² An independent physiologist and Home Office license holder, Thomas Jessop Bokenham, at St. Bartholomew's Hospital in London, assisted them with assays from September 1894 and became an employee of the firm from 27th April 1895.¹⁶³ To great acclaim, commercial production of diphtheria antitoxin began in the first week of January 1895, ahead of the BIPM.¹⁶⁴ Burroughs Wellcome initially provided it free of charge during the period it was under the trial.¹⁶⁵ They also prepared a convenient dried concentrated version.¹⁶⁶

¹⁵⁹ Geoffrey Tweedale, (1990): 120.

¹⁶⁰ J. Liebenau, (1987): 72, 75, 100, 110.

¹⁶¹ E. M. Tansey, (1989): 1- 41.

¹⁶² G. Pearson, (1936), WF: 88/24:41d: 4.

¹⁶³ E. M. Tansey, (1989): 1- 41 on p. 4; Staff record book, (1879 – 1902): 35, WF: P2; T. Bokenham to Burroughs Wellcome, (19 August 1896), WF: 86: 92:1; "The Supply of Diphtheria Antitoxin in England" British Medical Journal (10 November 1894): 1063; G. Pearson, (1936), WF: 88/24:41d: 4-5; "Trade Notes, Diphtheria Antitoxin" Chemist & Druggist 44 (24 November 1894).

¹⁶⁴ Diphtheria antitoxin was also produced by Evans Sons, Lescher & Webb, the Goldsmith Co., Royal College of Physicians and Surgeons, British Institute of Preventative Medicine (BIPM) and Royal Veterinary College, Chemist & Druggist 44 (24 November 1894): 736; H. Chick, M. Hine, M. MacFarlane, "BIPM- War on Disease: a History of the Lister Institute" Pharmaceutical Journal (1898) 61: 462- 4; "The Antitoxin Treatment of Diphtheria" Lancet (5 January 1895); "The Antitoxin Treatment of Diphtheria" British Medical Journal (12 January 1895):101-2; G. Pearson, (1936), WF:88/24:41d: 5.

¹⁶⁵ A. W. Haggis, History of the Works: 5- 6, WF: 85/20:2: 4; (14 January 1899), WF: 86/92:1; "The Diphtheria Cure" Chemist & Druggist 46 (16 February 1895): 238; "Trade

Wellcome took advantage of the acclaim regarding the antitoxin to emphasise the importance of his laboratories, which offered a diagnostic service to analyse throat swabs for diphtheria and tuberculosis at a time when most physicians had limited access to laboratory facilities. Dr Bousefield, a pathologist at St. Bartholomew's Hospital performed the service on behalf of the WPRL and was allowed to charge a fee but from this he had to cover the tubes, medical costs and postage, and draw up accounts each month.¹⁶⁷

As sales of antitoxin increased Henry Wellcome applied to the Home Office for a licence to perform physiological tests within the firm, but their application was turned down in August 1896 on the grounds that it would create a monopoly.¹⁶⁸ The WPRL at Charlotte Street in London was extended to increase production of antitoxin.¹⁶⁹

Bokenham could not cope alone with the increasing workload and Wellcome sought assistance initially from Frederick Gowland Hopkins, who decided to pursue his academic career.¹⁷⁰

Instead Wellcome turned to Professor Michael Foster in Cambridge, the foremost physiologist in Britain for advice on staff.¹⁷¹ Foster recommended his own research pathologist A. A. Kanthack,¹⁷² but Wellcome secured two Cambridge graduates. Walter

Notes" Chemist & Druggist 46 (22 June 1895): 870; Anglo-American Newsletter (1896): 161-2, WF: E2.

¹⁶⁶ "Trade Notes" Chemist & Druggist 45 (1894): 857; WF: YL Box 23 (E2).

¹⁶⁷ WPRL Diagnostic Fees Memo's, (1 May 1901), and H. Wellcome to Dr Bousefield (21 December 1903), WF: YL Box 84.

¹⁶⁸ E. M. Tansey, (1989): 1- 41, especially on pp. 17 – 18, 23.

¹⁶⁹ For an early account of the WPRL see "History of Immunological Advances 1895-1972" WF 88/15; "Early printed material on BW. Business Correspondence 1895-1940", WF: E2 DW. The move to Charlotte Street was approved on 20 July 1896: G. E. Pearson, (1936), WF: 88/24:41d. However the laboratories were still being fitted out two years later, T. Bokenham to H. Wellcome, (23 August 1898), WF: 86/92:1.

¹⁷⁰ A. W. Haggis, "The Life and Works of Henry Solomon Wellcome", WF: 89/72 I-III.

¹⁷¹ Burroughs Wellcome to W. Dowson, (5 December 1900), WF: HSW Letterbooks 1900-1, WF: S/G/148/1: 607; W. Dowson to M. White Ridley, (15 February 1900), WF: 86/92; H. J. Parish, History of the Firm: 5- 6, WF: 85/ 20:2: 6.

¹⁷² A. A. Kanthack 1863 - 1898 was Director of the Pathological Department at St. Bartholomew's hospital, succeeding C. S. Roy: "Obituary, Alfredo Antunes Kanthack" British Medical Journal (31 December 1898): 1941-2; Mark Weatherall, Gentlemen,

Dowson had studied under Huxley at South Kensington, had been a General Practitioner in Bristol and was a Fellow of the Incorporated Society of Medical Officers of Health. He was doing 3 months research on tetanus under Kanthack in the pathology department of Prof. G. Sims Woodhead, who recommended him to Burroughs Wellcome.¹⁷³ The other was the bacteriologist Louis Cobbett.¹⁷⁴ Dowson initially assisted Bokenham and later replaced him as Director of the Laboratory in October 1897.¹⁷⁵

Despite the problem of getting assays done, Burroughs Wellcome sold not only diphtheria but also anti-syphilitic and anti-typhoid antitoxins, and anti-streptococcus sera.¹⁷⁶ In anticipation of further expansion of the WPRL, at Brockwell Hall, a site at Herne Hill was leased from November 1898.¹⁷⁷ In the spring of 1899 the WPRL moved there and Dowson recruited young scientists from the local school in Dulwich.¹⁷⁸ The headmaster, Herbert Brereton Baker was a chemist with a high reputation, who was later

Scientists and Doctors: Medicine at Cambridge 1800-1940 (Cambridge: Boydell Press, 2000): 152-6, 163-65, 172, 196.

¹⁷³ “Dale Reminiscences ” in 93HD 143.6; Sims Woodhead had a special interest in tuberculosis, L. Bryder in “Tuberculosis and the MRC” in Joan Austoker and Linda Bryder (eds.), Historical Perspectives on the Role of the MRC (Oxford: Oxford University Press, 1989): 5-7.

¹⁷⁴ “Obituary of Louis Cobbett, Bacteriologist” Lancet (22 March 1947): 391-2. Walter Dowson 1856-1919 studied science at Christ’s, Cambridge; H. H. Dale, 93 HD 143.6; Mark Weatherall, (2000): 155, 163, 171, 182, 200.

¹⁷⁵ W. Dowson to M. White Ridley, (15 February 1900), WF: 86/92:1; H. J. Parish, History of the Firm: 5- 6, WF: 85/20:2; Dale Archives, 93 HD 143.6; E. M. Tansey, (1989): 1- 41 on pp. 7-16.

¹⁷⁶ Medical diary, (1899): 115, WF: 86/92:1. See also A. E. Wright. “On the Results Which Have Been Obtained by Anti-typhoid Inoculation” Lancet (6 September 1902): 651 - 654; Z. Cope, Almroth Wright: Founder of Modern Vaccine Therapy (London & Edinburgh: Thomas Nelson, 1966).

¹⁷⁷ G. E. Pearson, (1936), WF: 88/24:41d: 7.

¹⁷⁸ Dowson lived in Alleyn Road opposite Alleyn’s school, which was associated with Dulwich College. Dowson contacted the headmaster regarding boys with promise in science: W. S. Feldberg, “H. H. Dale”, Biographical Memoirs of Fellows of the Royal Society 16 (1970): 95; W. Dowson to Wells, (27 July 1900), WF: 86/92:1.

Professor at Imperial College, London.¹⁷⁹ His students, Alexander Thomas Glenny and H. J. Sudmersen joined Burroughs Wellcome as assistants in the bacteriology laboratory and continued their education in the evenings.¹⁸⁰ A further chemist, Arthur James Ewins was recruited to the WPRL from the same school.¹⁸¹

Wellcome described the bacteriology laboratory within the WPRL as being “in close association with my physiological laboratory”. It was for “research in bacterial chemistry, a class of work distinct from that carried out in my chemical research laboratories (WCRL) in King Street”.¹⁸² Glenny gave an account of the bacteriological section of the laboratory where he performed research to increase the efficiency of serum production.¹⁸³ When a Home Office inspector visited the site he “did not attempt to conceal his satisfaction”; he “had not seen anything like it in Britain”.¹⁸⁴ The application for the Home Office licence was finally accepted on 5 September 1901 making the physiological testing of antitoxins prepared at the WPRL finally possible on site.¹⁸⁵ Only one other firm, John Richardson & Co., who established the Bacteriological Institute in Leicester, applied successfully for a license and it was not until 1905 and 1908 that further licenses were granted.¹⁸⁶ The Home

¹⁷⁹ Baker later became Professor of Inorganic Chemistry at the University of London: J. F. Thorpe, “H. B. Baker” Obituary Notices of Fellows of the Royal Society 1 (1935): 523 - 526.

¹⁸⁰ C. L. Oakley, “A. T. Glenny (1882-1965)” Biographical Memoirs of Fellows of the Royal Society of Medicine 12 (1966): 163 - 180. Glenny studied mathematics at University College, London. His laboratory notes (1899-1900) give an insight into his work under Dowson, WF: 84/7:7. Henry J. Sudmersen was at the WPRL 1898 - 1901 and 1905-1925: Staff Record Book 1571; WF: YL Box 46; In 1901-5 he researched a PhD in Berne.

¹⁸¹ Both Glenny and Ewins were made permanent staff when they graduated. H. H. Dale, “Arthur J. Ewins (1882-1958)” Biographical Memoirs of Fellows of the Royal Society of Medicine 4 (1958): 81-91; Dale Archives, 93 HD 143.6: 26.

¹⁸² H. Wellcome to C. T. Ritchie M.P., (25 February 1901), WF: 86/92:1:5.

¹⁸³ C. L. Oakley, “A. T. Glenny” (1966): 163-80; H. J. Parish, History of the Firm: 5- 6, WF: 85/20:2: 6.

¹⁸⁴ “Wellcome Physiological Research Laboratories” Chemist & Druggist 55 (11 November 1899): 780 - 781.

¹⁸⁵ C. S. Murdoch to Burroughs Wellcome, (21 May 1900), WF: 86/92:1.

¹⁸⁶ E. M. Tansey, (1989): 1- 41.

Office license gave Burroughs Wellcome a clear advantage over Evans & Sons and Allen & Hanbury's who still relied on external supplies of antitoxin or had to have each batch tested elsewhere.¹⁸⁷ The sales of diphtheria antitoxin by Burroughs Wellcome rose dramatically from 84,000 vials in 1905 to 239,000 in 1910, and 627,000 in 1915.¹⁸⁸ The main points to emphasise from this 'diversion' into the WPRL are that Burroughs Wellcome continued to employ scientists, their scientific reputation was enhanced and they continued their drive towards standardised medicines. In addition to antitoxins, the licensing of the laboratories allowed them to further advance their work on purifying, and characterising alkaloids and glucosides extracted from plants and organ extracts from animals, so they could compare the biologically standardised preparations with synthetically prepared equivalents.

3.5 Interactions Between the Burroughs Wellcome Laboratories and Works after 1901.

Burroughs Wellcome obtained their vivisection license, conditional upon taking on an additional physiologist, which Wellcome again arranged through his contacts at Cambridge University. John Mellanby of Emmanuel College, Cambridge, qualified in physiology and chemistry in 1900 under Michael Foster, J. N. Langley and F. G. Hopkins who recommended his appointment to the staff of the WPRL in October 1901.¹⁸⁹ A further pathologist, Dr. W. V. Shaw from St. Mary's Hospital was appointed in January 1902.¹⁹⁰ Burroughs Wellcome also collaborated with a Dr. Hamilton of Dartford and the previously mentioned Dr. Bousefield, a pathologist at St. Bartholomew's Hospital in London, where

¹⁸⁷ An Epitome of Therapeutics; Wyeth (Philadelphia: Wyeth, 1901).

¹⁸⁸ H. J. Parish, The Wellcome Research Laboratories and Immunisation, WF: 85/20:2.

¹⁸⁹ J. B. Leathes, "John Mellanby" Biographical Memoirs of Fellows of the Royal Society 3 (1940): 173-195; H. Wellcome to C. T. Ritchie, (25 February 1901), WF: 86/92:1; Gerald L. Geison, Michael Foster and the Cambridge School of Physiology: the Scientific Enterprise in Late Victorian Society; J. N. Langley, "Sir Michael Foster – in Memoriam" J. Physiology 35 (1907); W. H. Gaskell, "Sir M. Foster 1836-1907" Proc. Roy. Soc. Biol. 1380 (1908) lxxi-lxxxii; W. S. Feldberg, "Henry Hallett Dale 1875 – 1968" (1970) 77-174 on p. 95.

¹⁹⁰ Shaw was appointed in January 1902: E. M. Tansey, (1989): 35-6.

Dowson had trained.¹⁹¹ Wellcome had an “uncanny knack for selecting staff that were to achieve outstanding reputations”.¹⁹² Several of his staff went on to become Fellows of the Royal Society.¹⁹³

Special provisions had to be made in order to attract promising young scientists to work in a commercial environment. Wellcome had to convince John Mellanby that his independence would be maintained and he had to slacken the strict terms of employment regarding review of publications, secrecy and hours of work.¹⁹⁴

The granting of the Home Office licence opened the floodgates for the firm to evaluate a backlog of preparations requiring assay in animals.¹⁹⁵ This encouraged the firm to pursue further active principles and to characterise chemically them, which in turn led to an expansion of the chemical staff of the WCRL from two in 1896 to four in 1898, whereas in 1900 there were seven. In the period between 1901 and 1914 a new kind of pharmaceutical industry was created in Britain. Burroughs Wellcome established a system whereby the extraction and purification of novel alkaloids and glucosides such as emetine

¹⁹¹ W.P.R.L. Diagnostic Fees, 1903-4 and W. Dowson to Dr. Hamilton, (1 May 1901), WF: YL Box 84. Production of tuberculin likewise enabled Allen & Hanbury to establish good contacts with the medical profession: Geoffrey Tweedale, (1990): 102.

¹⁹² G. MacDonald, (1980): 35.

¹⁹³ The Burroughs Wellcome staff elected FRS (with date in parentheses) are listed in WF: 85/20:1 given with the dates they were at the firm: John Mellanby 1900-04 (1940), P. Laidlaw 1909-13 (1927), A. Glenny 1899-1909 (1944), H. King 1911-1919 (1933), G. Barger 1903-09 (1919), A. J. Ewins 1899-1947 (1943), J.H. Burn 1914 (1942), P. Hartley 1919-21 (1937), C. Kellaway 1944-52 (1940), C. Wenyon 1907- 1944 (1927), H. Wellcome 1880-1936 (1932), F. L. Pyman 1906-1919 (1922), C. L. Oakley, 1934-1953 (1957), H. H. Dale 1904-1914 (1914).

¹⁹⁴ Tough contracts were still in use up to 1911 when Frederick Alfred Pickworth worked at Burroughs Wellcome. He had to take no other business and keep as a solemn secret all formulae and processes, structure and working of machinery, and not divulge these, buy or sell copied machinery after leaving. All improvements-rights had to go to Burroughs Wellcome; “Obituary of Frederick Alfred Pickworth” British Medical Journal (11 November 1967): 363.

¹⁹⁵ Dr. Ponthieu, a chemist at Parke Davis in Detroit acknowledged the difficulties caused by the Cruelty to Animals Act in Britain: “Standardisation” Chemist and Druggist 59 (7 September 1901): 412. Similar Acts, on the statute in some states, did not affect firms in America. Tests performed at the WCRL WF: 88/94:89; WF: WPRL Diagnostic fees 1903-4, YL Box 84.

and hyoscyamine from plants, was controlled by developing methods to assay the concentrations of active ingredients. Firstly this was by simply testing the extracts in animals, but then crucially this was taken one step further by synthesising the proposed active ingredients to prove their identity to the extracts. Once this was achieved the chemically synthesised preparation were maintained as a technical standard. This was important because the extraction method used by other firms produced extracts of variable activity, despite attempts to standardise procedures and conditions. Furthermore the pure chemical could then be used to evaluate the more subtle activities of the drug in physiological experiments. Because of its purity it could be used at lower doses and untoward reactions from additional alkaloids in an extract could be excluded. Furthermore, chemical homologues could be prepared to test the relationship of chemical structure to activity. For the first time a British firm sold organic drugs according to the strength of their pure active principles rather than the total alkaloid content without having to rely on external support for assays as they had with Dunstan. The whole process was commercially driven, aiming to produce novel preparations that were more active, more concentrated, more potent or more pure, giving Burroughs Wellcome a differential advantage over other firms. Encouraged by early successes the firm prepared further *de novo* synthetic chemicals, which were also tested for physiological activity.

In addition to plant extracts, Jowett prepared the human hormone, adrenaline, for testing in the WPRL in 1903.¹⁹⁶ However instead of selling adrenaline in competition with other firms, Burroughs Wellcome prepared and sold its own unique standardised synthetic isoquinoline derivative of adrenaline, collaborating with the chemists Robert Robinson and William H. Perkin jnr. at the Liverpool Medical Institution and Manchester School of Chemistry.¹⁹⁷ Further collaborations were arranged with chemists such as William Tilden, Emeritus Professor at the Royal College of Science in Kensington on research regarding

¹⁹⁶ G. Barger, H. A. D. Jowett, "The Synthesis of Substances Related to Epinephrine" J. Chemical Society 87 (1905): 967; G. Barger, H. A. D. Jowett, "Synthesis of Compounds Similar to Adrenaline from Piperonal" J. Chemical Society 93 (1908): 563.

¹⁹⁷ This applied especially to the search for a synthetic systemically active antiseptic: R. Robinson, W. H. Perkin jnr., "Harmine and Harmaline" J. Chemical Society 103 (1913): 1973-85; "Liverpool Medical Institution" British Medical Journal (29 March 1913): 667; F. L. Pyman, F. G. P. Remfry, "Isoquinoline Derivatives VII. The Preparation of Hydrastine from Cotarnine" J. Chemical Society 101 (1912): 1595.

terpenes and various oils.¹⁹⁸ Fred Power was in touch not only with British chemists through his role on the Society for the Chemical Industry but also with top chemists throughout Europe.¹⁹⁹ Carr's mentor Henry Armstrong turned to the firm for assistance in "working up a rather large quantity of material for which I have scarcely the appliance".²⁰⁰ As Burroughs Wellcome increased their focus on chemistry they corresponded with Sir William Ramsay, Professor of Chemistry at University College, London; Sir James Dewar, Professor of Chemistry at Cambridge; Raphael Meldola, Professor of Chemistry at Finsbury Technical College, London; Jocelyn Field Thorpe at Owens College, Manchester; Frederick Stanley Kipping at Nottingham University, and Arthur George Perkin at Leeds University.²⁰¹

The novel chemicals or routes of synthesis were patented to secure protection from other firms copying them.²⁰² Patenting and testing these products in animals gave Burroughs Wellcome a new form of monopoly, especially in the form of synthetic derivatives, although at this stage the synthetic preparations were primarily used as standards as it was cheaper to prepare standardised extracts on a larger scale. Outside Germany few firms held patents in the medical field, because many produced the same drugs with limited innovation. In the USA patenting slowly increased only after the Sherman Act of 1907, which "forbade restraint of trade by sharing markets and by price fixing but not by making exclusive arrangements for the use of patents, secret processes

¹⁹⁸ W. A. Tilden to F. B. Power, (13 June 1906), WF: 88/94:41.

¹⁹⁹ Discussions on the recruitment of chemists may be found in W. Ramsay to F. B. Power, (20 March 1907), WF: 88/94:40; A. G. Perkin to F. B. Power, (5 May 1907): WF: 88/94: 41; J. F. Thorpe to F. B. Power, (2 October 1905), WF: 88/94: 41; Tilden enquired about posts for 2 chemists, W. Tilden to F. B. Power, WF: 93:37.

²⁰⁰ H. E. Armstrong to F. B. Power, (11 July 1907), WF: 88/94:41.

²⁰¹ Alexander Findlay, and William Hobson Mills (eds.), British Chemists (1947).

²⁰² Frank Pyman's name appeared with that of Wellcome on several patents e.g. "Manufacture of New Therapeutic Compounds (Phenylarsonic Acids)" British Patent BP 855 (1908); "Manufacture of a New Therapeutic Compound (from Laudanosine), BP 314" (1909); "Manufacture of New Therapeutic Compounds, BP 11108, 13828, 14633" (1909); "Therapeutic Compound, Thiolaminomethylglyoxaline", BP 25,873 (1910); physiologically active base 4 (or 5) beta-aminoethylglyoxyline, BP 28,538 (1910). Wellcome patented with F. H. Carr, "Manufacture of emetine", BP 14,677 and 17,483 (1913); Wellcome alone patented aminophenylselenonic acid, BP 2787 (1914), C. M. Wenyon, 'Henry Wellcome', Obituary Notices of Fellows of the Royal Society 2 (1938): 229-238.

and technical knowledge generally”.²⁰³ The American firm of E. R. Squibb had only one patent before 1920.²⁰⁴ We will see later how patents were to become central in controlling medical discoveries and how this on occasions was associated with controversy.

Another means of controlling the quality of drugs was to ensure the correct starting materials for extracts were used. Burroughs Wellcome already had one botanical expert in Frederick Power and they grew some of their own medicinal plants under standard conditions but they took on another expert in George Barger, who trained in chemistry and biology at University College, London (1896) and Kings College in Cambridge (1898). He gained a Ph.D. after research in Botany at the University of Brussels and joined the WPRL in 1903 after “considerable reflection” over his concerns about commercial links.²⁰⁵ Barger’s botanical and chemical expertise enabled researchers at the WPRL to examine the chemical constitution of further alkaloids and glycosides - his first published research at Burroughs Wellcome (with W.V. Shaw) was on the constitution of digitalis extracts.²⁰⁶

The scientific stature of the WPRL was cemented by the appointment of Henry Hallett Dale in 1904. Dowson, Barger, Mellanby and Dale all came from Wellcome’s connections with Frederick Gowland Hopkins, who acted as a consultant and Walter Fletcher.²⁰⁷ Dale had studied experimental physiology in Michael Foster’s prestigious department at Cambridge between 1894 and 1900.²⁰⁸ He knew Barger from Cambridge as a member of the Natural Science club. Since then Dale had performed research in Ehrlich’s laboratory in

²⁰³ W. J. Reader, Imperial Chemical Industries; a History. The Forerunners 1870-1926 volume 1 (London: Oxford University Press, 1970): 199.

²⁰⁴ John P. Swann. (1988): 31; Richard Harrison Shryock, American Medical Research Past and Present (New York: The Commonwealth Fund, 1947): 140.

²⁰⁵ H. H. Dale, “George Barger” (1940): 63-83.

²⁰⁶ “The Chemical and Physiological Assay of Digitalis Tinctures” Pharmaceutical Journal 19 (1904): 249.

²⁰⁷ H. H. Dale, “Reminiscences: WPRL 1904 – 1914”, Dale Archives, 93HD 143.6.

²⁰⁸ G. L. Geison, Michael Foster and the Cambridge School of Physiology: The Scientific Enterprise in Late Victorian Society (Princeton: New Jersey, Princeton University Press, 1978); J. N. Langley, “Sir Michael Foster – in Memoriam” J. Physiology 35 (1907); W. H. Gaskell, “Sir Michael Foster 1836-1907” Proc. Roy. Soc. Biol. 1380 (1908) lxxi-lxxx; Hopkins recommended Dale to Dowson: H. H. Dale, “Reminiscences, WPRL 1904-14.” Dale Archives, 93 HD143.6; 143.3.

Germany.²⁰⁹ He returned to England to perform research at University College Hospital (UCH) in London in 1900,²¹⁰ and enjoyed fruitful collaborations with Thomas Renton Elliott, both in Cambridge and later at UCH.²¹¹

When Dale considered the Burroughs Wellcome post he felt “my chances in academic physiology revealed so blank a prospect”. He knew little about Burroughs Wellcome’s research laboratories but knew that in addition to familiar remedies, the firm had some of greater novelty. Wellcome explained to Dale that he required “research of a serious and permanent nature” like the work on the action of strophanthus by Sir Thomas Fraser in Edinburgh. He also referred to ergot and according to Dale had “a sounder and more enlightened appreciation of research than I had been inclined to expect”.²¹²

Academic colleagues reactions were “less favourable”: some younger researchers were “genuinely scandalised”. Dale had a similar reaction when he met Prof. Arthur Cushny, the first Professor of Medicine at UCH, who was “interested in his work until he found out where he was from” and Dale was “crestfallen” by this attitude to pharmaceutical industry associations.²¹³ Dale was placed in two ground floor laboratories at Brockwell Park fitted for chemistry and bacteriology research and set about a research career that eventually broke down such barriers.

²⁰⁹ Dale liaised with T. R. Elliott and taught at the university where one of his students and a future employee was Laidlaw; H. H. Dale. “Patrick Playfair Laidlaw” Biographical Memoirs of Fellows of the Royal Society 3 (1941): 427-447; Dale Archives, 93 HD 143.3.

²¹⁰ In 1900-02 under Gee and T. Lauder Brunton he was in daily contact with William Bayliss and E. H. Starling and it was during this period he first met Otto Loewi with whom he later shared the Nobel prize in 1936: W.S. Feldberg, “H. H. Dale (1875 – 1968)”: 79-174; H. H. Dale, F. Himmelweit (eds.), The Collected Papers of Paul Ehrlich (London: Pergamon, 1956).

²¹¹ Sir Henry Dale, “Thomas Renton Elliott (1877-1961)” Biographical Memoirs of Fellows of the Royal Society (1961) 7: 53-74; H. H. Dale to T. R. Elliott, (22 July 1958), Dale Archives, Royal Society 93 HD 143.6.

²¹² H. H. Dale. “Reminiscences: WPRL 1904-14”, Dale Archives, Royal Society 93 HD 143.6: 2-3

²¹³ H. H. Dale, “Reminiscences WPRL 1904-14”, Dale Archives, Royal Society 93 HD 143.6: 8.

In 1904 Marmaduke Barrowcliff joined the WCRL from Nottingham University and worked on the chemical constitution of various essential oils.²¹⁴ At Sudlow's retirement dinner in 1905, Wellcome stated that since Sudlow had started in 1879, the premises of the firm had increased 800-fold and the staff was now at 4,300.²¹⁵ In order to deal with the increasing specialisation of work, the WCRL established its own Experimental department in December 1905. Although Jowett was its manager, it was Pyman who ran the laboratory on a daily basis.²¹⁶ Frank Lee Pyman was an experienced chemist who joined the laboratory staff of the Experimental laboratory in February 1906. He had graduated from Victoria University, Manchester, and after a period of research in Zurich University took up a short tenure in the laboratory of Thomas Edward Thorpe, the Government chemist.²¹⁷ A pre-war maximum of nine chemical staff was reached in 1906.²¹⁸

This department took on an increasingly 'academic' and yet practical role, investigating the properties of new drugs, finding efficient routes of synthesis for the standards, better means of isolation and better means of scaling up the extracts to manufacturing capacity. Jowett's encouragement of original scientific enquiry and publications reflected his own academic background:

“the laboratory was spacious and well equipped with a library next door, and two or three assistants available for the preparation of intermediates required in syntheses and for analyses, but most important of all were the research

²¹⁴ M. Barrowcliff, “The Constituents of the Essential Oil of American Pennyroyal” J. Chemical Society (1907): 875 – 87; M. Barrowcliff, F. B. Power, “The Constitution of Chaulmoogric and Hydnocarpic Acids” J. Chemical Society (1907): 557 – 78; M. R. Fox, Dyemakers of Great Britain 1856-1976 (Manchester: ICI plc, 1987): 200 note 6; Laboratory Notebook 13, WF: 85/9.

²¹⁵ R. C. Sudlow's retirement dinner was on 14 September 1905, WF: 90/14:3.

²¹⁶ Jowett took up the role before the opening of a new laboratory in February 1906: Mr. Hogg, WF: 89/57 I-III; G. E. Pearson, (1936), WF: 88/24:41d: 10; “Private, Dr. Jowett”, WF: 85/9:88; H. King, “Frank Lee Pyman” (1944): 681-97 on pp. 682- 683.

²¹⁷ Sir Thomas Edward Thorpe 1845-1925 was the Government scientific officer. From 1885-1894 he had been Professor at the Royal College of Science in London. He wrote several texts on chemistry including “A Dictionary of Applied Chemistry”, “A Manual of Inorganic Chemistry”, “Qualitative Chemical Analysis and Laboratory Practice”;

Obituary” J. Chemical Society (1926) 1031.

²¹⁸ Mr. Hogg, WF: 89/57 I-III.

atmosphere fostered by the firm and the magnificent opportunities presented to those capable of grasping them”.²¹⁹

Pyman’s team immediately prepared synthetic derivatives of salicylic acid, which Burroughs Wellcome patented, explored in animal experiments and sold as potential alternatives to Bayer’s ‘Aspirin’.²²⁰ Aspirin was a great success, but there were many poor substitutes, which Burroughs Wellcome demonstrated “were very variable in free acid number, iodine absorption and melting points, especially those from the German markets”.²²¹ Pyman synthesised berberine, and phenacetin before taking up Jowett’s pioneering interest in glyoxylines, (the alkaloids of the *Pilocarpus sp.*) and isolated jaborine, pilocarpidine, pilosine and pilocarpine, extending the research into synthetic modifications.²²² As the work of the WCRL expanded over the next 10 years, a steady stream of new recruits joined.²²³

Wellcome’s relationship with Dunstan, already close through the hiring of Jowett, Carr and other colleagues was extended when Wellcome agreed to collaborate with the Imperial Institute in November 1905, to develop any drugs arising from research there. Jowett had absolute discretion about which products to take up. However, Wellcome was

²¹⁹ H. King, “Frank Lee Pyman” (1944): 683.

²²⁰ F. L. Pyman, H. S. Wellcome, H. A. D. Jowett, “Manufacture of a new salicylic acid cinnamyl derivative, (cinnamylsalicylic acid)” B.P. 7125 (1906); F. L. Pyman, H. A. D. Jowett, “Some Derivatives of Salicylic Acid” J. Chemical Society 22 (1906): 317.

²²¹ C. Edward Sage to F. B. Power, (10 June 1904), WF: 88/94: 58 (quote); W. Dowson to Burroughs Wellcome & Co., (23 January 1901), WF: 94:36.

²²² H. King, “Frank Lee Pyman” (1944): 681-697; Pharmaceutical Journal (8 October 1927): 375; F. L. Pyman, “The Synthesis of Glyoxaline Derivatives Allied to Pilocarpine” J. Chemical Society 101 (1912): 530; G. Pearson, (1936) WF: 88/24: 41d: 10; Pyman’s laboratory books dating from 7 February 1906 are in WF: 85/9.

²²³ The names are given in several publications from the laboratory and included F. H. Shedden, B.Sc. and Mr H. W. Clewer in 1899, C. E. Potter in 1901, F. H. Gornall in 1902, and Mr. Frank Tutin in 1903, Mr. A. C. O. Hann in August 1904, Marmaduke Barrowcliff in October 1904, Dr. H. Rogerson in November 1905 and Mr. W. Thomas who worked on Atoxyl in December 1905, Dr. A. H. Salway in October 1906, C. W. Moore in December 1907, Mr. H. W. Caton in September 1907, Dr. T. Callan in October 1910, Mr. H. Browning M.Sc. in November 1911, Mr. W. J. S. Naunton B.Sc. in January 1912, and Mr. S. J. Green M.A. in November 1913, Staff WCRL Box 25 and S/G/145.

keen to preserve his monopoly of new drugs and sought assurance from the Government that other firms would not profit from new drugs arising from the collaboration, seeking to withhold details of the active ingredients and manufacturing processes, while delaying reports until the firm could procure sufficient raw materials for the sales launch. Although the Imperial Institute was prepared to delay publication, Dunstan stated that: “neither the Imperial Institute nor the Colonial Office would be in a position to guarantee your firm should enjoy anything approaching a monopoly”.²²⁴ Jowett recognised from this dialogue that: “We can only hope to be the first in the field and get the credit of the scientific investigation and we cannot obtain a monopoly such as we could with a synthetic drug”²²⁵.

This quote summarises the emerging Burroughs Wellcome strategy to extract new drugs, chemically characterise them and standardise them, but also to prepare synthetic versions or at least semi-synthetic salts, which could be patented and protected and increasingly some of these were sold as synthetic products. Dunstan sent a series of raw materials to the Experimental laboratory, where Pyman isolated various glucosides and alkaloids that were assayed for physiological activity, and some led to isolation of novel chemical structures.²²⁶ These contributed to a series of new products from 1908 including arsenicals, Orsudan, pituitary extract, bismuth salts, mercury succinate, Epinine, a synthetic haemostatic and the alkaloidal extracts, Brucine, Epicine and Ergamine and extracts of Kurchi Bark from India, together with ferri-glycerophosphates and some further proprietary preparations.²²⁷

Tropical medicine played an important role in colonial expansion towards the end of the nineteenth century as several causative agents of infection were identified, together with

²²⁴ Henry Wellcome to W. Dunstan and replies (17, 20, 27, 28 February 1906), Business Correspondence 1895-1940, WF: D3 DWE. The quote is from 27 February.

²²⁵ H. A. D. Jowett to G. Pearson, (22 February 1906), re. Interview with Henry Wellcome on 28 November 1905, WF: Business Correspondence 1895-1940, WF: D3 DWE.

²²⁶ H. King, “Frank Lee Pyman” (1944): 683-84.

²²⁷ List of Products in “Organisation of the Wellcome Chemical Research Works”, Mr. Hogg, WF: 89/57 I-III.

the specific means of killing them - principally through research in Germany.²²⁸

Throughout his life Henry Wellcome maintained a healthy interest in colonial development and tropical medicine, and even in the early years of the firm, they had regular requests for drugs from tropical countries, leading to important clinical collaborations in Britain.²²⁹ The Wellcome Tropical Research Laboratories were established at the Gordon Memorial College in Khartoum, Sudan in 1902.²³⁰ As with the WPRL and WCRL, Henry Wellcome attracted top scientists. The first Director of the Tropical laboratories was Dr. (later Sir) Andrew Balfour who had trained in Edinburgh.²³¹ A floating laboratory was added in 1907 under Dr. Charles Morley Wenyon, who returned to England in 1908,²³² and a further tropical diseases expert, Dr. Cecil A. Hoare was employed.²³³ Wenyon studied zoology at Yorkshire College in Leeds, and zoology and chemistry at University College, London, and completed a medical education at Guy's Hospital in 1904. After a short career as a General Practitioner he was appointed as Head of the Protozoological Department of the London School of Tropical Medicine in 1905. He studied the action of drugs on trypanosomes at the Pasteur Institute, and at the Zoological Institute in Munich before moving to Khartoum

²²⁸ M. Worboys, "The Colonial World as Mission and Mandate: Leprosy and Empire, 1900- 1940" *Osiris* 15 (2000): 207-18; M. Worboys, "British Medicine and its Past at Queen Victoria's Jubilees and the 1900 Centennial" *Med. History* 45.4 (2001): 461-82; M. Worboys, "The Comparative History of Sleeping Sickness in East and Central Africa" *Hist. Sci.* 32 (1994) (95 pt 1): 89- 102.

²²⁹ Sir John Keith of Zanzibar corresponded with Burroughs Wellcome about supplies of the drug strophanthus in 1885. H. Wellcome to S. M. Burroughs, (17 December 1885), Letterbooks, WF: S/G/148-2: 381, 430-2.

²³⁰ For a general background see H. Harold Scott, (1939); Gen. Sir Reginald Wingate Bart. "Khartoum – The Story of Gordon College and its Work" undated, WF: PB/86; A. A. Abdel-Hammeed, "The Wellcome Tropical Research Laboratories in Khartoum 1903-1934" *Med. Hist.* 41 (1997): 30-58.

²³¹ Wellcome supported the exploration of H. M. Stanley. World attention was drawn to the war in Sudan in 1898 and Wellcome visited in 1900 to see war damage and levels of disease. H. Turner, (1980): 21-2.

²³² C. A. Hoare, "Charles Morley Wenyon (1878- 1948)" *Biographical Memoirs of Fellows of the Royal Society* 6 (1949): 627-42. Wenyon became the protozoologist to the Metropolitan Asylums Board in 1922, MRC Minutes II (1922): 376. In 1932 Wenyon became Director of the Wellcome Research Institute.

²³³ C. A. Hoare contributed 179 papers in 60 years with Burroughs Wellcome up to 1980, Papers at WI/GC/57; G. MacDonald, (1980): 49-51.

in 1907.²³⁴

New botanical discoveries were sent to the Burroughs Wellcome headquarters from India, Africa and South America, either through the Colonial Office and Jowett's links with Dunstan, or through the firm's colonial houses established in Sydney and in Cape Town in 1902, Montreal in 1906, and New York in 1907.²³⁵ Plant specimens would be identified and sent for further testing of physiological activity at the WPRL²³⁶ One product arising was hyoscyamine, isolated among other alkaloids from *Datura metel* by Reynolds, Carr and Pyman and released onto the market in March 1908.²³⁷

Following the success in the preparation of pilocarpine salts, scientists based at the WCRL and at the WPRL collaborated on a number of projects. Wellcome asked Barger to follow the lead of Parke Davis in purifying and testing active ingredients of ergot alkaloids, derived from the fungus used in medicine for hundreds of years. Extracts of ergot were prepared at the experimental laboratory of the WCRL and were sent to Dale at the WPRL for physiological testing; if any individual purified alkaloids showed promising activity they were further investigated. Carr and Reynolds then made supplies on a large scale at the Works and selected batches of this material were sent back to Dale to check the purity and physiological activity.²³⁸

²³⁴ Cecil A. Hoare, "Charles Morley Fletcher" (1949): 627 – 642.

²³⁵ "History of the Firm of Burroughs Wellcome" West Kent Advertiser (21 March 1924), WF: YL box 25 D3DW.

²³⁶ P. A. Felix- Perredes prepared a series of articles on the plants of the London tropical gardens: "Comparative anatomy of the barks of the *Salicaceae*" Pharmaceutical Journal (1 August 1903). He was honoured by Philadelphia College in 1906 and by Am. J. Pharmacy for a series of articles on botanical gardens, WF: 88/94:41. (12 March and 14 November 1906); F. B. Power to Philadelphia College, (12 March 1906). Barger also trained in botany in addition to chemistry: H. H. Dale, "G. Barger 1878-1939" (1940): 63-83.

²³⁷ T. A. Henry, (1939): 69-71.

²³⁸ W. S. Feldberg, "H. H. Dale" (1970): 94-5; H. H. Dale, "G. Barger" (1940): 66; H. Dale, F. Carr, "The Alkaloids of Ergot" J. Chemical Society (1907): 337; B. J. Clark in J. Bruinvels, M. J. Parnham (eds.), Haemodynamics, Hormones and Inflammation (Oxford: Elsevier, 1984): 3 - 33. W. Sneader, (1985): 106-108.

Barger and Carr prepared the ‘active principles of ergot’ including a complex of alkaloids, called ergotinin which Dale assayed in anaesthetised cats.²³⁹ His findings opened up new avenues of research on the physiological control of blood pressure.²⁴⁰ The team of Barger, Dale, Reynolds and Carr then isolated several separate active principles from ergot including chrysotoxin, which reversed the stimulatory action of adrenaline on the heart, and ergotoxine, enabling it to be assayed as a single alkaloid. Dale showed that commercial preparations of ergot from other firms were very variable and only had around 2% ergotoxine in them.²⁴¹ In a sample of ordinary *Extractum ergotinae liquidum* B.P. from another company Dale found that a minute quantity caused stoppage of animal hearts, and this alarming consequence was due to an impurity, which Ewins identified as acetylcholine.²⁴²

By combining synthetic chemistry and physiological assays, Burroughs Wellcome created a standardised preparation of ergotoxine, the activity of which was demonstrated in their advertisements using kymograph traces to create a ‘scientific image’ to convince doctors of the quality of their ergot preparation.²⁴³ This scientific rationale, offering the benefit of safer prescribing, gave their product a clear competitive advantage over rivals such as Parke Davis and H. K. Mulford whose preparations were standardised only against the total alkaloid content, where many of the alkaloids did not contribute to the desired

²³⁹ H. H. Dale, *Adventures in Physiology* (London: Pergamon, 1953); H. H. Dale, “George Barger 1878 - 1939” (1940): 63 - 83; W. Sneader, (1985): 106 – 108; G. Barger, F. H. Carr, “Note on Ergot Alkaloids” *Chemical News* 94 (1906): 89.

²⁴⁰ H. H. Dale, “The Active Principles of Ergot” *British Medical Journal* (19 November 1910): 1610.

²⁴¹ Dale emphasised the efforts over 2 years by Carr and Reynolds when he received the acclaim: W. S. Feldberg, “H. H. Dale (1875 – 1968)” (1970): 128; H. H. Dale, “On Some Physiological Actions of Ergot” *Journal of Physiology* 34 (1906): 163 - 206; H. Dale, G. Barger, “Ergotoxine and Some Other Constituents of Ergot” *Biochemical Journal* 2 (1907): 240 - 299.

²⁴² A. J. Ewins, “Acetylcholine. A New Active Principle of Ergot” *Biochemical Journal*, 8 (1914): 44.

²⁴³ J. Parascandola, “The Search for the Active Principle of Ergot. Laboratory Science and Clinical Medicine in Conflict”: in ‘Neue Beiträge zur Arzneimittelgeschichte’. Fortschritte für Wolfgang Schroeder, *Veröffentlichungen der Internationalen Gesellschaft fuer Pharmazie* (Stuttgart: Wissenschaftliche Verlagsgesellschaft für Pharmazie 1982).

activity and some might be toxic.²⁴⁴ This policy was applied to other products and enabled Burroughs Wellcome to obtain prestige prices for their differentiated products.²⁴⁵

Ewins and Barger then identified the alkaloid that seemed to be responsible for the obstetric effects of ergot. Taking their idea from the stench that accompanied the large-scale production of ergot derivatives by Carr at the Works, they found similar activity in extracts of putrefying meat.²⁴⁶ Dale and Barger found that histamine was present in both ergot and in animal gut.²⁴⁷ This in turn led Barger to characterise, then chemically synthesise, other amines like adrenaline, which represented the first synthetic analogue of a natural human hormone.²⁴⁸ Pure samples of these amines stimulated animal's hearts in Dale's studies.²⁴⁹ Over fifty chemical derivatives were synthesised at the WCRL allowing Dale to gain a thorough understanding of the relationship between physiological activity and chemical structure.²⁵⁰ The ergot example represents the most lasting and important

²⁴⁴ J. Liebenau, (1987): 43. Parke Davis did not attempt to separate out the various alkaloids and argued that secondary principles would be present in the same ratio though this was known not to be true for ipecacuanha, G. Ponthieu, "Standardisation" Chemist & Druggist 59 (7 September 1901): 412; WF: 84/7:14; H. H. Dale, "George Barger" (1940): 67; H. H. Dale, G. Barger, "The Water Soluble Active Principles of Ergot" Journal of Physiology 38 (1909): Proc.lxxvii.

²⁴⁵ G. MacDonald, (1980): 26; "Price List of Pharmaceutical Products, 1917": WF: DB/68; H. H. Dale, F. H. Carr, "Ergot and its' Preparation, a Critical Review of the Requirements of the British Pharmacopoeia" Pharmaceutical Journal 37 (1919): 130.

²⁴⁶ G. Barger, A. J. Ewins, "The Alkaloids of Ergot II" J. Chemical Society 97 (1910): 284.

²⁴⁷ G. Barger, H. H. Dale, "4-Beta -aminoethylglyoximine (beta- iminazolylethylamine) and other Active Principles of Ergot" J. Chemical Society 97 (1910): 2592; G. Barger, H. H. Dale, J. Physiology 41 (1910): 318- 344; J. Physiology 43 (1911): 182 –195, 499.

²⁴⁸ G. Barger, H. H. Dale, "Chemical Structure and Sympathomimetic Action of Amines" J. Physiology 41 (1910): 19 -59; G. Barger, G. S. Walpole, "Further Syntheses of p-hydroxyphenylethylamine" J. Chemical Society (1909): 1720; G. Barger, G. S. Walpole, "Pressor Principles from Putrid Meat" J. Physiology 38 (1909): 23, 343; H. King, A. J. Ewins, "The Synthesis of Some New Dimethyl-tetrahydroquinolines" J. Chemical Society 103 (1913): 104; H. A. D. Jowett, J. Chemical Society 93 (1908): 563.

²⁴⁹ W. S. Feldberg, "H. H. Dale (1875 – 1968)": 128.

²⁵⁰ G. Barger, "Isolation and Synthesis of p-Hydroxyphenylethylamine, an Active Principle of Ergot, Soluble in Water" J. Chemical Society 95 (1909): 1123; G. Barger, H. H. Dale, "A Third Active Principle in Ergot" J. Chemical Society (1910): 128; G. Barger,

contribution to this new form of knowledge, but there were many dozens of further examples where plant extracts were characterised allowing Burroughs Wellcome to go far beyond the standards laid down by the British Pharmacopoeia, which only defined a wide range of strengths for total alkaloidal extracts, even when there was more than one putative active ingredient.²⁵¹ In the pharmacopoeia the strength of alcohol used to extract alkaloids was not even specified and varied markedly in strength.²⁵²

A second role for the WCRL was to evaluate novel German synthetic drugs arising primarily from the 'dye' firms. These were standardised in a similar way to the alkaloids, but to facilitate the compressing and tableting as Tabloids, salts of the active ingredients were prepared.²⁵³ Pyman produced acetosalicylates, quinine salts and a version of phenacetin for incorporation into Tabloids.²⁵⁴ The growing influence of German chemistry at the WCRL was readily apparent in references to German publications within many Burroughs Wellcome company documents.²⁵⁵

A third function of the WCRL, the special synthesis of chemicals with potential medical uses is given in Power's annotation on a copy of the *British Medical Journal*, commenting on the work of Professor Werner in Heidelberg, who had suggested that the beneficial effect of radiotherapy on animal cancers was due to production of the amine,

H. H. Dale, "The Presence in Ergot and Physiological Activity of Beta-aminazolyethylamine" *J. Physiology* 40 Proc.: 34. Dale presented data at the International Physiological Congress in Vienna in 1910, 93 HD 143.6: 32 - 36; H. H. Dale, W. E. Dixon, "The Action of Pressor Amines Produced by Putrefaction" *J. Physiology* 39 (1909): 25.

²⁵¹ P. A. Felix-Perredes, "The Anatomy of the Bark of *Robinia pseud-acacia*" *Pharmaceutical Journal* (3 August 1901), a paper read at the British Pharmaceutical conference in Dublin, July 1901; F. B. Power, "The Chemistry of the Bark of *Robinia pseud-acacia*" *Chemist & Druggist* 59 (3 August 1901): 224-5.

²⁵² The B. P. *Cannabis indica* was 5% while that in the USA was 15%, *Pharmaceutical Journal* 69 (1902): 245; *Ipecacuanha* strengths varied according to source, *Pharmaceutical Journal* 69 (1902): 256-7, as did alcohol: R. B. Wild, "The Clinical Use of *Ipecacuanha Alkaloids*" *Lancet* (6 September 1902): 654; Wellcome cascara differed from others, WF: 90/14:1: 99.

²⁵³ G. Pearson, (1936), WF: 88/24:41d: 8.

²⁵⁴ Pyman Laboratory Notes, (7 February 1906), WF: 85/9 Book 1.

²⁵⁵ Demand for sulphonal rose after Lauder Brunton's Croonian lecture describing sulphonal as the ideal sedative: "Sulphonal; a New Hypnotic" *British Medical Journal* (21 April 1888): 864.

choline. Power therefore asked Jowett to prepare a similar amine from *Apocynum*, and a supply of 155 g was sent to Prof. Cushny at UCH for clinical experiments.²⁵⁶

Jowett, Hann and Pyman prepared a series of synthetic chemicals called tropeines for physiological studies by Dale and Marshall at the WPRL.²⁵⁷ Some of these were mirror images of the same chemical structure and they developed techniques to resolve these different ‘optical isomers’ of tropeine and hyoscyamine, and made the important observation that one form could be many hundreds of times more active than its mirror image. This meant that if Burroughs Wellcome could prepare and purify the most active form, it would be significantly better than the extract containing a mixture of the two. They found that this technique could also be applied to a number of alkaloids.²⁵⁸ Harold King,

²⁵⁶ Report from H. A. D. Jowett to F. B. Power, “F. B. Power Notes 1883-1921”, WF: 88/94:58; H. MacGillivray, “A Personal Biography of Arthur Robertson Cushny, 1866 – 1926” Ann. Rev. Pharmacology. (1968); 1-24; W. B. Fey, “Arthur Cushny” Clin. Cardiol. 18 (1995): 360-1; J. Parascandola, “Arthur Cushny, Optical Isomerism, and the Mechanism of Drug Action” J. Hist. Biol. 8.2 (1975): 145-165.

²⁵⁷ H. A. D. Jowett, A. C. O. Hann, “Preparation and Properties of Some New Tropeines” J. Chemical Society (1906): 357 –65; F. L. Pyman, H. A. D. Jowett, “Relationships Between Chemical Constitution and Physiological Action in the Tropeines” J. Chemical Society 91 (1907): 92; J. Chemical Society 95 (1909): 1020; F. Pyman, “Relationship Between Chemical Constitution and Physiological Action in Certain Substituted Aminoalkyl Esters” J. Chemical Society 93 (1908): 1793; J. Chemical Society 111 (1917): 167 (on the basis of a lecture given to the Chemical Society, 6 December 1917).

²⁵⁸ M. Barrowcliff, F. Tutin, “The Configuration of Tropine and [psi]-Tropine and the Resolution of Atropine” J. Chemical Society 95 (1909) 1966-77; F. H. Carr, W. C. Reynolds, “The Specific Rotatory Power of Hyoscyamine and the Relation Between that of Alkaloids and their Salts” J. Chemical Society (1910) T1328: 180; H. King, “The Possibility of a New Instance of Optical Activity Without an Asymmetric Carbon Atom” J. Chemical Society (1914): 249. It was known in 1815 that some compounds exhibited differential rotation of light. Pasteur demonstrated this clearly with tartaric acid in 1848. Van’t Hof and Le Bel realised that it was with carbon attached to 4 different groups; E. S. Taylor, A History of Industrial Chemistry (London: Heinemann, 4th edition 1933): 220-224; H. King, “The Resolution of Hyoscine and its Components, Tropic acid and Oscine” J. Chem. Soc. 115 (1919): 476; H. King, “The Stereochemistry of Hyoscine” J. Chemical Soc. 115 (1919): 974.

who we will meet again later, had joined the experimental laboratory in November 1912 and he became much involved in this work, before he transferred to the WCRL in 1914.²⁵⁹

Many examples exist where Burroughs Wellcome characterised natural products to identify the active ingredient and prepared standardised medicines such as strophanthus, willow- bark extracts, and novel extracts including Apocynum, diuretics, and tyramine.²⁶⁰ Frank Tutin joined the WCRL in December 1903 and examined the chemical constitution of various chemically substituted natural products.²⁶¹ From 1908 Pyman, Reynolds, Barrowcliff and Remfry, influenced by Ehrlich's success with Atoxyl, an arsenic derivative for treating syphilis, prepared a series of synthetic aromatic arsonic and arsinic acids which were patented.²⁶² They analysed iron arsenate to characterise it.²⁶³ However, only one completely synthetic product, given the Burroughs Wellcome trade- marks of Soamin or Kharsin, was a significant commercial product for the firm. This was a straight copy of the German drug, freed of its patent because the active mercurial product represented by

²⁵⁹ Sir Charles Harrington, "Harold King" Biographical Memoirs of Fellows of the Royal Society 2 (1956): 157-171.

²⁶⁰ H. H. Dale, P. P. Laidlaw, C. T. Symons, "Acceleration of the Mammalian Heart by Stimulation of the Vagus Nerve" J. Physiology 39 (1909) Proc. xiii; P. P. Laidlaw, "An Active Principle of Apocynum Cannabicum" J. Physiology 38 (1909): 76; P. P. Laidlaw, H. H. Dale, "The Action of an Active Principle from Apocynum" Heart 1(1909): 138; H. H. Dale, P. P. Laidlaw, "The Physiological Action of beta – Iminazolyethylamine" J. Physiology 41 (1910): 318 - 344; H. H. Dale, P. P. Laidlaw, "The Presence in Ergot and Physical Activity of beta – Iminazolyethylamine" J. Physiology 40 (1909) Proc. xxxviii; H. H. Dale, "P. P. Laidlaw (1881-1940)" Obituary Notices of Royal Society of London 3 (1941): 444 ; P. P. Laidlaw, H. H. Dale, "The Action of Some Diuretics" Proceedings of the Royal Society of Medicine 3 (1909) Therapeutic Pharmacology section: 38.

²⁶¹ F. B. Power, F. Tutin, "Some Observations Regarding 'Oleuropein' from Olive Leaves" Pharmaceutical Journal (5 December 1908): 714-21; F. Tutin, F. W. Caton, J. Chemical Society 97 (1910): 2524-34.

²⁶² F. L. Pyman, W. C. Reynolds, "Aromatic Arsonic and Arsinic Acids" J. Chemical Society 93 (1908): 1180; F. L. Pyman, W. C. Reynolds, "A New Solanaceous Alkaloid" J. Chemical Society (1908): 2077; F. L. Pyman, M. Barrowcliff, F. G. P. Remfry, "Aromatic Arsonic Acids" J. Chemical Society 93 (1908): 1893.

²⁶³ F. B. Power, Harold Rogerson, "The Characters of Official Iron Arsenide" Pharmaceutical Journal 81 (19 September 1908): 342-44.

Soamin, had been prepared in Germany.²⁶⁴ Burroughs Wellcome recognised that they could not compete directly on a manufacturing capacity with the German firms in producing synthetic drugs, but they created their own market niche with their purified and standardised drugs.

3.6 Conclusions: The Impact of the Laboratories.

In the period coming up to the First World War, Burroughs Wellcome was a diversifying pharmaceutical company. Not only did they produce the original successful Wyeth brands, inorganic drugs and alkaloidal extracts, but they also produced novel chemical compounds and non-sterile sera, which were controlled for strength and purity. This became increasingly important and Dowson was both blamed and sacked on an occasion when he allowed poorly standardised biological medicines onto the American market, leading to Dale becoming head of the WPRL.²⁶⁵ Dale recalled that “Glenny was making the best that he could of what he knew not to be really suitable conditions”.²⁶⁶ Processing, labelling and bottling were moved to a new building, specially designed and constructed and with ventilation by sterile air, and with Glenny as the Head of the Immunology department.²⁶⁷

²⁶⁴ B. Moore, “The History of Organic Compounds of Arsenic in the Treatment of Protozoan Diseases” British Medical Journal (29 April 1916): 616-8. Kharsin was produced from 17 March 1908, Mr. Hogg, WF: 89/57 I-III.

²⁶⁵ Dale was offered a temporary post at £800 p.a. increased to £1,000 when he became Director. In comparison a university lecturer received around £600: Dale Archives 93 HD 143.8; W. S. Feldberg, “H. H. Dale 1875 – 1968” (1970): 79-174; F. B. Power to Henry Wellcome, (31 January 1902), WF: 88/94; 28a; E. M. Tansey, (1989): 11- 16; E. M. Tansey, “What’s in a Name? Henry Dale and Adrenaline” Medical History 39.4 (October 1995): 459-76; H. O. Schild, “Dale and the Development of Pharmacology” Br. J. Pharmacology (February 1997), 120 (4 Suppl): 504-8; “Obituary, Dr W. C. Fowler” British Medical Journal (24 June 1967): 846-47.

²⁶⁶ The quote is from W. S. Feldberg, “H. H. Dale 1875 – 1968” (1970): 165; Output of diphtheria antitoxin in millions of units was 86 in 1900, 130 in 1905, 240 in 1910, 480 in 1915 and 640 in 1920. From 1909 it was available in concentrated form, WF: 84/7 12 - 13; Glenny Notebook (August 1899 – 1900); Laboratory Reports (October 1889 - October 1895); Chemicals Used September 1903 - March 1905, WF: 84/7:11.

²⁶⁷ H. H. Dale, “Reminiscences” 93HD 143.6; H. J. Parish History of the Firm: 5- 6, WF: 85/20:2:14.

A further consequence of the laboratories was that they brought Burroughs Wellcome scientists to the forefront of efforts to standardise drugs. Unstandardised preparations of some firms remained in the pharmacopoeia simply because certain doctors were convinced of the benefit of the total extract, and because the pharmacopoeia had not been updated since 1898.²⁶⁸ A new Codex was prepared in 1907 to aid the practitioner:

“perplexed by numerous circulars from different sources to be told on good authority that most of the fanciful names (of drugs) refer to one article with which he has been familiar....it may save repeated trials of a drug upon which he may have already formed a definite opinion”.²⁶⁹

As a result of their expertise in drug development and standardisation, Burroughs Wellcome were represented on several committees. Fred Power on the standards committees advised on the use of trade names, allowable levels of impurities and he detailed the tests that were impossible to perform and the standards that it was not possible to meet.²⁷⁰ He prepared a 5 -page list of differences between the British and American Pharmacopoeias, emphasising the need for biological standards and assay of active principles rather than total alkaloids. All ethical manufacturers aimed to differentiate their products from those with lesser standards.²⁷¹ Several firms contributed to the Codex and to the medical literature on drug purity.²⁷² The emphasis on purity and standards recognised

²⁶⁸ E. Bülbring, J. M. Walker, “J. H. Burn” Biographical Memoirs of Fellows of the Royal Society (1981): 45-89.

²⁶⁹ The Codex was coordinated by the Pharmaceutical Society and supplemented the British Pharmacopoeia. The Codex was more authoritative but did not carry the same authority as conferred to the B.P. by the medical acts: “The B.P. Codex: an Imperial Dispensatory for the Use of Medical Practitioners and Pharmacists” Lancet 72 (2 November 1907): 1247.

²⁷⁰ British Pharmaceutical Codex, comments and reports by F. B. Power and others, WI/GC/5 Acc 35.

²⁷¹ D. L. Howard, who lectured to the Pharmaceutical Society in 1907, C. A. Hill and T. D. Morson were key figures. All were in favour of official measured limits, at the highest practicable level, balancing public health with the increased costs of striving for a greater purity. Ethical firms all objected to subjective terms such as 'pure', 'commercially pure'; C. A. Hill, “The Purity of Pharmaceutical Chemicals- with Suggestions for Commercially Obtainable Standards” Chemist & Druggist 72 (23 May 1908): 792-797.

²⁷² Charles A. Hill, “The Essential Oils of the B.P.” Chemist & Druggist 77 (12 February 1910): 271; “The Most Suitable Limit Tests for Arsenic in Official Substances and Preparation and the Limits for Arsenic that may be Reasonably Adopted.” Chemist &

that these were measurable, whereas the clinical benefit was not readily quantified, a point to which I will return.

In the period up to the war attitudes to drug manufacturers became polarised. Those that emphasised purity and standardised drugs, and invoked science came to represent the ethical side of drug development and were supported by physicians, whereas patent medicine manufacturers became the focus of government activity. Dale chaired an international conference on physiological drug standardisation on 29 November 1906.²⁷³ The emphasis on pure standardised drugs contrasted markedly to the waves of protest concerning adulterated medicines in Britain and in America, which led to legislative controls on the advertising of secret or patent remedies. Even the ethical pharmaceutical industry was held at length from the medical profession. The American Medical Association banned members who joined the pharmaceutical industry.²⁷⁴ In Britain the medical journals would not allow reprints of published papers to be used as promotional items.²⁷⁵

While the Pharmaceutical Society favoured preparation and dispensing of drugs by pharmacists, doctors resented the influence of pharmacists on prescribing, so helping to forge a common bond between themselves and proprietary medicine manufacturers, though unwittingly they often prescribed German brands. The common ground between the medical profession, the regulators and the ethical firms was the campaign against patent

Druggist 67 (30 September 1905): 348; “The Purity of Pharmaceutical Chemicals with Suggestions for Commercially Obtainable Standards” Chemist & Druggist 72 (23 May 1908): 792-7; “B.P. Arsenic Test”, Chemist & Druggist 81 (29 July 1912): 122-123; T. Tusting Cocking, “The Contamination of Zinc and its Compounds with Lead” Chemist & Druggist 69 (29 September 1906): 507; “Pharmaceutical Chemical Standards” Chemist & Druggist 85.1 (4 July 1914): 49-55; “The British Pharmaceutical Codex: an Imperial Dispensatory for the use of Medical Practitioners and Pharmacists, Pharmaceutical Society of Great Britain” Lancet (2 November 1907): 982.

²⁷³ “The Unification of Official Formula's for Potent Medicaments” Lancet (23 February 1907): 527 and Lancet (27 April 1907): 1178.

²⁷⁴ John P. Swann, (1988): 31 -34.

²⁷⁵ P. W. J. Bartrip, Mirror of Medicine: a History of the British Medical Journal (Oxford: British Medical Journal: Clarendon Press, 1990).

medicine manufacturers.²⁷⁶ Burroughs Wellcome wanted to establish high reference standards for their prepared proprietary products and one of their analysts, E. F. Harrison, contributed significantly to the campaigns of the *British Medical Journal*.²⁷⁷

The laboratories and the staff employed significantly enhanced the reputation of Burroughs Wellcome, not only from the discoveries and publications emanating from the laboratories, but also the goodwill created by being the first British supplier of diphtheria antitoxin and by offering a laboratory service to doctors. Whereas Tabloids defined Burroughs Wellcome in the nineteenth century, as reliable medicines in easy to administer tablets, the new century brought a focus on purified active ingredients, which were chemically characterised and standardised. The work on ergot derivatives made at the WCRL and tested at the WPRL created a worldwide reputation, particularly for Barger and Dale.²⁷⁸ In the field of physiology the firm produced no publications prior to 1903, yet in the next eleven years 99 papers were published on the chemical structure of alkaloidal extracts, mostly by Barger, Burn, Carr, Ewins, Laidlaw, Mellanby and Walpole. A further 9 papers were published by bacteriology staff such as Glenny, Sudmersen and O'Brien, who were involved more in routine production, maintenance of sterility and standards relating to antitoxins. Links with the Lister Institute were good through G. S. Walpole and the bacteriologist R.A. O'Brien who came from there.²⁷⁹

²⁷⁶ "Convention of Home Representatives, Dartford" (31 December 1907): 9, WF: 90/14:5. The representatives were concerned about the poor quality (small) leaflets produced (p. 8), the lack of comparative studies with Nizin antiseptic and zinc sulphocarbolate (p. 40), and the poor definitions such as 'slight reaction' or just a 'trace' in tests.

²⁷⁷ Secret Remedies: What they Cost and What they Contain- the Composition of Certain Secret Remedies, XXII Medicines for General Use (London: British Medical Association, 1909); More Secret Remedies (London: B.M.A., 1912). A select committee on patent medicines was established in 1912; G. Urdang, Bull.W.H.O. 4 (1951): 577-603.

²⁷⁸ As well as immediate scientific recognition and in addition for his work on chemosynaptic transmission of nerve impulses, Dale was awarded the Nobel Prize in 1936. G. Barger, H. H. Dale, Journal of Physiology 41 (1911): 17; W. S. Feldberg, "H. H. Dale 1875 – 1968" (1970): 77-174.

²⁷⁹ W. S. Feldberg, "H. H. Dale 1875 – 1968" (1970): 95; Harriet Chick, Margaret Chick, Margaret Hume, Marjorie MacFarlane, War on Disease, a History of the Lister Institute (London: Lister Institute 1971); "Jenner Institute of Preventative Medicine" Pharmaceutical Journal (1898) 61: 462- 4.

Dale recalled ten years later "there was something of a pioneering character in those days in this creation of laboratories with serious research in view, in connection with a British pharmaceutical business".²⁸⁰

The scientific acclaim achieved by Burroughs Wellcome was a double-edged sword. The downside was that it made the staff attractive to other firms and to academic centres. George Barger returned to academia in 1909 after six years at Burroughs Wellcome, to become head of Chemistry at Goldsmith College in the University of London. In 1913 he took the chair of chemistry at Royal Holloway College.²⁸¹ Such was the success in establishing Wellcome's research laboratories that many of the key researchers were sought to join the newly formed Medical Research Committee, of which more in the next chapter.²⁸² Laidlaw left Burroughs Wellcome in 1913 for the Sir William Dunn lectureship in Pathology at Guy's Hospital and continued his work on ergot in his new role and from 1 January 1914, he and Dale began testing the potency of posterior pituitary lobe extracts as well as amides, alkaloids, and further extracts of ergot and digitalis.²⁸³

It is clear that by creating laboratories where science could flourish, Wellcome was able to attract into industry staff of the calibre that otherwise may not have considered such a career. Many of his recruits came to him via pre-existing networks of young scientists,

²⁸⁰ W. S. Feldberg, "Henry Hallett Dale 1875 – 1968" (1970): 92.

²⁸¹ H. H. Dale, "G. Barger" (1940): 66. He continued to collaborate with Burroughs Wellcome; P. van Romburgh, G. Barger, "Preparation of the Betaine of Tryptophan and its Identity with the Alkaloid Hypamorphine" *J. Chemical Society* 99 (1911): 268; G. Barger, E. Stedman, "Physostigmine (I): Alkylation Products of Eseroline" *J. Chemical Society* 123 (1923): 758; *J. Chemical Society* 125 (1924): 1373.

²⁸² A. Landsborough Thompson, *Half a Century of Medical Research: Origins and Policy of the Medical Research Council* volume 1 (London: HMSO, 1973); J. Austoker, "Walter Morley Fletcher and the Origins of a Basic Biomedical Research Policy" in J. Austoker and L. Bryder (eds.), (1989): 23-33.

²⁸³ This began a major interest for Burn who became involved in biological standards at the M.R.C.; J.H. Burn, H. H. Dale, "On the Physiological Standardisation of Extracts of the Posterior Lobe of the Pituitary Body" *MRC Report on the Biological Standards*, number 69 (1922). E. Bülbring, J. M. Walker, "J. H. Burn" (1981): 49.

notably from Cambridge. Hopkins' former student, Patrick P. Laidlaw based at the physiological laboratory of Guy's Hospital, was attracted to join Dale.²⁸⁴

In summary Burroughs Wellcome did not attempt to compete with Germany in the large-scale manufacture of synthetic drugs though they were able to produce some of these, at least on a small scale. The larger German firms based their synthetic drugs on the readily available waste materials from the dye industry, whereas Burroughs Wellcome and German pharmacy-based pharmaceutical manufacturers such as Merck concentrated on plant extracts. In Britain there was not such a ready supply of manufacturing chemists and chemical engineers to produce drugs efficiently on a large scale, but the main commercial disadvantage was that the scale of chemical production at Burroughs Wellcome remained small in comparison to the dye firms.

I have shown that considerable chemical expertise was developed in producing synthetic alkaloids on a small-scale so that extracts could be standardised against their active ingredients in order to produce reliable activity. The strengths of Burroughs Wellcome were chemical characterisation, small-scale chemical synthesis, biological standardisation and the production of Tabloids or other novel dosage forms. The growing expertise in chemistry and large-scale manufacture, however, enabled them to so rapidly manufacture Salvarsan and other complex synthetic drugs when the war broke out.

In 1913 Henry Wellcome consolidated all of his laboratories under one umbrella, creating the Wellcome Bureau for Scientific Research (WBSR) under Balfour, leaving Wenyon as Director of Research in the Tropics. Walter M. Fletcher of the MRC had concerns about firms supporting research where they could influence publishing of results as firms are 'tied houses' but he suggested that the apparent freedom conferred by the

²⁸⁴ Laidlaw, previously Dunn Professor of Pathology at Guy's hospital took up a permanent post at the N.I.M.R. at an initial salary of £750 p.a.: MRC Annual Reports 1914-1920: MRC Committee Minutes II, (16 December, 1921): 167; H. H. Dale, "P. P. Laidlaw" Biographical Memoirs of Fellows of the Royal Society (1941): 427-447. Laidlaw did work on histidine and toxins; P. Laidlaw, A. Glenny, "Detection and Concentration of Antigens by Ultrafiltration, Pressure Dialysis etc. with Special Reference to Diphtheria and Tetanus Toxins": Biochemical Journal 9 (1910): 298; The Cambridge connection included Mellanby, Barger, Dale, Laidlaw, Burn, Dowson, Kanthack; H. H. Dale, "Patrick Playfair Laidlaw, 1881-1940" Obituary Notices of Fellows of the Royal Society 3 (1941): 427-447.

WBSR was optimal.²⁸⁵ Soon after its establishment, War broke out and the WBSR was placed at the disposal of the War Office, offering training and support on Tropical Research.²⁸⁶ Henry Wellcome maintained an interest in Tropical Medicine throughout his life and this was important to the firm's ability to test their new drugs in the colonies when they had difficulty in getting drugs tested in England. I will return to this in chapter six.

In the next chapter I will examine the challenges that Burroughs Wellcome faced in replacing German drugs after the outbreak of the war, and the problems that were created by the loss of several of their key staff to the M. R. C. and to other pharmaceutical firms.

²⁸⁵ Maisie Fletcher, The Bright Countenance: a Personal Biography of Walter Morley Fletcher (London: Hodder & Stoughton, 1957): 187.

²⁸⁶ Cecil A. Hoare, "Charles Morley Wenyon 1878-1948"(1949): 627-42.

CHAPTER FOUR

War and the Establishment of a British Synthetic Drug Industry

“We cannot recover what we have never had...the production of fine chemicals have from the first been a German industry”.¹

4.1 Introduction: the Reliance on German Drugs and Chemicals.

Chapter Two showed that Britain relied on Germany for synthetic drugs, chemical intermediates and certain alkaloids. The Royal Commission on Vivisection, which reported in 1912, listed the drugs that had recently been introduced as a result of animal studies and most were from Germany: the soporifics, chloral, sulphonal and veronal; local anaesthetics, cocaine, eucaïne and stovain; the analgesics and antipyretics, antipyrine, antifebrin, phenacetin and exalgin; physostigmine (or eserine) for glaucoma; amyl nitrites for angina; and the diuretics, caffeine, theobromine, diuretin and urotropine.²

This reliance on Germany for synthetic drugs in 1914 was not apparent in the British Pharmacopoeia. The version in use up to 1914 (i.e. that produced in 1898) only listed 3 synthetic drugs; even the draft 1914 version only listed 7 synthetic drugs. This was because standards of specification had not been agreed for many of the newer drugs: Britain did not have a system for assaying drugs.³ But it is clear by reviewing the *British Medical Journal* and *Chemist & Druggist* that German synthetic drugs held a dominant position in the British market.⁴ Furthermore, because the use of German trade names was frowned upon,

¹ F. H. Carr, “Recovery of Trade Lost to Germany” *Chemist & Druggist* 85.2 (29 August 1914): 51.

² “Final Report of the Royal Commission on Vivisection” *British Medical Journal* (16 March 1912): 626-27.

³ These were acetylsalicylic acid (Aspirin), barbitone (Veronal), benzamine lactate (β -Eucaïne lactate), chloral formamide, dicimorphine hydrochloride (Heroin), hexamine (Urotropine), phenolphthalein (Purgen) *British Medical Journal* (17 October 1914): 672-73; *British Pharmacopoeia 1914* (London: Constable & Co, 1914); “The British Pharmacopoeia” *Chemist & Druggist* 85.2 (3 October 1914): 49-58; “The British Pharmacopoeia 1914” *Pharmaceutical Journal* (3 October 1914): 452-55.

⁴ “Synthetic Medicinal Chemicals” *British Medical Journal* (23 January 1915): 168-169; “Medical News – Reply by Burroughs Wellcome” *British Medical Journal* (6 February 1915): 257.

British doctors often used drugs, distributed by wholesalers, not even realising that they were German.⁵

Figures from the Commercial Intelligence Branch of the Board of Trade show that imports from Germany in 1912 included small quantities of natural products; £24,500 of opium, £237,100 of Peruvian bark and rhubarb root, and a larger portion, (£264,600) of purified quinine; but also £895,500 of “prepared medicines” and £742,500 of “chemical products for medicine”.⁶ Although German synthetics were seen as a threat as described in chapter two, there was however, a recognition that some efforts were being made in Britain: “Although prior to the war, the manufacture of organic fine chemical products by synthesis was to a very large extent a continental monopoly, there was nevertheless a beginning made within this country”.⁷

In chapter 3, I demonstrated that Burroughs Wellcome had the chemical skills required to prepare many alkaloids synthetically on a small- scale, in order to estimate the purity of extracted alkaloids and to carry out complex structure-activity relationship studies.⁸ However, the only synthetics they produced commercially were Atoxyl, isoquinoline derivatives of adrenaline (Suprarenin synthetic) and codeine, while May & Baker only prepared phenacetin and Sulphonal under contract from Bayer, after importing late-stage intermediates.⁹

Smith’s, Morson’s, Howard’s, Whiffen’s, and MacFarlane’s did not perform any chemical synthesis, but between them extracted various alkaloids, concentrating on the most profitable lines, morphine, strychnine and caffeine and so they still relied on Germany for others.¹⁰ Burroughs Wellcome produced pilocarpine salts, hyoscine, atropine, emetine,

⁵ For example John Bell distributed ‘Marlesen’ for Bayer. British Medical Journal (5 September 1914): 55.

⁶ “Drugs and Medicinal Preparations” Chemist & Druggist 85.2 (3 October 1914): 34.

⁷ D. L. Howard, British & Colonial Pharmacist (August 1926): 243.

⁸ Burroughs Wellcome letter. Chemist & Druggist 85.1 (22 August 1914): 46; B. Dott, “Vegetable Alkaloids; How the War has Affected Production” Chemist & Druggist 88.4 (29 July 1916): 777; T. A. Henry, The Plant Alkaloids (London: J. & A. Churchill, 3rd edition, 1939); R. Robinson, J. Chemical Society 111 (1917): 876.

⁹ Judy Slinn, A History of May & Baker 1834 – 1984 (Cambridge: Hobson’s, 1984): 44-45.

¹⁰ “Board of Trade Notes” Chemist & Druggist 85.2. (5 September 1914): 40; F. H. Carr, press cuttings in 2131 B/CARR 2 No. 143, Imperial Institute (5 September 1914): 1; D. Bolton, “The Development of Alkaloid Manufacture in Edinburgh 1832 – 1939”

apomorphine, aconite, colchicines, cotarnum, homatropine, hydrazoline and spaline.¹¹ There were shortages of formamine (hexamine), quinine and sanatogen, and these amounted to over £1m. worth of synthetic drugs.¹²

The 1907 patent law had aimed to stimulate synthetic manufacture of patented (hence German) drugs in Britain, and thereby stimulate the training of chemists. However, it became apparent that after a modification of the law in 1909, only the latter chemical stages of synthesis were being performed in this country and near-finished goods were being imported. As a result, chemists here did not gain much experience, but prices were kept low due to German efficiency of large-scale production.

The patents of many of the earliest German synthetic drugs, such as Antipyrin, patented in July 1883 had expired, but British firms still could not prepare it competitively against German firms.¹³ It was stated that: “before the war it would have been very difficult to produce the salicylates here”. Even simple synthetics such as Aspirin were not manufactured commercially in Britain because it could not be manufactured: “at prices which could compete with those at which Germany was able to offer them”.¹⁴

German firms created a series of trusts and cartels to maintain monopolies and discourage counter-measures.¹⁵ Thus, the lack of competitiveness was also due to:

“Enhanced selling by cartels and a gradual drawing together of large manufacturing concerns. The first achievements were the elimination of competition within Germany and the organisation of concerted efforts to undersell rivals in those lines where there seemed to be a likelihood of dangerous competition arising: owing to our inferior organisation we thus became the shuttlecock of German men of business”.¹⁶

British firms found that cartels were not the only anti-competitive practice:

Chemistry & Industry (1976): 701 -708; “London Pharmaceutical Industry” Chemistry & Industry (1933): 667 - 698.

¹¹ T. A. Henry, (1939).

¹² F. H. Carr, “Synthetic Organic Drugs: their Manufacture as Affected by the War” Chemist & Druggist (29 July 1916): 778-9.

¹³ “Manufacture of Antipyrin” Chemist & Druggist 85.1 (15 August 1914).

¹⁴ A cartel existed for iodine and other drugs. “The War and the Scarcity of Some Drugs” British Medical Journal (27 March 1915): 559-61.

¹⁵ L. F. Haber, The Chemical Industry 1900 – 1930: International Growth and Technological Change (Oxford: Clarendon Press, 1971): 110, 118, 275-6.

¹⁶ F. H. Carr, text of his 1926 SCI speech, “Manufacture of Organic Medicinal Chemicals” in his Archives at Imperial College. B/CARR/III Lectures 1920-60.

“International trading is not on a reciprocal basis... foreign chemicals and pharmaceutical preparations are admitted into this country, practically duty free whilst goods exported from this country to countries abroad are subject to an exceedingly high 'ad valorem' duty. One vast country (America) ... directly prohibits the import of pharmaceutical preparations of other countries while other immense states do so indirectly by means of (the) high duty”.¹⁷

Throughout the nineteenth century Britain had maintained a free trade policy in marked contrast to increasing protectionism in France, Italy, the United States, New Zealand and Canada. Allen & Hanbury's found this particularly costly in Australia.¹⁸ American tariff protection had effectively killed off British alkali exports and now prohibited importation of some pharmaceuticals and controlled advertising to physicians.¹⁹

In this chapter I will examine how Britain reacted to the loss of German drugs at the outbreak of the war. I examine the collaborations established to determine which drugs were essential and how these could be made or replaced, and how the shock of the War brought home the need for firms to collaborate to make the best use of resources. This chapter will show how the pre-war efforts of Burroughs Wellcome described in chapter 3 formed a valuable technical base for the preparation and analysis of new drugs, both internally through their experienced staff such as Pyman and Jowett, and externally through Henry Dale and Arthur Ewins, who joined the Medical Research Committee (MRC) and arranged studies by their Salvarsan Committee to show that British - produced drugs were as safe as the German versions. These studies were the foundation for further developments in biological standardisation of drugs and of clinical trials. Francis Carr, Arthur Ewins and others spread the Burroughs Wellcome model of chemical research and development and large-scale manufacturing to other pharmaceutical firms. Finally, I will examine some of the collaborations that established the British pharmaceutical industry on a more secure footing.

¹⁷ “British Chemical Industries” British Medical Journal (5 March 1921): 347.

¹⁸ L. F. Haber, (1971): 239; “British Dyestuffs” Chemist & Druggist 94.2 (8 October 1921): 39; D. Chapman-Huston and E. C. Cripps, Through a City Archway: The Story of Allen & Hanbury's 1715-1954 (London: John Murray, 1954): 245.

¹⁹ W. J. Reader, Imperial Chemical Industries Ltd. A History: The Forerunners 1870 - 1926 volume 1 (London: Oxford University Press, 1970): 169; B. E. Reuben and M. L. Burstill, A Guide to the Technology and Economics of the Chemical Industry (London: Longman, 1973); J. Bishop, “Drug Evaluation Programs of the A.M.A. 1905-66” Journal of the American Medical Association 196 (1966): 496.

4.2 Government Responses to the Conditions of War and Drug Shortages

The outbreak of War led to a massive demand for dyes to make uniforms, and drugs, especially antiseptics, anaesthetics, painkillers and antitoxins.²⁰ Many of the same chemicals were required both for the production of explosives and of drugs. However, synthetic drugs, many chemical intermediates and some alkaloids were soon no longer available. Miall recalled: “The chemical manufacturers of this country were very ill-prepared for such a catastrophe”.²¹ The British government had to make rapid decisions to manage this situation. They had to ensure that no essential materials were exported, and they had to find alternative sources of German drugs, chemical intermediates and raw materials. Longer-term solutions included growing some medicinal plants in Britain²² or importing drugs from allied countries, but there were many urgent requirements.

In passing the Trading with the Enemy Act of August 5th 1914 (under section 8 of the Customs and Inland Revenue Act), the Government immediately specified a list of essential chemicals including drugs, which could not to be exported to the continent without a special licence: glycerine, lead, saltpetre, nitrate of sodium, carbolic acid, ethyl and methyl alcohols, alkali iodides, belladonna and its preparations and alkaloids, bismuth and its salts, boric acid, bromine and alkali bromides, castor oil, chloroform, cinchona, quinine and salts, coca preparations, and alkaloids, colloidin, corrosive sublimate, cresol and preparations, nitro-cresol, digitalis, ether, ethyl chloride, formic aldehyde, henbane and preparations, iodine and preparations, Lysol, mercury and salts, morphia and other alkaloids of opium, nux vomica and alkaloids, paraffin, protargol, salicylic acid, Salvarsan and all fine chemicals.

Certificates of origin were required for Norway, Sweden, Denmark, Italy and The Netherlands.²³ Before an export licence was granted, applicants had to specify the nature

²⁰ “Effect of the War on Drug Supply” Pharmaceutical Journal 93 (12 December 1914): 797.

²¹ S. Miall, History of the British Chemical Industry (London: Ernest Benn Ltd., 1931): 36.

²² Prof. H. G. Greenish, “Drug Cultivation” in “Effect of the War on Drug Supply” Pharmaceutical Journal 93 (12 December 1914): 797.

²³ “Customs and Inland Revenue Act” Chemist & Druggist 85.1 (15 August 1914): 34; “Trading with the Enemy - its Limitations and Possibilities” Chemist & Druggist 85.2 (22 August 1914): 47; “Trading with the Enemy” Chemist & Druggist 85.2 (17 October

and quantity or weight and value of goods, where it was going and why, and which ports and ships would be used.²⁴ The Army immediately requisitioned all quinine, phenacetin, and formaldehyde produced, as well as several chemical intermediates.²⁵ The Germans immediately reciprocated, banning exports to Britain of chemicals required for making munitions, dyestuffs and drugs.²⁶ This made a bad situation even worse. For example, Britain had relied on Germany for phenol, used itself as an antiseptic, but also needed for the production of drugs such as Aspirin and Phenacetin.²⁷

The Germans did not believe it was possible for British firms to produce synthetic drugs on a commercial scale. Perkin quoted a senior figure within the German Chemical Industry, probably Duisberg of Bayer as stating:

“England talks not only of holding her own in the war, but of beating us in the chemical industry. She cannot do it, because the nation is incapable of the moral effort to take up such an industry, which implies study, concentration, patience, and fixing the eye on distant consequences, and not merely on the monetary result”.²⁸

British drug firms had relied on the dye industry for chemical intermediates but even the larger British dye firms such as Clayton's, Read Holliday and Levinstein's relied on imports from Germany of chemical intermediates such as benzene, toluene, and carbolic acid.²⁹ British firms were “muddling through”.³⁰ The raw material supply of inorganic chemicals such as bromides (used for epilepsy) and potash from mineral deposits in Germany was immediately compromised by the War, but at least there were alternative sources in South America.³¹ However supplies “all over the world were cornered by Germany”.³²

1914): 33; “Trading with the Enemy Proclamation” Chemist & Druggist 85.2 (12 September 1914): 34; “Absolute alcohol” Chemist & Druggist (19 September 1914): 48.

²⁴ “Proclamation on Exportation of Medicines” Chemist & Druggist 85.2 (3 October 1914): 33-5.

²⁵ “Medical News” British Medical Journal (5 May 1917): 603.

²⁶ F. H. Carr, “Synthetic Organic Drugs: their Manufacture as Affected by the War” Chemist & Druggist 87 (29 July 1916): 778-779.

²⁷ “Trade Prior to the War” Chemist and Druggist 85.1 (15 August 1914): 48; W. J. Reader, “Ministry of Munitions” (1970): 250-1, 286-7.

²⁸ Quoted by W. H. Perkin in W. M. Gardner, (1915): 407 - 427 quote on p. 415.

²⁹ L. F. Haber, (1971): 121, 148.

³⁰ W. J. Reader, (1970): 267.

³¹ B. Dott, “Vegetable Alkaloids: How the War has Affected Production” and F. H. Carr, “The Manufacture of Drugs Affected by the War” from British and Colonial Pharmacist (June 1915): 436-7. A copy of this paper is in the Archives of Francis H. Carr:

Many chemical intermediates such as organic acids, alcohols and aldehydes were soon in short supply. Chemicals required for the manufacture of drugs included liquid chlorine, sulphur dioxide and trioxides, phosphoric anhydride, chlorides and oxychloride of phosphorus, acetic anhydride, acetyl chloride, carbonyl chloride, the chloroacetic acids, monochlor-toluene (benzyl chloride), acetoacetic acid ester, and phenylhydrazine.³³ Other essential intermediates from dye makers were amidophenols, dimethylalanine, dimethylsulphide, beta-naphthol, and phthalic anhydride.

Some British companies had made efforts in case of war to avoid shortages. Sir Edward Evans of Evans Sons, Lescher & Webb had attended the British Pharmaceutical Congress as President in 1912 in which the general topic of “drug trade in war” was discussed. His firm bought up supplies of German drugs from Spain and Portugal; they cultivated herbs and planned increased efforts to make digitalis, henbane, colchicum, olearin, belladonna, peppermint, lungwort and aromatics. Burroughs Wellcome, like most others were ill prepared for the sudden outbreak of war.

In summary the war brought an immediate shortage of some natural plants, inorganic drugs, alkaloids and biologicals and an absolute lack of German synthetic drugs. The first strategy adopted was to seek alternative sources or alternative drugs. The second was to try to make the German drugs. Although some shortages were immediately obvious, there were also more subtle requirements for chemical intermediates, some of which were not immediately recognised.

4.3 Which Drugs were Required and Could They be Manufactured in Britain?

Before legislation could be put in place to alleviate the shortages, the Government had to decide which drugs and chemical intermediates were most needed for the War Office

B.CARR 2130 B/CARR: 3 at Imperial College, London; “The War and the Scarcity of Some Drugs” *Chemist & Druggist* 85.2 (5 September 1914): 4; “Board of Trade Returns to 31 August” *British Medical Journal* (3 September 1914): 47.

³² C. A. Hill, T. D. Morson, “Manufacture of Fine Chemical in Relation to British Chemical Industry” from *British and Colonial Pharmacist* (June 1915): 436-7. A copy of this paper is in the Archives of Francis H. Carr: B.CARR 2130 B/CARR: 3 at Imperial College, London.

³³ F. H. Carr, “The War and British Production of Fine Chemicals, Synthetic Organic Drugs and Alkaloids” *British & Colonial Pharmacist* (June 1916): 436-7 in 2130 B.CARR Press cuttings IV.

and this was poorly understood until Moulton began collating data.³⁴ Fortunately, the Pharmacopoeia Commission had just completed work on the new Pharmacopoeia, which was due to be published in December 1914.³⁵ The Commission on Patent Medicines, which met between May 1912 and June 1913, also reported just before the outbreak of War. Their extensive report of 782 pages included many recommendations to over 14,000 questions.³⁶ There had also been a recent Proprietary Medicines Inquiry.³⁷ Together with the British Pharmaceutical Codex of 1907, these formed a good basis for defining essential drugs.³⁸ Preparation of the Pharmacopoeia and Codex had included pharmaceutical industry input.³⁹ The next step was to check which drugs could be made in Britain, what chemical intermediates would be needed and where there were shortages.

Returns of the commercial intelligence branch of the Board of Trade in August 1914 confirmed actual shortages of natural and synthetic alkaloids, the local anaesthetics, Eucaine and Novocaine, and other natural extracts such as Thymol (oil of ajowan) used as an antiseptic, and lanolin (hydrous wool fat) needed for the preparation of ointments. However, the figures were not detailed enough to identify shortages of specific chemical intermediates or individual synthetic drugs and this made it difficult to predict requirements.⁴⁰

In order to assess which drugs were needed, who could make them and what intermediates were required a series of inter-related committees were established, led by the Board of Trade and the National Insurance Commission and with contributions from a number of Chemical Societies. Broadly, they covered the chemical intermediates required to make not only drugs, but also dyes and explosives, the drugs required, the possible alternatives, which firms made these drugs and how much of each was available. In order to

³⁴ A. J. P. Taylor, English History 1914-1945 (Oxford: Clarendon, 1988): 4-5.

³⁵ The British Pharmacopoeia (1914).

³⁶ "A Huge Revenue Threatened" British Medical Journal (11 May 1912): 1090.

"Patent Medicine Committee" Chemist & Druggist 85.1 (24 October 1914): 47.

³⁷ "Proprietary Medicine Inquiry" Pharmaceutical Journal 93 (8 August 1914): 218.

³⁸ "The British Pharmaceutical Codex" Lancet (22 November 1907): 1247.

³⁹ "The British Pharmacopoeia" British Medical Journal (13 August 1914): 884-5;

"The British Pharmacopoeia 1914" British Medical Journal (3 October 1914): 49-58. It came into force on 31 December 1914.

⁴⁰ F. H. Carr, "Synthetic Organic-Chemical Industry" Nottingham Journal (October 1918); Chairman's address by F. H. Carr to the Nottingham branch of the SCI. Copy in F. H. Carr archives at Imperial College. B/CARR/III Lectures 1920-60.

make many of the drugs, a complex web of chemical intermediates was required from many different firms and many of the same staff from pharmaceutical firms was represented on several committees.

Walter Runciman, educated in South Shields and Cambridge was the son of a ship owner whom he succeeded as Baron; he was a Liberal M.P from 1899-1900 and from 1902 onwards (until 1918 and then 1924-31).⁴¹ As newly appointed President of the Board of Trade, he established a Committee on Drug Supply within three weeks of the outbreak of War to quantify the requirements of various chemicals, to establish which firms produced them, and to set priorities for the allocation of chemical intermediates required for drug production, and so to coordinate supplies through a sub- committee on drugs chaired by J. Fletcher Moulton. As early as 23 November 1914, Runciman called for a Government sponsored national dye industry, not only to benefit dye production, but also as a source of chemical intermediates.⁴² Moulton, who had a long-standing interest in science and had campaigned against the antivivisectionists supporting his good friend Henry Wellcome who wrote of Moulton in 1896: "He, more than any other man, roused this country (England) to a realisation of the vital importance of scientific methods, research in medicine and in every branch of industry".⁴³ Moulton had played a significant role in defending scientific patents in the chemical, electrical and other industries. He was a member of parliament and a member of the judiciary committee of the Privy Council, and had previously lectured on the issues faced by chemistry, including a 1904 address to the Society of the Chemical Industry, "The trend of invention in the chemical industry." In his 1914 Rede lecture on "The Manufacture of Aniline Dyes in Britain" he stated: "We no more dare to leave our great industries at the mercy of a foreign country than we dare trust to a foreign country our guns and our ammunition".⁴⁴

⁴¹ Runciman remained at the Board of Trade until 1916, when he was replaced by Sir Albert Stanley, (later Lord Ashfield): A. J. P. Taylor, (1988): 15, 326; K. Middlemass, J. Barnes, Baldwin: A Biography (London: C. Tinkling & Co., 1969): 56-7, 65, 654.

⁴² H. Fletcher Moulton, The Life of Lord Moulton (London: Nisbet, 1922); F. B. Power, Nature (13 January 1923): 44; M. R. Fox, Dye Makers of Great Britain 1856-1976: a History of Chemists, Companies, Products and Changes (Manchester: I.C.I. plc, 1987): 38,48,53,85, 88-9, 91,146.

⁴³ J. Fletcher Moulton obituary by F. B. Power, WF: 88/94:62-63.

⁴⁴ *ibid.*

Moulton's committee aimed to integrate and coordinate overall supplies and this involved developing an understanding of the inter-relationships between firms and their reliance on each other for chemical intermediates. The committee included three professors of chemistry - William Henry Perkin junior, FRS, Professor of Chemistry at Oxford University and the son of the founder of the British dyestuffs industry;⁴⁵ Prof. Arthur George Green at Leeds University, who had been associated with the dyestuffs firms, Brooke, Simpson and Spiller and with Clayton Aniline⁴⁶; and Raphael Meldola, FRS, Professor of Chemistry at the Royal College of Chemistry, then at Finsbury Park.⁴⁷ The representatives of dyestuffs included Herbert Levinstein⁴⁸ of Levinstein's: Joseph Turner,⁴⁹ chairman of Read Holliday of Huddersfield, and Milton S. Sharp of the Bradford Dyers Association.⁵⁰ It also included two pharmaceutical manufacturers, David L. Howard, head of Howard's of Ilford, and past-president of the Institute of Chemistry and of the Society of the Chemical Industry, and Thomas Tyrer, the experienced head of T. Tyrer & Co., and past-president of the Society for the Chemical Industry. Howard and Tyrer represented two of the largest pharmacy-based manufacturers producing alkaloids and fine chemicals.⁵¹ The committee quickly organised increased supplies of sulphuric and nitric acids, liquid chlorine, synthetic benzol and phenol, to increase drug production.⁵²

It became imperative to define exactly which drugs were essential and what constituted a reasonable alternative. It was clear that anaesthetics, painkillers and

⁴⁵ M. R. Fox, (1987): 92; Chemistry & Industry (1929) 7: 1009.

⁴⁶ J. Baddiley, "Arthur George Green" Obituary Notices of Fellows of the Royal Society of Medicine 4 (1943): 251-70.

⁴⁷ For background see Alexander Findlay and William Hobson Mills (eds.), British Chemists (London: The Chemical Society, 1947): 96, 176-7, 247-8; W. J. Reader, (1970): 278; L. F. Haber, (1971): 353-5; M. Hainsworth, "Who was Raphael Meldola?" Biologist 39 (1992): 72; "Obituary of Raphael Meldola" Proc. Roy. Soc. Lond. 93 (1917): 29 - 37.

⁴⁸ "Herbert Levinstein," J. Soc. Chem. Ind. Jubilee edition (1931): 92.

⁴⁹ M. R. Fox, (1987): 42-43.

⁵⁰ M. R. Fox, (1987): 76- 92.

⁵¹ The committee also included George Beilby JP, F.R.S., a past-president of the S.C.I., Max Muspratt of the Patent Office, Sir Arthur Tedder of Customs & Excise (Chemistry and Pharmaceuticals) and Prof. James Johnston Dobbie, F.R.S. British Medical Journal (5 September, 1914): 40; W. J. Reader. (1970): 266 -70; W. H. Perkin in W. M. Gardner. (1915): 345, 407, 419.

⁵² F. H. Carr, "The Manufacture of Synthetic Organic Drugs Affected by the War", British and Colonial Pharmacist (June 1915) 436-7, (quote) in 2130 B/CARR cuttings IV: 3, Archives at Imperial College.

antiseptics would be needed in great quantities. The National Health Insurance Commission, created in 1911, and responsible for civilian Government spending on healthcare, took a central role in defining the problems of drug supply. The health insurance provided British working men earning less than £16 per year and some working women with health benefits.⁵³ Because the Government was to pay for medicines, it already had an increased interest in ensuring that the most appropriate drugs were prescribed.

Sir Robert Morant,⁵⁴ a civil servant previously at the Board of Education, became chairman of the National Health Insurance Commission and set up two advisory committees. The “Committee on Drug Supply” decided which specific drugs were most needed;⁵⁵ its members included the President of the Pharmaceutical Society, Mr Edmund White, the Vice-President, Mr E. T. Neathercott,⁵⁶ and the Secretary, Mr W. J. U. Woolcock, who was employed at the War Office.⁵⁷ John C. Umney of the Pharmaceutical

⁵³ S. W. F. Holloway, Royal Pharmaceutical Society of Great Britain 1841-1991. A Political and Social History (London: The Pharmaceutical Press, 1991): 52, 324–40.

⁵⁴ Sir Robert Morant was named as the first Commissioner of the NHI on 28 November 1911: S. W. F. Holloway, (1991): 338; for a life history of Morant see D. Cox-Maksimov, “The Making of the Clinical Trial in Britain, 1910- 1945. Expertise, the State and the Public” (Cambridge: PhD, September 1997): 90-97.

⁵⁵ Members of the committee included the NHI Commissioner Mr Jack Smith Whitaker, as chairman; Sir Thomas Barlow Bart; Sir Thomas Lauder Brunton Bart; Dr. A. Cox, Medical Society of BMA; Prof. A. R. Cushny, Professor of Pharmacology at University College, London; Dr. E. Rowland Fothergill, Council of BMA; Dr. B. A. Richard, Secretary of London Panel Commission; Dr. F. J. Smith; Dr. William Hale White; President of the Royal College of Physicians; Dr. E. W. Adams, medical officer, NHI; “Committee on Drug Supply” Chemist & Druggist 85.1 (22 August 1914): 33 and (29 August 1914): 59 and (5 September 1914): 40-42.

⁵⁶ “Pharmaceutical Society of Great Britain” Chemist & Druggist 99.1 (28 July 1923): 117; E. T. Neathercott was President of the Pharmaceutical Society 1920-24, S. W. F. Holloway, (1991).

⁵⁷ William James Uglow Woolcock was one of two pharmacists represented on the first National Advisory Committee on Insurance created after the National Insurance Act of 1911. He was appointed as Local Associations Officer and from 1913 was Secretary and registrar of the Pharmaceutical Society, until his appointment as General manager of the Association of the British Chemical Manufacturers formed in 1916. In December 1918 he was returned as Coalition Liberal M.P. for Central Hackney: S. W. F. Holloway, (1991): 337, 339, 355, 392.

Society and Charles A. Hill of British Drug Houses, who had been involved in production of both the 1898 and 1914 Pharmacopoeia, were also members.⁵⁸

In parallel, representatives of the London Chamber of Commerce including Pharmaceutical manufacturers, met with John Anderson (later Viscount Waverley)⁵⁹ of the National Health Insurance Commission and Sir Robert Morant to establish the second committee as an “Emergency Committee of Trade Section” to

“consider and advise us as to the best means of obtaining for the use of British industries, sufficient supplies of chemical products, colours and dyestuffs of kinds hitherto largely imported from countries with which we are presently at war”.⁶⁰

John Anderson was one of the few senior officials who understood chemistry, having read science in Scotland and Germany before joining the civil service; he became instrumental in directing British firms to produce synthetic drugs.

John C. Umney of the Pharmaceutical Society (who was also on the Committee on Drug Supply) chaired this Emergency Committee of Trade, which included the pharmaceutical manufacturers David Lloyd Howard of Howard’s, Charles A. Hill of British Drug Houses, T. D. Morson, Thomas Tyrer, with T. E. Lescher,⁶¹ and E. A. Webb of the firm Evans Sons, Lescher & Webb.

Overall, the National Health Insurance Commission was characterised by a lack of red tape; it helped to avoid famines of alcohol, glycerine and sugar, and yet manufacturers

⁵⁸ J. C. Umney was a Board member of the firm Wright, Layman and Umney Pharmaceutical Journal (22 August 1914): 294; John Charles Umney, “Publication of the Pharmacopoeia” Chemist & Druggist 83.2 (26 July 1913): 53; “Obituary, Charles Umney” Chemist & Druggist 88.5 (25 November 1916).

⁵⁹ Lord Bridges, “John Anderson, Viscount Waverley” Biographical Memoirs of Fellows of the Royal Society 4 (1958): 307-325.

⁶⁰ “Exportation of Medicines” Chemist & Druggist 85.2 (19 September 1914): 33; for background see Major General Sir W. G. MacPherson. History of the Great War Volume 1. (London; H.M.S.O., 1921): 178- 179.

⁶¹ Thomas E. Lescher joined the firm of Evans Sons, Lescher & Webb in 1895. After taking the Pharmaceutical Society exam he travelled extensively to the Far East, Australia and New Zealand, establishing the international business. He became a partner in 1900. T. E. Lescher, British Pharmaceutical Congress: “Pharmacy Today – its Responsibilities” Chemist & Druggist 127.1 (31 July 1937): 118-9; “The Late T. E. Lescher” Pharmaceutical Journal 140 (30 April 1938): 460.

still had to beg the War Office for supplies of sulphuric and nitric acids.⁶² At the start of the War, the President of the Board of Trade, and the President and Secretary of the Pharmaceutical Society were in daily contact with the War Office, National Health Insurance Commission and other Government departments. The Secretary of the Medical Research Committee, Walter Morley Fletcher, also “was constantly attending innumerable meetings at the War Office, at the Home Office and with the Royal Army Medical Corps, the Air Force and the Royal Society”.⁶³ The Medical Research Committee had been established in 1913, and was to play an important role, particularly relating to the assay of newly -produced Salvarsan as will be described later in this chapter.⁶⁴

In addition to the central question of which drugs were needed and who could provide them, or alternatives, a series of further committees contributed to the more detailed discussions required regarding chemical intermediates needed and sources of them. Even the supply of some of the drugs already made in Britain was potentially compromised by the lack of essential intermediates. Thus the Chemical Society were concerned with the preparation of inorganic and organic chemicals: “most important of these are medicinal drugs, aniline etc.,” so they set up a committee involving academic chemists, and the Society of Chemical Products for Industrial Purposes, to discuss synthetic chemicals. The pharmaceutical manufacturers, David Howard and Thomas Tyrer, gave continuity with the other committees,⁶⁵ and were joined by Hill, Hewitt, White, and even Jowett of Burroughs Wellcome, and were also represented on a committee with members of the Institute of Chemistry and the Society of Public Analysts to address the supply of laboratory research chemicals. A further Laboratory Agents Committee concerned itself with materials required

⁶² C. A. Hill, T. D. Morson, The British & Colonial Pharmacist (June 1915): 436-7.

⁶³ Maisie Fletcher, The Bright Countenance: a Personal Biography of Sir Walter Morley Fletcher (London: Hodder & Stoughton, 1957): 128; T. R. Elliott, “Walter Morley Fletcher (1873 – 1933)” Obituary Notices of Fellows of the Royal Society of Medicine (1934) I: 153- 163.

⁶⁴ Linda Bryder, “Tuberculosis and the MRC” in Joan Austoker and Linda Bryder (eds.), Historical Perspectives on the Role of the MRC (Oxford: Oxford University Press, 1989): 1- 21.

⁶⁵ “Board of Trade Notices – The Manufacture of Salvarsan” Chemist & Druggist 85.2 (5 September 1914): 40.

for manufacture as, for example, glassware for performing reactions was also in short supply.⁶⁶

Sir Robert Robertson was the Government chemist who took charge of wartime research in chemistry. He dealt mostly with the heavy chemical industry members such as Brunner Mond, the United Alkali Co., and Albright & Wilson, who all made tremendous efforts to meet demands for munitions. Brunner Mond and the South Metropolitan Gas Company produced large supplies of phenol and this helped the pharmaceutical industry.⁶⁷ Alcohol supplies were improved further by the merger of the principal whisky distillers to form the Distillers Co. Ltd, with a subsidiary British Industrial Solvents making acetone at Hull.⁶⁸

4.4 Calls for Further Government Intervention.

As described previously, pharmaceutical firms in Britain were very small and had no representative Trade Association. However, it was immediately recognised that the War offered “an opening for British manufacturers”.⁶⁹ The main protests about the reliance upon Germany and called upon the Government for assistance were University chemistry professors who consulted widely for the dye firms, and were members of the Society of the Chemical Industry.⁷⁰ Sir William Tilden⁷¹ was also a member of the Council of the Institute of Chemistry and the Society of Public Analysts. He had warned since the 1880’s about the potential consequences of a weak British chemical industry.⁷² Just weeks before the war

⁶⁶ The Laboratory Agents Committee included R. Meldola, C. A. Hill, David Howard, H. A. D. Jowett, J. T. Hewitt, Sir William Tilden and Edmund White while the Glassware committee included Meldola, Tilden, and Professor H. B. Baker; “British Salicylic Acid” *Chemist & Druggist* 85.2 (3 October 1914): 35.

⁶⁷ Robertson was made FRS in 1917 and Chief Government Chemist in 1921: R. C. Farmer, “Robert Robertson” *Obituary Notices of Fellows of the Royal Society* 6 (1949): 539-61; S. Miall, (1931): 38-56.

⁶⁸ S. Miall, (1931): 110.

⁶⁹ “An Opening for British Manufacturers” *Pharmaceutical Journal* 93 (22 August 1914): 292.

⁷⁰ Arthur Marwick, *The Deluge: British Society and the First World War* (Boston; Little Brown, 1965); A. Findlay and William Hobson Mills (eds.), (1947).

⁷¹ In 1912 he was Prof. of Applied Chemistry, Royal College of Science, 1913 Chair of Chemistry at Finsbury Technical College and in 1919 became Mason Professor of Chemistry, Birmingham: *Minerva* 8 (1970): 406.

⁷² For a series of articles on this see W. M. Gardner, (1915).

Tilden gave a series of lectures as Professor of Chemistry at the Royal College of Science, “The Progress of Scientific Chemistry in our Own Times”⁷³ and on 14 August 1914 he wrote to ‘*The Times*’:

“Probably the British public is not aware that nearly all the so-called synthetic drugs are made in Germany.... and to a considerable extent also the alkaloids quinine, morphine, eucaïne, etc.” “[British] manufacturers will not fail to take advantage of their positions to prevent a famine in these necessary medical materials. In doing so there seems no sufficient reason why the manufacture of these substances cannot be performed here for the benefit of ourselves and our dependencies”.⁷⁴

In his address to the Royal Society of Arts on 27 November 1914 on “The Supply of Chemicals to Great Britain and her Dependencies”, he asked that the protection already promised to the dye industry, in the form of definite financial aid from the Government, should be extended to fine chemicals, and chemical intermediates and he explained that:

The establishment of what will be a practically new industry in this country will require consideration and assistance from the State if it is to survive the period fierce competition, which will follow the conclusion of the war.⁷⁵

Tilden described how British firms might produce some of the alkaloids and synthetic drugs, hitherto only commercially available from Germany. They could not yet do so on a cost-efficient basis and would certainly not be able to compete with Germany after the War. The Germans might:

“keep any markets they can retain outside the British Empire, but every man who cares for his country will surely demand that business at home shall be limited to British goods. Existing conditions offer a great opportunity to the British Drug Manufacturing trade: it would be not only profitable but also patriotic to take advantage of it. There is no reason why the majority at least of the synthetic drugs most generally used should not be manufactured in this country if the necessary enterprise and capital be forthcoming. The home demand would at once be very considerable”.⁷⁶

Tilden described the organisation of German companies, where management was by competent specialists, who were constantly on the lookout for new discoveries and who

⁷³ “Chemistry Past and Present” *Chemist & Druggist* 85.1 (25 July 1914): 197.

⁷⁴ Tilden’s letter written on 14th August 1914 was printed on 18th August.” Trade in Drugs and Chemicals” *Chemist & Druggist* 85.1 (22 August 1914): 33-34.

⁷⁵ W. Tilden in W. M. Gardner, (1915): 315 – 334.

⁷⁶ “Drug Stocks and the Drug Trade” *British Medical Journal* (15 August 1914): 379.

had a large technical staff to make discoveries commercially viable by securing cheap materials, improving processes and creating a demand. They had a legal staff that patented all improvements and described them vaguely to prevent copying. German companies influenced their Government on aspects of tax and freight costs, and they had agencies spread around the world that encouraged an extensive credit system. The Germans usually aimed to create a monopoly situation and then to increase prices.⁷⁷

Prof G. Henderson⁷⁸ spoke on the subject of “British Chemical Industry and the War”.⁷⁹ Frederick M. Perkin, by now a freelance chemistry consultant to the dye industry, also summarised the position of British manufacturers. He noted: “The starting of chemical manufacturing requires great experience and special plant”. Several manufacturers had approached him willing to help but asking: “Will the Government assist them in founding these new industries”. One had said: “We shall be establishing a new industry at a time of great stress... will the infant be given a chance to become a healthy child?”⁸⁰

The Government introduced the Patents, Designs and Trade Marks (Temporary Rules) Act 1914 amendment, which allowed for the weekly notification in Trade Mark Journals of the names of German drugs that had been suspended.⁸¹ From 8th September 1914, the Government abrogated patents of German drugs including Aspirin and Heroin (Bayer), Lysol (Schuelke & May), Stryphrin (E. Merck), Urotropine (E. Schering), and Sanatogen (Bauer & Co.), offering the rights of production to British firms. Eventually most of the synthetic patents were abrogated including Salvarsan.⁸² However, British firms

⁷⁷ F. H. Carr, (29 July 1916): 778-80; L. F. Haber, (1971): 129.

⁷⁸ Sir James Irvine and J. L. Simonson, “George Gerald Henderson (1862-1942)” Obituary Notices of Fellows of the Royal Society 4: 490. Henderson was Professor of Chemistry at the Glasgow and West of Scotland Technical College and was President of the Society of the Chemical Industry 1915-18.

⁷⁹ Prof. G. G. Henderson, “British Chemical Industry and the War” Pharmaceutical Journal 93 (7 November 1914): 615.

⁸⁰ F. M. Perkin, in W. M. Gardner, (1915): 298-314.

⁸¹ “Trade Marks of Alien Enemies” Chemist & Druggist 85.2 (19 September 1914): 52; Mr D. B. Dott, “Alkaloids” The British and Colonial Pharmacist (June 1916): 436-7.

⁸² “German Patents in Britain” Pharmaceutical Journal 93 (15 August 1914): 246; “Patents, Designs and Trade Marks Act, 1914” Pharmaceutical Journal 93 (29 August 1914): 319-21; “German Chemical Patents” Pharmaceutical Journal 93 (19 September 1914): 406-8; “The Patents and Trade Marks of Alien Enemies” Pharmaceutical Journal 9 (26 September 1914): 419; “German Patents and Trade Marks” Pharmaceutical Journal 93 (26 September 1914): 436; “German Patents and Trade Marks-Salvarsan” Pharmaceutical

also wanted full use of the familiar trademarks by which the drugs were widely known. For example, Burroughs Wellcome wanted to refer to Hexamine, as their form of urotropine rather than the complex chemical name of hexamethylenetetramine, which doctors would not recognise or remember, and they achieved this aim.⁸³ A series of drugs related to hexamine, including Urodonal, and Urotropine were said to sterilise acid urine and benefit rheumatism and gout. Suspension of the patents encouraged manufacture by British firms. Longer-term promises of supporting British manufacturers came from Runciman in 1915:

“The Act passed last autumn as an emergency measure provided that the operators of German patents in this country should have a full chance of conducting them under license and it was the intention of the Government not to cripple this company when the war was over, but to give them the opportunity of making the most of German patents”.⁸⁴

In addition to replacing German drugs, alternatives were sought. Alcohol could replace some of the roles of phenol, but the Government continued to place strong restrictions on the use of alcohol, as it was also required for the manufacture of explosives.⁸⁵ Companies continued to complain about the shortages of alcohol, as it was essential as a solvent for crystallising drugs and for preparing Chloral.⁸⁶ High-grade castor oil, glycerine, sugar and lanolin were requisitioned and firms had to keep accurate records of use.⁸⁷ Even a Royal

Journal 93 (10 October 1914): 530-31; “Salvarsan- British Firm Obtains License” Pharmaceutical Journal 93 (24 October 1914): 569.

⁸³ “Trade Marks of Alien Enemies” Chemist & Druggist (19 September 1914): 52; F. H. Carr, “The War and British Production of Fine Chemicals, Synthetic Organic Drugs and Alkaloids” The British and Colonial Pharmacist (1915): 436-7, cuttings in 2131 B/Carr at Imperial College; “Trade Marks of Alien Enemies” Chemist & Druggist (26 September 1914): 66; “Synthetic Medical Chemicals” British Medical Journal (23 January 1915): 168; Advert “British Made Hexamine Tabloid” Chemist & Druggist 85 (17 October 1914): 31; “Confiscated Drugs, Use of Trade Names” (14 May 1915), WF: 85/31:1-2.

⁸⁴ W. H. Perkin in W. M. Gardner, (1915): 422.

⁸⁵ W. M. Gardner, (1915): 322; S. Miall, (1931): 84-86.

⁸⁶ “Duty Free Alcohol in the Chemical Industries” and “Commercial Uses of Alcohol” Pharmaceutical Journal 93 (29 August 1914): 316-17, “Alcohol and the War with Germany” Pharmaceutical Journal 93 (29 August 1914): 339; 28,994 proof gallons had been imported from Germany in 1913. “Absolute Alcohol” Chemist & Druggist 85.2 (19 September 1914): 48. M. Fox, (1987): 43.

⁸⁷ F. H. Carr, “Fine Chemicals, their Manufacture in Relation to the British Chemical Industry”, presentation to the Society of the Chemical Industry, Chemist & Druggist 88.4

Commission on sugar supply was established, and this had an effect on drugs as sugar was needed to produce pill coatings.⁸⁸ According to Thomas E. Lescher of Evans, Lescher & Webb, who was honorary secretary of the Wholesale Drug Trade Association, “great stress was laid on large scale production of saccharin” so that people could still drink their tea and coffee”.⁸⁹

In addition to financial and immediate fiscal help, the pharmaceutical companies sought assurances from Government that it would be worthwhile in the longer term to invest in new manufacturing plant. Considerable inducements were made to encourage firms to produce phenacetin.⁹⁰ In return, the Government sought assurances that prices would be held firm until the end of the year. There had been some panic buying and sharp increases in the prices of drugs and surgical dressings and some speculative buying.⁹¹ Two pharmaceutical manufacturers served on the prices committee, which tried to fix realistic prices according to supply and demand.⁹²

Runciman expressed sympathy for the plea from the pharmaceutical firms for protection, though as a Liberal he remained a ‘free trader’.⁹³ In order to encourage production, the Government offered access to restricted building supplies, promised to defray costs and assured a guaranteed market during the war with significant enhanced

(29 July 1916): 778; Major-General Sir W. G. MacPherson, (1921): 178-9; Burroughs Wellcome Standing Orders, WF: 85/31: 1-2; W. J. Reader, (1970): 285-287.

⁸⁸ “Sugar-Further Government Action” Chemist & Druggist 85.1 (31 October 1914): 33; Later Glycerine, used for flavouring drugs and explosives was banned from use from February 1917 by the Ministry of Munitions (until January 1919) so it had to be replaced in pills by glucose or treacle. W. J. Reader, (1970): 250-1.

⁸⁹ T. E. Lescher, British Pharmaceutical Congress: “Pharmacy Today – its Responsibilities” Chemist & Druggist 127.1 (31 July 1937): 118-9.

⁹⁰ “The Manufacture of Phenacetin” Chemist & Druggist 85.2 (12 September 1914): 38; “Trade Marks- The War and the Shortage of Drugs” Chemist & Druggist 85.2 (19 September 1914): 51-2.

⁹¹ “A Proclamation Relating to Trading With the Enemy” Chemist & Druggist 85.1 (15 August 1914): 34; “The War and the Drug Trade” Pharmaceutical Journal 93 (8 August 1914): 219; “Buy Speculative” Pharmaceutical Journal 93 (15 August 1914): 255; “Prices of Drugs and Medicines” Pharmaceutical Journal 93 (15 August 1914): 246-7, 291; “War Prices” Chemist & Druggist 85.1 (1 August 1914): 48.

⁹² “Exportation of Medicines” Chemist & Druggist 85.2 (19 September 1914): 33.

⁹³ L. F. Haber, (1971): 188-191.

sales to the armed forces.⁹⁴ Further longer-term promises were less forthcoming. Early British efforts at replacing German drugs were described by Runciman to the Government on 23rd November as part “of a combined national effort on a scale which requires and justifies an exceptional measure of state encouragement”.⁹⁵

Despite vague promises of Government assistance, companies were initially reluctant to enlarge their own manufacturing plants. W. J. Bush was the first firm in Britain to make salicylic acid and its derivatives: “the beginning of a new epoch in the manufacture of fine chemicals in this country”.⁹⁶ When W. J. Bush⁹⁷ was asked to produce 5 tons of salicylic acid they stated:

“that is a very serious consideration, not only as regards salicylic acid but many other products, which we could undoubtedly manufacture profitably, just as we have been manufacturing synthetic perfumes for many years”.⁹⁸ “To what extent is a firm justified in spending capital on plant in the present circumstances? Money is scarce. No one has courage to make an expensive drug on a small scale. 18 months pre-war we put down new plant for manufacturing at £40,000 p.a. Few are the people in this country who are willing to be interested in fine chemicals as actual manufacturers”.⁹⁹

The government agreed that the expenses of plant development and advertising could be offset against royalties, but there was still reticence to put down plant to prepare complex drugs especially if, as expected, the abrogated German patents might not remain workable post-war.

Charles A. Hill of British Drug Houses summarised the complexity of the issues faced by British firms in preparing synthetic drugs when he wrote:

“As regards synthetic remedies, one cannot expect to build up in a few months, an industry, which by stress of circumstances, has grown up in Germany during two generations. The great difficulty is that each product hangs on others, the raw materials for one synthetic substance being the by-product in the manufacture of another. Not only does this dovetailing apply

⁹⁴ “The Manufacture of Phenacetin” Chemist & Druggist 85.2 (12 September 1914): 38.

⁹⁵ Hansard (House of Commons), fifth, 68, (23 November 1914), cols, 759-62.

⁹⁶ “War Prices” Chemist & Druggist 85.1 (1 August 1914): 48.

⁹⁷ Centenary Album: a Pictorial Record of Bush Worldwide Development, Establishments and Personalities During One Hundred Years of Progress 1851 – 1951 (London: W. J. Bush, 1951).

⁹⁸ “Exportation of Medicines” Chemist & Druggist 85.2 (19 September 1914): 33.

⁹⁹ “Makers and Buyers” Chemist & Druggist 85.1 (24 October 1914): 58.

to the products themselves but the apparatus and plant employed are common to many products. It would obviously not pay to put down expensive plant for the manufacture of a few products, the whole consumption of which is only a matter perhaps hundredweights, but it would easily pay a factory which would turn out a hundred products each with a consumption of some hundredweights".¹⁰⁰

Maintaining supplies of essential drugs and chemicals was too vital to be left to the uncoordinated actions of individual pharmaceutical firms, so the control of supplies was coordinated under Moulton, initially within the Ministry of Supply, then under the Ministry of Munitions, created by the Munitions of War Act of 9 June 1915.¹⁰¹ One of the chief achievements of the Ministry was the rationalisation of dye manufacturing by establishing British Dyes Ltd. in July 1915, with the purchase of a number of dye firms including Read Holliday. With a market capitalisation of £2 m. the merged company still represented only one fortieth of the value of the large German firms and excluded the largest British firm of Levinstein's, for which the low government bid was refused.¹⁰² British Dyes Ltd. provided the chemicals required for munitions, while Levinstein's concentrated on dyes, trebling their assets in two years. Levinstein's also secured the services of Prof. Arthur G. Green from Leeds University, who performed research at the College of Technology at Manchester University, and set up small research colonies at the Universities of Cambridge, Oxford, Sheffield, Bristol and the Technical colleges of Glasgow, Finsbury and Huddersfield.¹⁰³ Gradually, further politicians were drafted into the Ministry of Munitions, including the Cabinet member and free-trade supporter, Sir Alfred Mond, as the first Commissioner of Works in 1916.¹⁰⁴

4.5 British Production of Salvarsan; MRC Testing of Quality.

¹⁰⁰ C. A. Hill, "Synthetic Medical Chemicals" British Medical Journal (23 January 1915): 168.

¹⁰¹ W. J. Reader, (1970): 250-51, 258, 268-70; A. J. P. Taylor, (1988): 30-31, 34.

¹⁰² Mond was Liberal MP for Swansea, and a member of the ABCM later; W. J. Reader, (1970) I: 272, 447; E. Hutchison, Minerva 8 (1970): 392-411.

¹⁰³ M. R. Fox, (1987): 49-53.

¹⁰⁴ A. J. P. Taylor, (1988): 249; Keith Middlemass and John Barnes, (1969): 89-90.

Salvarsan was the best therapy for syphilis, which was described as “the worst scourge of war” as venereal disease affected one in every 5 of the troops.¹⁰⁵ In the case of Salvarsan there was no question over its efficacy, only whether British firms could ever produce the synthetic drug to the same degree of purity and activity as the German product. When war broke out supplies of Salvarsan from Germany soon became unobtainable in Britain.¹⁰⁶

Salvarsan had been patented in Germany on 10 June 1909 and in Britain on 22 December 1910. It was produced according to the requirements of the 1907 Patent law by the Swiss firm CIBA in Manchester and by the German firm, Meister, Lucius, & Brüning (Hoechst) at a large plant in Ellesmere Port, along with ‘Novocain’, a local anaesthetic.¹⁰⁷ The firms took advantage of the 1909 ruling that only the latter stages of production needed to be performed in Britain, using late-stage intermediates imported from Germany.¹⁰⁸ Meister, Lucius & Brüning warned at the end of August, when the patent came under threat that:

“(Salvarsan) is extremely difficult to prepare. It has to be prepared by very scientific men, in silver crucibles. Each dose has to be very carefully sterilised and very carefully weighed and is passed by the firm Meister, Lucius & Brüning who give a guarantee with every dose they send out”.¹⁰⁹

Mr. E. H. Scholl, the British-born manager of the pharmaceutical department of Meister, Lucius, Brüning at Ellesmere Port, had been based at the works in Germany before moving to the London office in 1907. He offered to make all of the Salvarsan required by Britain and gave information on stocks to Robert Morant at the National Health Insurance Commission. Members of the Committee on the supply of laboratory reagents, including

¹⁰⁵ A. J. P. Taylor, (1988): 121.

¹⁰⁶ “Manufacture of Salvarsan Products in England and France” British Medical Journal (10 April 1915): 649 - 650; W. H. Willcox, J. Webster, “The Toxicology of Salvarsan” British Medical Journal (1 April 1916): 473, 492 – 493; “Report of the Royal Commission of Venereal Disease” British Medical Journal (30 September 1916): 477.

¹⁰⁷ W. J. Reader, (1970): 265-6; Chemical Trade Journal 57 (1916) no. 1534: 329; 1535: 352-3, 358; Chemical Trade Journal 61 (1917), 1589, 367; Chemical Trade Journal 65 (1919); no.1676: 13-51.

¹⁰⁸ M. R. Fox, (1987): 50, 52.

¹⁰⁹ Chemist & Druggist (29 August 1914): 41.

staff from the National Health Insurance Commission, were sent to Ellesmere Port to evaluate production methods.¹¹⁰ They reported back that the synthesis would not be easy.

German patents for Salvarsan were so vague as to be unhelpful with regard to methods of synthesis.¹¹¹ Furthermore, the German workers, anticipating war, departed in the summer of 1914 leaving only M. Dünchmann, the Works engineer, and a man named Hummerich who sabotaged the plant, and destroyed all the records. The Ellesmere Port plant was put up for sale, but it was November 1916 before the dye manufacturer Herbert Levinstein bought it.¹¹²

The President of the American base of the Farbwerke Hoechst emphasised that he considered it impossible for either America or Britain to synthesise Salvarsan:

“I do not think there is any possibility of engaging in the manufacture of these products here, even if there were patent laws to compel the carrying out of patents in this country and manufacture goods protected under such patents. England has tried this with the result that the Germans established plants in England, where they carried out just enough of the process to cover the patent, depending upon Germany for all raw materials and intermediate products. The result is that in spite of its laws England is left high and dry. Only today I received a cable from the Manchester branch of the German plant, asking if we could send any Salvarsan to Europe for the British army”.¹¹³

He had no idea that Burroughs Wellcome had already achieved the synthesis of Salvarsan. The outbreak of the war on 4 August 1914 changed the immediate research plans of Burroughs Wellcome. They diverted resources to emergency production of extra typhoid vaccines, tetanus and diphtheria antitoxins and anti gas-gangrene sera under Alexander Glenny. There was an immediate shortage of tetanus antitoxin.¹¹⁴ Burroughs Wellcome also prepared and standardised biological preparations of digitalis, ergot, squills and strophanthin.¹¹⁵

¹¹⁰ “New Patent Rules” Chemist & Druggist 85.1 (29 August 1914): 41.

¹¹¹ “The Salvarsan Patents” Chemist & Druggist 85.2 (19 September 1914): 51.

¹¹² M. R. Fox, (1987): 42, 49-52, 55.

¹¹³ “American Druggist” British Medical Journal (26 August 1914): 85. The quote states ‘Manchester’ but must refer to Ellesmere Port.

¹¹⁴ H. J. Parish, WF: 85/20:2: 12.

¹¹⁵ Chemist & Druggist 84.3 (23 May 1914) Evans advert S xii; Evans advert “Physiological Standardisation” Chemist & Druggist 85.1 (15 August 1914) suppl iii.

They also recognised that the single most important synthetic drug denied to Britain was Salvarsan, on which work commenced immediately.¹¹⁶ Henry Wellcome applied for the suspension of three Salvarsan patents on 17 September 1914, by which time his chemists at the WCRL had already synthesised a small supply of 10 grams of Salvarsan. He insisted on being granted the full term of the patent “so as to recoup the expense of laying down plant”.¹¹⁷ The Germans were disbelieving when they heard that Burroughs Wellcome had applied for the Salvarsan patents, complaining of unauthorised use and that it would be a danger to the public”. They requested royalties, insisting that it was not sold under its trade name of Salvarsan or referred to as ‘606’.¹¹⁸ Moreover, they were “very eager to know how the English firm will surmount the great difficulties in the preparation and whether the patients will have to pay for the “business thoroughness with grievous bodily harm”.¹¹⁹ They knew that Burroughs Wellcome had begun incorporating German lines as Tabloids in August 1896 and that the laboratory staff had synthesised several alkaloids on a small scale, but the only previous evidence of the skills required to produce an arsenical on a commercial scale was limited production of a version of Atoxyl, branded as Kharsin, produced commercially from March 1908.¹²⁰ Nevertheless, Pyman, Reynolds, Barrowcliff and Remfry had prepared further aromatic arsinic and arsonic acids during 1908 and many other workers were involved in small- scale synthetic projects.¹²¹

The Government were keen to secure further supplies of Salvarsan, but no other British firms were yet able to make it, reflecting the fact that others had not invested in synthetic chemistry as Burroughs Wellcome had. During the hearings for the next application in October, the comment was made by the German representative that: “if incompetent men were to make the drug, the chief industry to benefit would be that of

¹¹⁶ A. Duckworth, “Rise of the Pharmaceutical Industry” Chemist & Druggist 172 Centenary number (10 November 1959): 127-139; Diphtheria antitoxin increased from 240 mUnits in 1910 to 480mU in 1915 and 640mU in 1920, WF: 84//7:12-13.

¹¹⁷ “The Salvarsan Patents” Chemist & Druggist 85.2 (19 September 1914): 51.

¹¹⁸ *ibid.*

¹¹⁹ Quoted from Chemist & Druggist 85.2 (14 November 1914): 49.

¹²⁰ Mr Hogg, History of the Works vol. III, WF: S/G/145.

¹²¹ H. King, “Frank Lee Pyman” Biographical Memoirs of Fellows of the Royal Society 4 (1944): 684.

grave-digging,” such was the concern over impurities and side effects.¹²² A further British license for the production of Salvarsan was granted to the Société Anonyme des Etablissements Poulenc Frères of Paris, the largest French firm, on 11 November 1914, on the condition that their product was sold through May and Baker in England under the names of Arsenobenzol-Billon and Novarsenobenzol-Billon.¹²³ The French patent law specifically excluded protection of medicines and as a result workers at the Pasteur Institute had already prepared the synthetic arsenical, ‘Atoxyl’ in 1907.¹²⁴ This experience helped Poulenc to produce Salvarsan.

A research team was established at Burroughs Wellcome specifically to manufacture Salvarsan commercially.¹²⁵ The first full batch of 46 grams was produced on 23 October 1914, though it was poorly soluble.¹²⁶ By 7 November 1914 a continuous production process was in place. Pyman and his team at the Experimental laboratory of the WCRL tested early samples for solubility and toxicity, while 2 vials of the first batch were delivered to the Head Office in January 1915 and sent to William Henry Willcox FRCP, who was Lt. Colonel in the Royal Army Medical Corps, head of the outpatient clinic at St. Mary’s, and Senior Scientific Analyst to the Home Office.¹²⁷ Dr Jowett received a small sample for further tests and 6 vials were sent to “a doctor for a c. (clinical) trial”. Over the

¹²² “German Patents and Trade Marks” Pharmaceutical Journal 93 (24 October 1914): 601.

¹²³ May & Baker collaborated with Poulenc pre-war concerning the pricing of iodides, bismuth, mercurials and quinine, “German Patents and Trade Marks-Salvarsan” Pharmaceutical Journal 93 (14 November 1914): 675. May & Baker also sold Epsom salts, bath salts, sodium sulphate and several German imports. British Medical Journal (13 August 1914) Suppl; F. H. Carr, “Fine Chemicals: Their Manufacture in Relation to the British Chemical Industry” Chemist & Druggist 88.4 (29 July 1916): 778-9; C. A. Hill, T. D. Morson, “The British Association – The Synthetic Chemical Industry” Chemist & Druggist 88.4 (9 September 1916): 951-2.

¹²⁴ Walter Sneader, Drug Discovery: the Evolution of Modern Medicines (London: John Wiley, 1985): 252-3.

¹²⁵ These included Frank Pyman, Robert Fargher, Hubert William Bentley Clewer, Edward Jones, Alfred Bacharach, Harold King, Robert Reginald Baxter, Edward Charles Snell Jones, WF: Box 25. Pyman and Clewer worked on neosalvarsan from November 1914. WF: YL Box 46 Works Records.

¹²⁶ G. E. Pearson, A Chronology of the History of Burroughs Wellcome & Co. 1878-1936 (typescript), WF: 88/24:41d: 12.

¹²⁷ “The Toxicology of Salvarsan: Dioxydiamido-arsenobenzol”(Salvarsan or Kharsivan) British Medical Journal (1 April 1916): 473-8.

next year and a half, over 130 further batches were sent to Dr Lees in the analytical department.¹²⁸

Batches of Salvarsan were prepared at the Works under the direction of Francis Carr until the end of 1914. However, just when Burroughs Wellcome was getting to grips with synthesis of Salvarsan on a large scale, several of the staff involved left the company. At the end of November 1914 Dr. Power retired as Director of the WCRL to return to the USA as Director of the Phytochemical laboratory at the Government's Bureau of Chemistry.¹²⁹ Power was awarded a gold medal by Henry Wellcome for over 18 years outstanding service as Director of the WPRL. Frank Pyman from the Experimental Department was given the added responsibility to take over the preparation of Salvarsan and neosalvarsan from 1 December 1914.¹³⁰

Francis Carr decided to leave Burroughs Wellcome at the same time. In his own account Carr had written to Henry Wellcome without success on several occasions asking for a grant of £10,000 to extend the Works, "for making good the absence of fine chemicals then only obtainable in Germany".¹³¹ The final stimulus may have been that he was upset at the appointment of Pyman as the replacement for Power. Carr contacted Jesse Boot who was prepared to offer whatever he needed to establish a synthetic drug capacity at Boots Pure Drug Company. Carr was appointed as Director of Boots analytical department and Chief Chemist and he took a significant number of key staff from Burroughs Wellcome with him. I will return shortly to examine his work at Boots, and details of the staff that moved with him, and the implications for Burroughs Wellcome. Having resolved the means of producing Salvarsan, Jowett and Pyman turned their

¹²⁸ WF: 90/31 Kharsivan QA record book (23 October 1914 to 17 November 1915), Accession Box 160.

¹²⁹ "Staff at WCRL", WF: Box 25; "Evans" Chemist & Druggist 88.4 (29 July 1916): 775.

¹³⁰ "Personalities- Frederick B. Power Retirement" Chemist & Druggist 85.2 (7 November 1914): 15; WF: Box 25; Power maintained contact with his former colleagues, Dale, Henry and Tutin as late as 1925 e.g. Dale to Power, (25 June 1924). Henry to Power, (27 January 1925); Frank Tutin (University of Bristol) to Power (7 July 1925), WF: 88/94: 49.

¹³¹ Conversations with F. H. Carr by A. E. Guenther, B.CARR FH 6, Imperial College.

attention to neosalvarsan from 1 November 1914 to 7 January 1915.¹³² Some of the batches of Salvarsan made in December were kept for production of neosalvarsan.¹³³

With Power departing and the loss of Carr, Burroughs Wellcome had to re-deploy staff to fill the gaps. John Augustus Goodson, who had received his chemical training at Finsbury Technical College under Raphael Meldola, had worked at the Wellcome Bureau in Khartoum since 1906. He transferred to the WCRL in December 1914 to continue production of Salvarsan as well as benzyl chloride, and the cinchona derivative, hydroquinone.¹³⁴ A new chemical building was completed in December 1914 to extend the drug production facilities.¹³⁵ The chemists at the WCRL were organised into teams to prepare replacements of German drugs.¹³⁶ Of the team remaining, only a few were specifically named as involved in Salvarsan production. These included Robert Fargher D.Sc. and Robert R. Baxter, both of whom had trained in Manchester under W. H. Perkin.¹³⁷ Hubert William Bentley Clewer (at Burroughs Wellcome 1914-18) and Edward C. S. Jones (1913-18) were involved in neosalvarsan analyses between November 1914 and January 1915.¹³⁸

A team of operatives had supported Carr at the Works and it seems that this team was unaffected by his move. Jowett, who had originally been line manager over Carr was given the task of overseeing the Works in addition to his other duties and he represented the firm in detailed discussions with the Board of Trade over the quality of Salvarsan preparations, though it was ultimately the responsibility of George Pearson as General Manager.

¹³² Works History, Staff Records, WF: YL 46.

¹³³ WF: Records of Kharsivan – this was uncatalogued at the time of my research. - Record of batches 1-132.

¹³⁴ Works History, Staff Records, WF: YL 46.

¹³⁵ This also produced salicylic acid from January 1915, sodium salicylate from March 1916, phenacetin from May and Aspirin from September 1916: G. E. Pearson, (1936), typescript, WF: 88/24:41d: 12.

¹³⁶ The Laboratory books of 41 chemists detail the extent of chemical synthetic work undertaken: WF: 85/9 bundles 5-8 Accession box 5.

¹³⁷ Staff at WCRL, WF: Box 25.

¹³⁸ Hubert Clewer also worked on digitalis, chaulmoogra oil, emetine and pyramidone and Jones also produced digitalis and salicylic acid. Fargher produced alkaloids, pilosine derivatives, hydroquinone, benzyl chloride, lysidine and salol, Works History, Staff Records, WF: YL Box 46.

Although Burroughs Wellcome achieved the manufacture of Salvarsan, the question remained as to whether they had avoided the noxious impurities and had secured a product with similar efficacy to German preparations. The synthetic procedure for Salvarsan was complex and it was not easy to prevent the formation of intensely poisonous by-products. Ehrlich in Berlin had routinely tested the activity, strength and safety in animals of each batch of Salvarsan made by Hoechst.¹³⁹ Burroughs Wellcome realised that they would also have to perform such tests before human use. However, many of their expert staff had moved to the newly established MRC and they had to turn to them to perform physiological testing.¹⁴⁰

4.6 The MRC and the First Salvarsan Committee.

The MRC had been founded in 1913 as a result of research funding arising from the 1911 National Insurance Act. The MRC Executive Committee appointed in 1914, included six professional and three lay members: it was chaired by Lord Moulton of Bath and included Christopher Addison M.P., formerly Professor of Anatomy and Dean of St. Bartholomew's,¹⁴¹ who was to become the first Minister of Health in 1919; Waldorf Astor, who chaired the Departmental Committee on Tuberculosis from 1913; T. Clifford Allbutt, Regius Professor of Physic at the University of Cambridge; the Leicester surgeon Mr Charles John Bond; William Bulloch F.R.S, Professor of Bacteriology at the University of London and at the London Hospital¹⁴²; Matthew Hay, Professor of Forensic Medicine and Public Health at the University of Aberdeen; Frederick Gowland Hopkins, founder of

¹³⁹ W. S. Feldberg, "Henry Hallett Dale 1875 – 1968" Biographical Memoirs of Fellows of the Royal Society 16 (1970): 106.

¹⁴⁰ "British Made Salvarsan" Pharmaceutical Journal 94 (17 April 1915): 536.

¹⁴¹ Dr. Christopher Addison was M.P. for Hoxton and Professor of Anatomy at University College and Sheffield. In the War he was Minister for Reconstruction from 1917 and President of the Local Government Board. He went on to arrange the charter for the MRC and was the first Minister of Health, establishing a Committee with Lord Athlone on the provision of postgraduate medical education. Joan Austoker and Linda Bryder (eds.), (1989): 24, 222.

¹⁴² Sir John Ledingham, "William Bulloch" Obituary Notices of Fellows of the Royal Society 3 (1941) 819-52.

Biochemistry at the University of Cambridge;¹⁴³ and the bacteriologist Sir William Boog Leishman. Walter Morley Fletcher from Cambridge was appointed as Secretary.¹⁴⁴

At Frederick Hopkins's suggestion, Henry Dale was proposed for the post of Director of the Department of Biochemistry and Physiology at the new MRC central laboratories, the National Institute of Medical Research (NIMR) where he rejoined George Barger.¹⁴⁵ Although Dale had enjoyed his time at Burroughs Wellcome, he was displeased with Wellcome's reorganisation in 1913, placing Andrew Balfour as Director of the Wellcome Scientific Bureau with overall responsibility for all of the laboratories. Dale felt that as a result the laboratories would be less independent.¹⁴⁶

No sooner was the MRC established on 1 July than the war broke out in August "with what at the time only seemed a few days notice".¹⁴⁷ Barger and Dale returned rapidly from a visit to Germany, and soon after Barger moved to Edinburgh. Almroth Wright decided not to move from St. Mary's to the NIMR.¹⁴⁸ Of his staff only Leonard Colebrook¹⁴⁹ moved to the NIMR, under Captain S. R. Douglas.¹⁵⁰ W. E. Gye,¹⁵¹ previously at the Imperial Cancer Research Fund, was added.

¹⁴³ Sir H. Dale, "Frederick Gowland Hopkins" Obituary Notices of Fellows of the Royal Society 6 (1948) 115-145.

¹⁴⁴ L. Bryder in J. Austoker and L. Bryder (eds.), (1989): 5-6.

¹⁴⁵ Barger was Professor of Chemistry at Goldsmiths College, New Cross from 1909 and at Royal Holloway College from 1913. He served the Council of the Chemical Society 1913-7. In 1919 he took the Chair of Chemistry in Relation to Medicine at Edinburgh where he remained until a year before his death when he became Regius Professor of Chemistry at the University of Glasgow. Sir H. H. Dale, "G. Barger", Biographical Memoirs of Fellows of the Royal Society (1940) 3: 63-85.

¹⁴⁶ Lieutenant Colonel Andrew Balfour had been first Director of the Tropical laboratories in Khartoum from 1902. Dale questioned Pearson on his plans: Dale Archives, Royal Society, HD 143.6: 67.

¹⁴⁷ Dale Archives, Royal Society, HD 47. 13.144.

¹⁴⁸ Comments on a lecture by Sir C. Harrington, 23 November 1963. Dale Archives, Royal Society, HD 47.12.12.

¹⁴⁹ C. L. Oakley, "Leonard Colebrook" Biographical Memoirs of Fellows of the Royal Society 17 (1971) 17: 91-138.

¹⁵⁰ P. Laidlaw, "Stewart Ranken Douglas" Biographical Memoirs of Fellows of the Royal Society (1935) 1: 569-76.

¹⁵¹ C. H. Andrewes, "William Ewart Gye" Biographical Memoirs of Fellows of the Royal Society 8 (1953): 419-30; J. Austoker and L. Bryder in J. Austoker and L. Bryder (eds.), (1989): 42.

The movement of Burroughs Wellcome staff to the MRC decimated the firm's capacity to perform standardisation work, but left them well placed to collaborate with the MRC.¹⁵² Fortunately, the previous work at the Wellcome laboratories attracted further high calibre researchers. Joshua Harold Burn joined Burroughs Wellcome from Cambridge in January 1914¹⁵³ and continued Jowett and Pyman's research on nicotine and pilocarpine.¹⁵⁴ However, with the outbreak of war, Burn also left to register as a medical student, and to serve in France.¹⁵⁵

From their foundation, the MRC planned a central institute for testing drugs, along the lines of the Pasteur Institute in Paris, founded in 1888, the Institute Robert Koch founded in Berlin in 1891, and Rockefeller Institute founded in 1901 in New York. One possibility considered and rejected was at the Lister Institute for Preventative Medicine, founded in 1891. With the outbreak of the War, the requirement for testing biological and synthetic drugs took on a new urgency, but as Mount Vernon Hospital, the planned site for the NIMR was used as a military hospital, Dale had to take up temporary residence at the Lister Institute. Dale took with him Arthur J. Ewins and Patrick P. Laidlaw and even his administrator from Burroughs Wellcome.¹⁵⁶

In 1909 the Pharmacopoeia Committee had suggested that there should be a public institution for the pharmacological standardisation of potent drugs and serums. Whereas the Pharmacopoeia was based upon simple tests that analysts could perform, the newer drugs could not be assayed by chemical means. The MRC gave an early indication that they wanted to become involved in biological testing of drugs with "A proposal that the Committee should undertake the examination of Salvarsan manufactured in England under

¹⁵² A further researcher, Harold King joined the MRC from Burroughs Wellcome in 1919; Sir Charles Harrington, "H. King" Biographical Memoirs of Fellows of the Royal Society 1956) 2: 157-71.

¹⁵³ Burn studied physiology at Emanuel College, Cambridge in 1909 under F. Gowland Hopkins and joined the WPRL on 1 January 1914: E. Bülbring, J. M. Walker, "J. H. Burn" Biographical Memoirs of Fellows of the Royal Society (1981): 45-89.

¹⁵⁴ J. H. Burn, H. H. Dale, "The Action of Certain Quaternary Ammonium Bases", Journal of Pharmacology 6 (1915): 305.

¹⁵⁵ E. Bülbring, J. M. Walker, "J. H. Burn" (1981): 45-89.

¹⁵⁶ Laidlaw's post at the National Institute of Medical Research came with a salary of £750 per annum: MRC Annual Reports 1914-20; MRC Committee Minutes II, (16 December 1921): 167.

license from the Board of Trade,” and this request was referred to a sub-committee including Fletcher Moulton, Frederick Gowland Hopkins, and William Bulloch; as a result the Salvarsan committee met for the first time on 29 October 1914.¹⁵⁷ The proposal for MRC involvement was accepted on 10 December 1914 with the condition that the MRC name appeared on any vials tested by them. This suited Burroughs Wellcome as it could be exploited in their advertisements.¹⁵⁸ Pre-War there had been no formalised testing of drugs in Britain. The MRC staff made responsible for the testing “of Salvarsan and the analogous group of arsenicals” were Henry Dale, who wrote: “with Ewins I was immediately plunged into investigations required to enable a British manufacturer to produce the important drug, which had formerly been supplied entirely from Germany”.¹⁵⁹ Ewins concentrated upon examining arsenic impurities in samples of Salvarsan and other organic arsenicals.¹⁶⁰

From the outset Dale doubted the validity of the simple tests performed by Ehrlich on Salvarsan, in which a standard amount of drug was injected into 10 mice and as long as 8 or more survived the batch was passed. Dale found that variable results were achieved even by injecting the same batch into multiple groups of rats, so he modified the assays to take more account of biological variation and applied the statistical techniques that Glenny had established at Burroughs Wellcome in 1910-12 during work on the variable response of guinea pigs to diphtheria antitoxin. He also measured therapeutic effects, especially for the less toxic neosalvarsan, for which clinical relapses had been noted, despite passing Ehrlich’s tests. Dale learned how to produce an infection in mice that was sensitive to Salvarsan so that curative action could be determined.¹⁶¹

Occasional batches were substandard and this further established the case for MRC control of the quality of the sophisticated synthetic and biological drugs.¹⁶² By April 1915 the MRC were able to state: “at an early date the experimental work which has been done

¹⁵⁷ MRC Minutes I, (29 October 1914): 4.

¹⁵⁸ MRC Minutes I, (10 December 1914).

¹⁵⁹ Dale Archives, 93 HD 143.11: 3.

¹⁶⁰ A. J. Ewins, “The Estimation of Arsenic in Organic Compounds” *J. Chemical Society* 109 (1916): 1355.

¹⁶¹ W. S. Feldberg, “Henry Hallett Dale” *Biographical Memoirs of Fellows of the Royal Society* 16 (1970): 106-7.

¹⁶² Dale Archives 93HD, NIMR 47.13.144.

under their direction showed that the problem of the successful manufacture of Salvarsan compounds in England and France had been solved".¹⁶³ The May & Baker version of Salvarsan passed every time, but occasionally the Burroughs Wellcome version failed.¹⁶⁴ The MRC were keen to gain a better understanding of factors influencing the potency and safety of the new British synthetic drugs and when batches of Burroughs Wellcome's Kharsivan were released, the drug was tested in a large number of patients.¹⁶⁵ Willcox at the Home Office emphasised that Kharsivan was "practically identical in its physiological and therapeutic effects with Salvarsan" (the German drug). However, he acknowledged that "substitutions that are just as good as the original articles are looked upon with disfavour in this country" because we "regard German chemists as superior in ability to our own".¹⁶⁶ In other words, further work was needed to convince British doctors that the British synthetic drugs were as good as the German versions. Following their experience with Salvarsan, the MRC extended their laboratory testing to include various sera and antitoxins, which had previously been imported.¹⁶⁷ However, the questions that continued to be asked related to the clinical efficacy and safety of Salvarsan, and I will return to this as the reason behind the establishment of a second Salvarsan Committee. In the meantime there were significant changes in the structure of the British Pharmaceutical Industry.

4.7 Technology Transfer from Burroughs Wellcome to Boots and May & Baker.

As we have seen, at the outbreak of the War only Burroughs Wellcome had significant experience of complex chemical synthesis and even then primarily on a small scale. Burroughs Wellcome had experienced chemists such as Power, Barger and Pyman to work out the synthetic routes, but they also had gained experience in scaling up processes through Carr and Jowett. Other commercial firms in Britain were relatively small concerns; unable individually to bear the costs of hiring a large specialised and dedicated research and

¹⁶³ "British Made Salvarsan" *Pharmaceutical Journal* 94 (17 April 1915): 536.

¹⁶⁴ Dale Archives, 93 HD 143.11.

¹⁶⁵ H. C. Lucey, "The Therapeutic and Reaction Effects of Kharsivan. A Record of 600 Injections" *British Medical Journal* (29 April 1916): 614-6.

¹⁶⁶ W. H. Willcox, J. Webster, "Toxicology of Salvarsan" *British Medical Journal* (1 April 1916): 473-8.

¹⁶⁷ MRC Annual Report, 1914-15, (London: HMSO, 1916): 42-44.

drug development staff.¹⁶⁸ Even the larger firms had difficulty in attracting the few available chemists with experience of large-scale drug production. Chemistry in industry did not offer a rewarding career as “pay was generally inadequate and the employer looked too often only for immediate profit”.¹⁶⁹ Thus, it was a significant loss even when supporting staff such as Mr. H. Browning, who had 3 years experience at the WCRL, left in September 1914. Hiring experienced chemists from other industries was not an attractive option, as they did not have the experience of tableting or working under sterile conditions.

The retail trade of Boots Pure Drug Co. had expanded rapidly from 33 shops in 1893 to 250 by the turn of the century; and assisted by the passing of the Pharmacy Act in 1908 and the National Insurance Act of 1911, it had 560 shops in 1913, with takings of £2.5m per annum. However, they experienced a contraction of certain areas of their business at the outbreak of the war. Jesse Boot was a very rich and influential man, friendly with both Lloyd George and Christopher Addison, and a donor to Liberal Party funds.¹⁷⁰ Boot realised that the void left by the exclusion of German drugs, especially synthetics and the increased needs of War gave the potential for large profits to be made.

However, in order to achieve this he had to find an experienced manufacturing chemist. Francis Carr was persuaded to join Boots and he recruited five other Burroughs Wellcome staff, including his close assistant Marmaduke Barrowcliff, a plant engineer and a foreman.¹⁷¹ Francis Carr had first met Jesse Boot when Frank Pyman’s daughter married his son John Boot. As recently as 1909 Carr had been on a salary of only £250 p.a. and had two daughters undergoing education, so he had to supplement his salary by with fees as an external examiner for the University of London. Boot offered Carr not only an increased salary, but also a free hand in the laboratory and production design, whereas at Burroughs Wellcome, Carr had been under Jowett and also Power, and from November 1914 was to have been under Pyman.

¹⁶⁸ “Synthetic Medicinal Chemicals” British Medical Journal (23 January 1915): 168.

¹⁶⁹ W. Tilden, British Medical Journal (23 January 1915): 168.

¹⁷⁰ Chemistry & Industry (23 February 1963): 303.

¹⁷¹ S. Chapman, (1974): 96-98; S. A. B. Kipping, “The Research Department of Boots Pure Drug Co. Ltd.” Chemistry & Industry (23 February 1961): 302-10; W. H. Sims, “Notes, 8 November 1963” Boots library. Correspondence from Boots librarian.

At the start of the war Boots had been heavily advertising war-related low technology products such as anti-fly spray, vermin powders and compressed medicinals “for the men at the front”.¹⁷² Carr was a good friend of E. F. Harrison who had performed research with him under Dunstan, before taking on the analyst role at Burroughs Wellcome and then acting as a consultant and analysing patent medicines for the BMA. Harrison had joined the army as a private, but was promoted to corporal when the RAMC required an analyst at Millbank to quantify the threats of gas warfare and Harrison became Superintendent of the Anti-gas Department, that was a section of the Chemical and Warfare Department. His team tested a series of wide range of gases including chlorine, cyanogen bromide, phosgene, and mustard gas and the means of neutralising them. Boot put his staff behind developing gas masks containing absorbent materials.¹⁷³ At least 900 girls were employed in manufacturing box respirators, packed with absorbing granules and at one stage they produced 90,000 a week. Chapman wrote that “Elated with the success in securing Carr, Boot took the front page of the *Daily Mail* on 15 October and boasted: German science knows no secrets from my analysts”.¹⁷⁴ Whether he knew by then that he had secured Carr is not clear, but the records at Burroughs Wellcome show that Carr did not depart until 10 November 1914.¹⁷⁵ At the end of 1914 Boots extended their laboratories and built a new fine chemical manufacturing plant, which opened under Carr’s guidance in 1915 and produced aspirin, disinfectants, saccharin and iodine tinctures. Boot proclaimed “we have made more progress than any other firm... not previously manufacturing in this country”.¹⁷⁶

In order to fuel this expansion, Carr sought out Burroughs Wellcome staff members that were familiar with all of his former firm’s key secret processes. Carr himself knew the constitution of the firm’s bases, the solutions used in the Tabloid department, and the

¹⁷² C. Weir, *Jesse Boot of Nottingham* (Nottingham: Boots, 1994): 55-59.

¹⁷³ F. H. Carr, “Harrison Memorial Lecture”, *Pharmaceutical Journal* 103 (26 July 1919): 93-99.

¹⁷⁴ S. D. Chapman, (1974): 96.

¹⁷⁵ Staff Records, WF S/G/145.

¹⁷⁶ S. D. Chapman: (1974): 96.

processes used; he had practical experience in manufacturing of all of their main lines.¹⁷⁷ Many staff members were loyal supporters of Carr, who appears to have been popular. W. F. Thompson had been at Burroughs Wellcome for 17 years as a laboratory assistant to Carr and had also followed him from the Pharmaceutical Society and the Imperial Institute, where they had collaborated for a further 3 years.¹⁷⁸ S. C. Fidler, an engineer who joined Boots in February of 1915, had repaired and built new compressing machines, punches and eyes at Burroughs Wellcome from 1907 and was familiar with the organisation of the compressing room, and which machines to use for the various drugs: H. E. Wilson, who became Head of the Boots Chemical Department in May 1915 had been at Burroughs Wellcome since 1903 producing quinine salts, hexamines, cinchona, phenacetin and some basic salts.¹⁷⁹ F. C. Chapman was a warehouseman in the drug stock room of Burroughs Wellcome from 1897 and he saw all the formulae for compressed drugs and knew the number codes of the bases and solutions. He previously worked in the granulating section before moving to Boots in July 1915. W. H. Porter was an experienced tea tester, responsible for compression of tea into tablets using unique rotary machinery. He had been at Burroughs Wellcome since 1896 until he moved to Boots in October 1915. A document in the archives at Burroughs Wellcome entitled "Formulae and secret processes" discusses the impact that the loss of Carr and his handpicked colleagues had on Burroughs Wellcome.¹⁸⁰

The acquisition of Chapman and Porter:

"Enables a competing firm in whose services they are to obtain almost complete information as to the firm's secret processes and specially knowledge in the manufacture of compressed drugs. The combination of Carr with Chapman enables them to produce granules according to Burroughs Wellcome & Company formulae and the acquisition of Fidler enables them to use similar machines and punches and eyes whilst the addition of Porter enables them to obtain tea of a similar character to that used by Burroughs Wellcome & Company and to compress it on a machine,

¹⁷⁷ H. A. D. Jowett "Memo on Secret Processes", BA S/G/49, (13 January 1916), File 85; "Report from Various Sources re. 'B' affair - Boots Headhunting" Burroughs Wellcome Staff, 1915, WF Box 10.

¹⁷⁸ Works Records, WF: Box 25.

¹⁷⁹ Re. "Secret Processes", "Mr. Carr might deny this knowledge but H. E. Wilson could not, having actually made the solutions". WF: D3: DW Box 15, BA S/G/49. He had charge of the formulae books, (12 January 1916). WF Box 10; WF: D3.

¹⁸⁰ "Re: Formulae and Secret processes", WF: YL Box 25, Works Records.

the design of which is entirely due to Burroughs Wellcome and Company”.¹⁸¹

The internal enquiry held by Burroughs concluded that:

“The acquisition of Carr, Wilson and Thompson by a firm would enable them to obtain and work the more important secret processes worked out by Burroughs Wellcome & Co. Mr. Carr, having the general knowledge of all the processes, Wilson being acquainted with the manufacture of quinine salts and glycerophosphates, chloroform and possibly organics, while Thompson would supply the detailed practical knowledge for the manufacture of alkaloids”.¹⁸²

By this time Burroughs Wellcome had produced several alkaloids and synthetic drugs.¹⁸³ Thompson had produced solanaceous alkaloids, eserine, emetine, pilocarpine, hydrastine, homatropine, cocaine, and ergotoxine.¹⁸⁴ Boots would now be able to make all of these. Boots themselves had been hit hard by the loss of staff to the War, but the acquisitions from Burroughs Wellcome allowed them to restructure their business along the Burroughs Wellcome manufacturing model, though not as yet establishing their own laboratory research facilities.¹⁸⁵ The Director of Boots and manager of the chemical department at the time, Mr. H. B. Holthouse, recruited further chemists in 1916, including Belgian refugees.¹⁸⁶ He also recruited W. H. Sims who gave a vivid account of his early time at the company. Sims worked initially as an assistant to Thompson, preparing alkaloids and glucosides of Digitalis.¹⁸⁷

It took time for Boots to establish their new manufacturing capacity but they produced the antiseptic Chloramine T in 1916 and expanded their factory further during

¹⁸¹ “Reports from Various Sources re. 'B' Affair” 1915, WF: Box 10.

¹⁸² “Reports from Various Sources re. 'B' Affair” 1915, WF: Box 10.

¹⁸³ Fargher produced alkaloids, pilosine derivatives, hydroquinone, benzyl chloride, lysidine and salol. Edward Jones produced digitalis and salicylic acid. Hubert William Bentley Clewer, (1914-18) worked on digitalis, chaulmoogra, emetine and pyramidone. Pyman and Clewer worked on neosalvarsan from November 1914, WF: YL Box 25, Works Records.

¹⁸⁴ F. L. Pyman, “War Work at the WCRL”, WF: Box 25 DW.

¹⁸⁵ C. Weir, (1994): 56.

¹⁸⁶ Sims worked with C. A. Hudson, F. R. Parkin, and F. A. H. Stowell prepared hyoscine and homatropine. W. H. Sims, “Notes, 8 November 1963”, Correspondence from J. M. Leverton, Librarian at Boots Drug Company; S. D. Chapman, (1974): 96; C. C. Weir, (1994): 59.

¹⁸⁷ W. H. Sims, “Notes”, (8 November 1963).

1917 when they spent £200,000 on new buildings and laboratories and apparatus, built under government license to produce aspirin, phenacetin and atropine, claiming that phenacetin production would soon be large enough “to supply almost entirely the normal British demand”.¹⁸⁸ The first of three large extractors was installed in the chemical department to extract atropine; the wartime production reached 400 ounces per week. In order to meet these demands it was common for staff to work 12 hours each day and at weekends.¹⁸⁹ In preparing synthetic ‘Adalin’ (di-ethylbromoacetyl-urea) and ‘Flavine’ as safe wound antiseptics, Carr collaborated with Prof. F. S. Kipping at University College, Nottingham, whose son was a chemist at Boots.¹⁹⁰ Carr initially tried to make the antiseptics by methods not covered by the patents, but after failing to do so he asked to be allowed to work the patents. He initially made a few pounds and found them chemically and physiologically the same as the German versions; he was eventually able to make 40-50 lbs. per week.¹⁹¹ Once successful, Boots applied to the Board of Trade for permission to adopt the patented techniques to produce further new drugs.¹⁹² Thus, acriflavine cream (Burnol) was produced as well as large quantities of synthetic aspirin, phenacetin, atropine, saccharin and various alkaloids, chloroform, and Lysol. Boots produced Lewisite, formaldehyde and finely divided bismuth and became the most significant British pharmaceutical manufacturer after Burroughs Wellcome.¹⁹³

As Boots were encouraged by early wartime success, Carr attracted further Burroughs Wellcome staff including an expert in tablet manufacture, an authority on

¹⁸⁸ “The Report of the Royal Commission on Venereal Diseases” British Medical Journal (11 March 1916): 386-7.

¹⁸⁹ W. H. Sims, “Notes”, (8 November 1963): 2: Boots library.

¹⁹⁰ S. A. B. Kipping, “The Research Department of Boots Pure Drug Co. Ltd.” Chemistry & Industry (23 February 1961): 302-10; C. H. Browning, R. Gulbransen, E. L. Kennaway, L. H. D. Thornton, “Flavine and Brilliant Green, Powerful Antiseptics with Low Toxicity for the Tissues; their Use in the Treatment of Infected Wounds” British Medical Journal (20 January 1917): 73-78.

¹⁹¹ F. H. Carr, “British Chemical Industry” Chemist & Druggist 88.4 (29 July 1916): 799-800.

¹⁹² “The Manufacture of Adalin” Chemist & Druggist 89.1 (27 January 1917): 106.

¹⁹³ H. D. Dakin, J. B. Cohen, J. Kenyon, “Studies in Antiseptics II: on Chloramine; its Preparation, Properties and Use” British Medical Journal (29 January 1916): 160-2; H. D. Dakin, E. K. Dunham, A Handbook on Antiseptics (New York: MacMillan, 1918): 46;

pharmaceutics; and five more chemists from Leeds University including A. Nutter Smith (tablets), B. A. Bull (pharmaceuticals) and Dr. Marshall who had trained under Professor Arthur G. Green.¹⁹⁴ At the end of the war Francis Carr was awarded the C.B.E. for his team's wartime contributions.¹⁹⁵

Burroughs Wellcome had tried to protect themselves from further staff poaching by ensuring that individuals preparing Tabloids received the ingredients as A and B and were not familiar with the drug constitutions. The contract of Frederic Pickworth, who worked briefly as an analyst at Dartford in 1913 before going to medical school, exemplifies the care taken by Burroughs Wellcome; it forced him to "keep as a solemn secret all formulae and processes, structure and working of machinery". He had to promise not to sell or copy machinery, and on departure had to surrender all books and documents, and drawings of apparatus and agree not to imitate products.¹⁹⁶ They had not envisaged the wholesale plunder of staff led by the former Works manager. Frank Tutin made salicylic acid, but went to the MRC in October 1915. Alfred Louis Bacharach, who had joined the WCRL in February 1916 and prepared antiseptic cresols, local anaesthetics and salicylic acid, was persuaded to join Glaxo in 1920.

Harold King, who filled the gap vacated by Ewins, had graduated with first class honours in chemistry from University College, Bangor and joined the WPRL in 1912, collaborating with Dale and Ewins on alkaloids and with Barger, who had just left for Goldsmiths College.¹⁹⁷ King moved to the Experimental laboratory of the WCRL at Dartford under Pyman on 30 September 1915 and produced salicylic acid, and Aspirin by

"The Report of the Royal Commission on Venereal Diseases" British Medical Journal (11 March 1916): 386-7.

¹⁹⁴ S. Chapman, (1974): 96 – 97.

¹⁹⁵ Carr received the C.B.E. while other university chemists were awarded an M.B.E. or O.B.E.; C. Weir, (1994): 59.

¹⁹⁶ F. A. Pickworth, born 31 August 1889, B. Sc 1913, qualified analyst 1914, died 22 October 1967, WF: 86/68; "Obituary, F. A. Pickworth" British Medical Journal (11 November 1967): 363; "Obituary, F. A. Pickworth" British Medical Journal (2 December 1967): 559; "Obituary, F. A. Pickworth" British Medical Journal (10 February 1968): 387. The quote is from "Chemists, F. A. Pickworth 1911-17, WF: 86/68

¹⁹⁷ H. H. Dale, "G. Barger", (1940) 3: 63-85.

an economic process.¹⁹⁸ He produced methanol from acetone, and prepared glycerophosphates and their salts, acetyl salicylic acid and digitalis.

The first commercial batch of the 'Kharsivan' version of Salvarsan produced at Temple Hill was in January 1917, and the MRC team of Fletcher, Dale and Harrison visited the site in May 1917.¹⁹⁹ R. L. O'Brien at the WPRL wrote in February 1917, "I am sorry that I am again without any pharmacological assistant" and "it is impossible to do any tests for several weeks".²⁰⁰

May & Baker also benefited from the expertise of a former Burroughs Wellcome member of staff when they began their own production of arsenicals. May & Baker asked the permission of Dale to approach his "invaluable" Ewins who had "an exceptional promptitude in recognising possibilities of practical developments from new discoveries made elsewhere".²⁰¹ Following their success with Salvarsan, May & Baker built a factory at Bell Lane, Wandsworth, with the help of Poulenc of France, specifically for the synthesis of Salvarsan. In July 1917 Arthur J. Ewins, who had spent fifteen years at Burroughs Wellcome, was appointed as chief chemist and Director, responsible for their newly established research laboratories.²⁰² From 1917 the manufacture was under the supervision of a pharmacist, Charles Gilling who spent time in France learning the procedures. As agreed with Burroughs Wellcome, batches that passed were also given labels bearing "by authority of the MRC".²⁰³

Thus, the war marked a turning point of new career opportunities and Burroughs Wellcome scientists were found to be in demand, being offered university posts, important positions at the MRC, but also key positions at rival pharmaceutical firms such as Glaxo, May & Baker and Boots Pure Drug Company.

¹⁹⁸ C. R. Harington, "H. King"(1956): 158. King stayed at Burroughs Wellcome until his move to South Africa in 1947.

¹⁹⁹ G. E. Pearson, (1936), typescript WF: 88/24:41d: 12.

²⁰⁰ O'Brien to Taylor, Standing Orders, (1 February 1917), WF: 85/31:1-2.

²⁰¹ H. H. Dale, "Arthur James Ewins" (1958): 88.

²⁰² Judy Slinn, (1984): 92-3; Henry Dale, "Arthur James Ewins" (1958): 81- 91.

4.8 Production of Further Synthetic Drugs and Alkaloids in Britain.

Many examples have already been given of synthetic drugs and previously unavailable alkaloids manufactured by British firms. Of the drugs where the patents were abrogated, many were alkaloids, antiseptics or barbiturates that were relatively easy to prepare as long as raw materials were available. Burroughs Wellcome prepared new alkaloids commercially in 1914 and expanded the range in 1915-16. Fargher and Baxter, who had prepared Salvarsan, were also asked to prepare derivatives of phenacetin and Aspirin, arsenicals, alkaloids, resins, and lysidine, hydroquinone, benzoyl chloride, hydrochloric acid and Salol. Pyman directed production of neosalvarsan, emetine, digitalis, coca extracts, alkaloids of ipecacuanha, histidine, acetyl salicylic acid, lanolin, and chaulmoogra oil.²⁰⁴

By early 1915 many British firms produced a wide range of new alkaloids and chemicals.²⁰⁵ A. Boake Roberts produced the oils, cineol, menthol, and oenanthic ether.²⁰⁶ Supplies of ether, chloroform, quinine salts, ethyl chloride, and nitrous oxide were increased dramatically. T. H. Smith and Duncan Flockhardt produced the anaesthetic gases, chloroform, ether and opium alkaloids and medicinal glucosides, while J. F. MacFarlan produced chloroform and ether, surgical dressings and galenicals in Scotland.²⁰⁷ In March 1915, W. J. Bush of Hackney and Thomas Kerfoot in Manchester were the first in Britain to produce salicylates used for rheumatism, influenza and neuralgia.²⁰⁸ At

²⁰³ MRC Minute Book I, (10 & 13 December 1914).

²⁰⁴ WF: YL Box 25.

²⁰⁵ Howard's J. F. McFarlan, Morson's, T. H. Smith, Duncan Flockhardt and May & Baker produced emetine, digitalis and cocaine, and new alkaloids of ipecacuanha. In 1915 they produced synthetic histidine, lysidine, cresols, local anaesthetics, glycerophosphates and pilocarpine: "Society of the Chemical Industry" Chemist & Druggist 86.2 (6 March 1915): 53; W. J. Reader, (1970): 258, 267-8; M. R. Fox, (1987): 48 - 49, 86 - 88; "Evans-Physiological Standardisation" Chemist & Druggist 85.1 (15 August 1914), Suppl iii.

²⁰⁶ "Society of the Chemical Industry" Chemist & Druggist 86.2 (6 March 1915): 53.

²⁰⁷ Evans advert in Chemist & Druggist 85.2 (29 August 1914): 33; "What is a Fine Chemical?" Chemist & Druggist 85.2 (29 August 1914): 51; G. Tweedale, At the Sign of the Plough: 275 Years of Allen & Hanbury's and the British Pharmaceutical Industry 1715-1990 (London: Murray, 1990): 78, 85; Duncan Flockhardt adverts Chemist & Druggist 88.4 (29 July 1916): 147.

²⁰⁸ "Manufacture of Salicylic acid" Chemist & Druggist 85.1 (22 August 1914): 37-38; "A. H. Cox, The Patriotic Poster" Chemist & Druggist 85.2 (5 September 1914): 1.

Howard's, even though only the senior partners were chemists, they made Aspirin by a batch process "easy to produce on a large scale",²⁰⁹ in their "splendid range of up-to-date laboratories".²¹⁰ Howard's made as much quinine as they could with available supplies of bark.²¹¹

Thereafter, British firms went to great lengths to emphasise the British origins of their goods. British Drug Houses were the first to offer guarantees of conformity to definite specifications of purity, more stringent than the Food and Drugs Act and the British pharmacopoeia of 1898.²¹² They influenced prescribers by producing a guide to the 1914 British pharmacopoeia.²¹³ After his appeal for government support, Charles Hill invested heavily in manufacturing facilities around Graham Street in London. A further 3 acres were bought on the opposite side of the Regent's Canal. In addition to shortages of funds and building materials there were also staff shortages. BDH had 150 enlisted men and these were replaced by 150 women and by as many older men. A new US telephone system was installed and an extended automated pill department with facilities for finishing and coating. Hill wrote: "Our policy in regard to the production of so-called German chemicals has been to manufacture those articles which would otherwise be unobtainable". Hexamine was made at the start of the war but was discontinued when there were sufficient supplies. Many tons of salicylic acid and sodium salicylates were produced but the limiting factor had been plant capacity as "increased manufacture is done at the expense of something else".²¹⁴ Arthur H. Cox advertised in his 'Patriotic Poster' that: "We cannot take up arms against our country's enemy but we can...put up a grand fight for our country by refusing to buy German goods".²¹⁵ British wholesalers who had previously distributed German drugs such

²⁰⁹ Quoted from "After One Year of War- The Supply of Fine Chemicals" Chemist & Druggist 87.1 (14 August 1915): 45; for a photograph of Howard's of Ilford factory see Chemist & Druggist 88.4 (29 July 1916): 127.

²¹⁰ "Howard's of Ilford" Chemist & Druggist 85.1 (1 August 1914): suppl. ii-iii.

²¹¹ H. S. Abrahamson, "The War Contract", Chemist & Druggist 99.2 (3 November 1923): 625-26.

²¹² "What is a Fine Chemical?" Chemist & Druggist 85.1 (29 August 1914): 51.

²¹³ The BDH Guide to the British Pharmacopoeia 1914 (London: British Drug Houses, 1915) at Wellcome library.

²¹⁴ "A Quinquennial Record. How the BDH have grown since the 4 Constituent Houses Merged into One", Chemist & Druggist 88.4 (29 July 1916): 788-89.

²¹⁵ Quoted from British Medical Journal (12 September 1914): 43; C. Fearon, "The History of A. H. Cox & Co. Ltd." Pharmaceutical Historian 23 (1993): 4-6; A photograph

as Lysol, for Schering now emphasised it was “made by a British firm with British capital, by British labour, using British raw materials”.²¹⁶ Evans Sons, Lescher & Webb grew herbs but also extended their manufacturing capacity to produce Salvarsan and other drugs at Runcorn in Cheshire, appointing Dr. W. A. Caspari as Research Director. He was a science graduate of the Victoria University and of Jena University in Czechoslovakia. They also produced serums and vaccines in the bacteriology laboratories.²¹⁷

Academic researchers also dealt with “practical problems of national importance”.²¹⁸ Within 3 weeks of the start of the War, Imperial College of Science made 2-3 synthetic drugs on a small scale.²¹⁹ Duncan Flockhardt distributed medical and dietetic preparations, vaccines and tuberculin made by staff at the Royal College of Physicians, Edinburgh under Prof. Ritchie,²²⁰ and the Lister Institute produced additional vaccines.²²¹

Robert Robinson, who had trained under W. H. Perkin junior at Manchester, secured the newly created Heath Harrison chair of Organic Chemistry at Liverpool University in 1915. Before the war Robinson had contributed significantly to the literature on alkaloid synthesis, proposing the chemical structures of strychnine, and brucine, and from 1916 he prepared beta-eucaine, novocaine and atropine.²²² His team at Liverpool collaborated with Evans Sons, Lescher & Webb through an advisory board established in July 1917.²²³ The laboratories at Liverpool, like that at Oxford were occupied by ‘colonists’ from industry taking advantage of university facilities for production. Oxford had representatives of British Dyes, W. J. Bush and Boake Roberts.²²⁴ Henry Dakin

of the A. H. Cox laboratories is shown in an advert in Chemist & Druggist 88.4 (29 July 1916).

²¹⁶ “Lysol” Chemist & Druggist 86.2 (6 March 1915): 8.

²¹⁷ “A Cheery Chat with Sir Edward Evans on the Wars Effect on British Pharmacy” Chemist & Druggist 88.4 (29 July 1916): 775-6.

²¹⁸ Trevor I. Williams, (1990): 91.

²¹⁹ “The Imperial College of Science” British Medical Journal (3 June 1916): 800; “The War and the Supply of Drugs” British Medical Journal (10 March 1917): 339.

²²⁰ “Medicinal and Dietetic Preparations- Vaccines and Tuberculins- Duncan Flockhardt” British Medical Journal (17 March 1917): 367.

²²¹ “The Lister Institute” British Medical Journal (20 May 1916): 728.

²²² Lord Todd and J. W. Carnwath, “Robert Robinson 1886 – 1975” Biographical Memoirs of Fellows of the Royal Society 22 (1976) 415 – 527.

²²³ Lord Todd, J. W. Carnforth, “Robert Robinson” (1976); Geoffrey Tweedale, (1990): 120.

²²⁴ Trevor I Williams, (1990): 91.

produced flavines to make Chloramine T in association with Prof. J. B. Cohen at Leeds, as part of his work to develop antiseptics that did not break down on contact with wounds, as hypochlorites did and Browning and others investigated these.²²⁵ W. E. S. Turner at the University of Sheffield offered to supply authoritative information on patents.²²⁶ Ether was also prepared at Government factories in quantities up to 5,000 tons.²²⁷

After securing the Ellesmere Port factory, Levinstein's dye firm built up a research department of 30 chemists and made Novocain and Acriflavine from November 1916 as well as Trypaflavine, Proflavine and Euflavine. Substantial amounts (254 kg.) were given free to the Government. For this work their chief chemist, Arthur William Burger received the Certificate of Merit.²²⁸ Some German drugs, such as procaine and barbitol were available in Britain from American firms such as Abbott, while Smith, Kline & French sold antiseptics.²²⁹ The war transformed the production of alkaloids, synthetic chemicals, and chemical intermediates in Britain in the absence of German competition though concerns remained about the competitive position of British firms post-war.

4.9 The Training of Chemists and the Coordination of the Pharmaceutical Industry.

4.9.1 Establishment of the Association of British Chemical Manufacturers (ABCM).

²²⁵ "Medical Research Committee – The Antiseptic 'Flavine' (Acriflavine)" British Medical Journal (9 June 1917): 769-70; E. K. Dakin, H. D. Dakin, Report to the MRC, "Observations on Chloramines as Nasal Antiseptics" British Medical Journal (30 June 1917): 865-7; "Dakin's DiChloramine T in the Treatment of the Wounds of War" British Medical Journal (25 August 1917): 249-51. Chloramine was sold by Burroughs Wellcome as Halozane, H. D. Dakin, E. K. Dunham, "The Disinfection of Drinking Water" British Medical Journal (26 May 1917): 682; "Health of Munitions Workers" British Medical Journal (7 July 1917): 13; C. H. Browning, R. Gulbransen, L. H. D. Thornton, "The Antiseptic Properties of Acriflavin, Proflavine and Brilliant Green, with Special Reference to their Suitability for Wound Treatment" MRC Report, British Medical Journal (21 July 1917): 70-75; C. H. Browning, R. Gulbransen, E. L. Kennaway, L. H. D. Thornton, "Flavine and Brilliant Green. Powerful Antiseptics with Low Toxicity to the Tissues: their Use in Infected Wounds" British Medical Journal (20 January 1917) I: 73-78.

²²⁶ Chemist & Druggist 85.2 (12 September 1914): 40.

²²⁷ The Pharmaceutical Journal and Pharmacist (14 February 1910) in B.CARR

²²⁸ W. J. Reader, (1970) I: 266, 276.

²²⁹ L. F. Haber, (1971): 144. The Americans, in the same situation passed a similar law in 1917.

Unlike Germany in 1914, Britain had no trade association representing pharmaceutical manufacturing firms to coordinate with central government.²³⁰ In part this function had been taken up by the more academically oriented, Society of the Chemical Industry. At their annual conference on 7 November 1914 the Society discussed the “Present and Future of the British Chemical Industry as Affected by the War”.²³¹

Since the outbreak of war, several of the senior staff of British firms were forced to collaborate closely on the various government committees in order to evaluate which drugs they could make and which chemical intermediates were needed. In sharing the problems and challenges these key individuals recognised the potential advantages of establishing more formal longer-term collaborations in which the industry had a collective voice. Previously many firms produced the same lines and each coordinated their own supplies of raw materials. They relied individually on dye firms, including those in Germany for chemical intermediates and also relied on the British dyestuffs consultants as a campaigning voice.

Members of the Chemical Society, the Society of Dyeists & Colourists and the Society for the Chemical Industry established a Joint Committee to organise the chemical manufacturers to address the issues not covered by other committees - such as which less common chemical intermediates were needed, investment in manufacturing plant, coordination of production and the lack of trained chemists. The first joint meeting for all members was held on 27 May 1916 in the rooms of the Chemical Society, under the chairmanship of the President of the Chemical Society, Alexander Scott²³² who explained:

It is essential that in their own interests there should be formed an Association of Chemical Manufacturers powerful enough to influence legislation and to indicate to the Government what is necessary in the national interests.²³³

²³⁰ L. F. Haber, (1971): 232.

²³¹ “The Production of Fine Chemicals in Britain” Pharmaceutical Journal 93 (14 November 1914): 696.

²³² Scott was also a member of the Society of the Chemical Industry: T. S. Moore, J. C. Phillip, The Chemical Society 1841-1941. A Historical Review (London: The Chemical Society, 1947).

²³³ The quote is from “ABCM” Chemist & Druggist 88.3 (27 May 1916): 39- 41, Further background on the ABCM is given on page 87.

The 16 members of the organising committee of the ABCM included one Fellow of the Royal Society, two DSc's and five Fellows of Royal Institute of the Chemical Society.²³⁴ Francis Carr (Boots) was a founder member with the pharmaceutical industry representatives Ralph Dodd and Kenneth Allen (Allen & Hanbury.) Mr. G. A. Pearson (Burroughs Wellcome), C. A. Hill (British Drug Houses), W. A. H. Naylor, T. D. Morson, L. J. Morson, (of Morson's), E. T. Brewis, E. J. Boake (of Boake Roberts, Stratford, London) as well as Prof. Henry E. Armstrong and Dr. Edward Frankland Armstrong²³⁵. The first Director of the ABCM was W. J. Uglow Woolcock, former committee member of the Society of the Chemical Industry and of the Pharmaceutical Society. Boake suggested that the ABCM should be limited to British firms.²³⁶

The ABCM aimed to promote closer cooperation between chemical manufacturers, to act as a medium for placing before the Government officials, its views upon matters affecting the British chemical industry and to promote industrial research thereby facilitating the development of a new British industry. They advocated closer cooperation with universities and technical colleges, financing and supervising research, advising its members in regard to particular research to undertake and on the most suitable institute or authority to work with.²³⁷

²³⁴ "Organising Chemical Industry" Chemist & Druggist 88.3 (27 May 1916): 39-41. At the meeting on 22 June 1916 the following were co-opted Sir A. Mond, Mr. F. W. Brock, Mr. G. B. Merrian, Mr. Max Muspratt F.R.S. of Liverpool, Mr. R. B. Pullar, Mr A. T. Smith, Mr Norman Holden, Mr John Gray, Mr W. J. Wilson.

²³⁵ E. F. Armstrong had studied at the Royal College of Science in London, then the Central Technical Institute, gaining his PhD at Berlin University and D.Sc. from London University. He had been a Director of the South Metropolitan Gas Co., then scientific advisor to the Ministry of Works and Ministry of Home Security. He had managed other firms before being appointed Managing Director of the British Dyestuffs Corporation in 1925, C. S. Gibson, T. B. Hilditch, "Edward Frankland Armstrong" Obituary Notices of Fellows of the Royal Society 5 (1948) 619 – 633.

²³⁶ Chemist & Druggist 88.3 (27 May 1916): 39, 41, 87.

²³⁷ Chemist & Druggist 88.3 (24 June 1916): 665; "ABCM" Chemist & Druggist 88.3 (1 July 1916): 35; "ABCM" Chemist & Druggist 88.4 (22 July 1916): 36; "British Chemical Industry: One Year On" Chemist & Druggist 88.4 (29 July 1916): 45; "After the War – How Stand Our Chemical Industries (Chemical Section of the London Chamber of Commerce) Chemist & Druggist 88.4 (4 November 1916): 1110; "Secrets of Chemical Manufacturers", ABCM Chemist & Druggist 88.4 (11 November 1916): 1134; "Salvarsan – Several Fatalities, Alcohol Prices (18 November 1916): 1148, "Secret Chemical Processes" Chemist & Druggist (18 November 1916): 1160.

John T. Brunner²³⁸ of Brunner Mond emphasised the neglect of technical education and lack of chemical knowledge by Government officials, and pointed out that the Imperial College of Science had many buildings unequipped through want of funding.²³⁹ The ABCM believed that these problems could be overcome if the ABCM financed and supervised research in co-operation with teaching institutions, in the interests of the chemical industry as a whole, and making this available to members. It would organise systematic conferences between manufacturers and teachers. Regarding wartime supplies, the ABCM had to ensure that even the unusual but important chemicals were freely available. They appointed a chemically trained administrator to work with a governing body of academic professionals to keep records of all British chemical products and their manufacturers, avoiding duplication and unnecessary development of plant. Pharmaceutical manufacturers warned that: “The real establishment of a British fine chemical industry upon an adequate scale cannot take place until the natural resources in materials, plant, labour and chemical knowledge are freely available”.²⁴⁰

One of the leading ABCM men, Francis Carr gave a paper to the Society of the Chemical Industry on 20 July 1916 in which he “recalled how capitalists and bankers were reluctant to invest in the pharmaceutical industry. The German strategy was to charge high prices for intermediates, arrange long term contracts and systematic dumping of drugs.” He continued:

“Representatives of each branch of the chemical industry must define the extent of their requirements from other branches. We look to the ABCM to take the lead in these matters and to set afoot the necessary organisation to prevent overlapping and gaps, to arrange by mutual concessions that too many do not manufacture the same chemicals, and to secure the manufacture of those chemicals already provided for. A further function of the Association was to call upon certain branches of chemical manufacturer to supply raw materials such as

²³⁸ John Tomlinson Brunner started the ammonia business in Northwich, Cheshire in 1873 and this firm was one of the precursors of I.C.I., M. R. Fox, (1987): 34-35; W. J. Reader, (1970): 111; L. F. Haber, (1971): 101, 157, 189.

²³⁹ J. T. Brunner, “Organising Chemical Industry” Chemist & Druggist 88.3 (27 May 1916): 39 – 41. Regarding debates on Imperial College there are extensive records at the archive including those of F. H. Carr.

²⁴⁰ C. A. Hill, T. D. Morson, “Manufacture of Fine chemicals in Relation to British Industry” and D. B. Dott, “Vegetable Alkaloids –How the War has Affected Their Production” British and Colonial Pharmacist (June 1915) 436-7, (quote) in 2130 B/CARR cuttings IV: 3, Archives at Imperial College.

sulphate, chloresulphonic acid, carbonyl chloride, phenylhydrazine, acetoacetic ether, phosphorus pentachloride etc. even though on account of the quantities at first demanded such undertakings could only be regarded as business propositions only by those observers whose motives are tempered by the needs of the chemical industry as a whole".²⁴¹

He concluded:

"whether or not the manufacture of synthetic drugs will develop to a large industry able to hold its own in the worlds' markets will be determined by the dye industry. With a large dye industry the supply of intermediates would be assured. At the conclusion of the war the new coke oven plants that have been established, will, we hope, be able to supply immense quantities of by-products".²⁴²

However, one of the perceived problems of collaborative projects as a wartime measure was that individuals from rival firms would be granted access to each other's company secrets because the Ministry of Munitions had powers, "to require any person to communicate to a person...all knowledge of his process".²⁴³ Because of this and because of their experience of having staff poached, Burroughs Wellcome refused to send representatives to many committees, despite an approach by Moulton.²⁴⁴ Thus the pharmacy-based manufacturers dominated discussions between the pharmaceutical industry and the Government.²⁴⁵

As the War progressed, the price of certain drugs increased by 50% due to decreased availability and increased transport costs. This especially applied to salicylates, Aspirin, bromides, Phenacetin, potassium permanganate, morphine, quinine, atropine and cocaine, either because they were originally from Germany, or made from chemicals from Germany, and because of the increased demand. The Excess Profits Act was passed

²⁴¹ F. H. Carr, "Synthetic Organic Drugs: Their Manufacture as Affected by the War" Chemist & Druggist 88.4 (29 July 1916): 778-79.

²⁴² F. H. Carr, (29 July 1916): 778.

²⁴³ "Trade Marks Applied For" Chemist & Druggist, 88.5 (4 November 1916): 44.

²⁴⁴ Although O'Brien did serve on a committee regarding vaccine production: H. J. Parish, WF: 85/20:20 chapter 3.

²⁴⁵ Under Sir Robert Morant this committee consisted of Edmund White, Chairman of the Pharmaceutical Society. C. A. Hill, and John C. Umney who together wrote "The Essential Oils of the B.P." Chemist & Druggist (12 February 1919): 271. Both contributed to the B.P. of 1914. Chemist & Druggist 85.2 (3 October 1914): 30, 49-58. It also included W. J. U. Woolcock – he was Secretary of the British Pharmaceutical Conference

because some firms took advantage by only producing the most profitable lines, while the aim was to ensure that all essential drugs were made.²⁴⁶ The ABCM lobbied the Government about the Excess Profits Tax that threatened to leave manufacturers without the cash to extend their research facilities and plant capacity. The Association was also very active in the assessment of new legislation on factories, trade agreements, patents, trade marks and various technical aspects with the aim of promoting British interests, but kept away from labour relations or trade disputes. The ABCM was a British attempt to counter the close collaboration already existing between large firms in Germany where strategic alliances of the group referred to as the 'Little IG' (BASF, Bayer and AGFA) was further extended on 18th August 1916 when they merged with Hoechst- Cassella-Kalle plus Weilerter-Meer and Griesheim Elektron under the direction of Carl Duisberg of Bayer.²⁴⁷ The reaction to the German merger was that:

“an enormous engine of commercial warfare has been created expressly for the expected war after the war, and that it is intended to undertake still more efficiently and on a larger scale, the various methods by which German attacks upon all competition were carried out”.²⁴⁸

Just before the merger was finalised the Council of the British Medical Association summed up the recognition that: “The country and profession cannot afford to be left at the mercy of foreign supply of substances many of which are essential”²⁴⁹.

The ABCM represented a mixed group, including the heavy chemical manufacturing companies, and there were “signs it will be confined to representatives of the larger firms”.²⁵⁰ The main committee included Mr. C. A. Hill of British Drug Houses and

in 1913. “National Insurance Act” Chemist & Druggist (5 July 1913): 55-58; Bernard M. Allen, Sir Robert Morant: a Great Public Servant (London: MacMillan, 1934).

²⁴⁶ “The Price of Drugs” British Medical Journal (3 April 1916): 420; A. J. Taylor (1971): 40; “Excess Profits Act” Chemist & Druggist (27 April 1918): 43.

²⁴⁷ W. J. Reader, (1970): 256, 321, 451-2, 476.

²⁴⁸ Reports of the Alien Property Custodian Journal of Industrial Chemistry (April 1919): 355.

²⁴⁹ “Imported Synthetic Drugs” British Medical Journal (10 June 1916): 828, 868.

²⁵⁰ British Chemical Industry Chemist & Druggist (19 June 1915): 46-7.

subsequently from November 1916 two more pharmaceutical men, Francis Carr from Boots and Mr. David Howard from Howard's,²⁵¹ forming a fine chemicals subgroup.

The ABCM helped to coordinate matters of importance to the chemical industry, but it was not an immediate fix for the chronic shortages of chemists, general labour shortages, high raw material prices, and the lack of availability of some chemical intermediates.²⁵² The establishment of the British Dyestuffs Corporation had not really helped as much as had been hoped.²⁵³ Despite the massive rises in production of some chemicals, there still remained a lack of cheap and reliable sources of such basic commodities as methyl and ethyl alcohols and acetic acid.

And yet by the middle of 1916 the ABCM claimed with pride that: "we have passed the stage of making fine chemicals because we are obliged to and are now laying the foundation of an extensive industry". Their list had extended by 70-80 articles in the last year and more than twice as much was being made. The ABCM stressed the need for strong support of this 'Key' industry in Britain.²⁵⁴ Francis Carr of the ABCM gave a rallying call for protection of the infant industry in his 1916 speech to the SCI when he stated:

"as of the future some form of protection is of vital necessity to our chemical industry, for without it anything accomplished will be demolished rapidly and completely by competition from abroad...no opportunity should be lost of impressing upon the nation and its rulers that the possession of a powerful and self-contained chemical industry had the same degree of importance as the great engineering industry had proven to be...we must as a nation do something to safeguard new industries".²⁵⁵

He was concerned that "German competition will adopt every skilful manoeuvre to combat new developments in this country such as charging high prices for intermediate products,

²⁵¹ "ABCM" Chemist & Druggist 88.3 (1916): 37, 41, (665, 683,); "ABCM – Carr and Howard Elected" Chemist & Druggist 88.5 (18 November 1916): 36.

²⁵² J. Davidson Pratt, "The Economics of the Fine Chemical Industry" Chemistry and Industry (20 January 1951): 38.

²⁵³ L. F. Haber (1971): 234.

²⁵⁴ "British Chemical Industry" Chemist & Druggist 88.4 (22 July 1916): 799- 800.

²⁵⁵ F. H. Carr, "Synthetic Organic Drugs: their Manufacture as Affected by the War" Chemist & Druggist (29 July 1916): 778. Transcript of a paper given to the SCI on 20 July 1916.

offering low terms for finished products, or long period contracts, systematic dumping etc.”²⁵⁶

Carr suggested that there should be an immediate declaration that there would be a period of protection from German imports after the War to give confidence for further capital investment. He recognised that “scientific efficiency in production will determine in the long run which nation shall be the strongest”.²⁵⁷ Carr’s also addressed the Chemical Section of the British Association, calling for the education and the training of men to conduct work in synthetic factories, both as technical managers and expert operatives. As the war progressed Carr cautioned that the Germans had already recognised the growing importance of the British fine chemical industry. He considered that they would concentrate more on wiping out this new competition than in the recovery of lost colonies, and he recalled the loss of an early lead in both the dye and camphor industries.²⁵⁸ France proposed exclusion of all German products and was not allowing German manufacturing in France, and Russia was considering the same.²⁵⁹

Carr considered that in order to understand these problems the Board of Trade needed somebody from the chemical trades on its Reconstruction committee.²⁶⁰ Initially the Board of Trade excluded ABCM representatives until they recognised their growing contribution to chemical manufacture, as the group, which was “the most representative...at present in existence in the country”.²⁶¹

Runciman’s committees eventually agreed to protection, not only in chemicals, but also for textiles, iron and steel, and engineering. At the British Association meeting in September 1916, Prof. G .G. Henderson²⁶² presented a paper to the chemical section

²⁵⁶ *Ibid.*

²⁵⁷ *Ibid.*

²⁵⁸ *Ibid*

²⁵⁹ Sir William Ramsay, “Society of the Chemical Industry” Chemist & Druggist 86.2 (6 March 1915): 53.

²⁶⁰ The Ministry of Reconstruction committee was set up address the potential post war trade wars, and social and economic problems of facing a strong Germany and central European 'Zollverein' or customs union. A. J. Taylor, (1971): 93.

²⁶¹ Nature 102 (1918) no. 2562: 272-3; Nature 103 (1919) no. 2568: 383.
Chemical Trade Journal 63 (1918) no. 1647: 38.

²⁶² Sir James Irvine, J. L. Simonsen, “George Gerald Henderson” Obituary Notices of Fellows of the Royal Society (1944) 4: 491-502.

summarising the recommendations of the subcommittee of an advisory council to the Board of Trade. This related to scientific-industrial research and training, suggesting larger funds for the Privy Council for extending industrial research, tariff protection for articles of vital importance to the national safety, uniformity of patent protection across the Empire, and rigorous enforcement of the working of patents in Britain. One proposed model was the Australian Commonwealth Institute for Science and Industry, which was run by scientific men of high standing with the hope of establishing a National Physical Laboratory.²⁶³

In 1917 the Minister for Reconstruction, Christopher Addison heard from the ABCM that the pharmaceutical and dyestuffs firms wanted specific protections and from 15 May 1918 they were granted ten years protection under the Key Industries Act, which together with the loss of the ‘most favoured nation’ status and the Trading with the Enemy (Amendment) Act, restricted German imports.²⁶⁴ In June 1918 the Economic Defence and Development Committee was set up with the aim of promoting pharmaceuticals and other key industries. Clear strategies were therefore put in place to allow the British industry to consolidate and to become competitive post-war.

4.9.2 The Department of Scientific and Industrial Research and the Training of Chemists.

When Raphael Meldola wrote to *The Times* on 20 January 1915, his main worry about the proposed creation of British Dyes Ltd. was that the directorship suggested did not include a representative of scientific chemistry; then in July of that year he was invited to chair the Advisory Council of British Dyes. Meldola urged the Board of Trade to set up a committee regarding chemical supply and proposed a scheme for the “organisation and development of Scientific and Industrial research”. However he died on 15 November 1915 before seeing this to completion.

The Royal Society, the British Science Guild, the Society of the Chemical Industry, and the Institute of Chemistry acknowledged the problem of a lack of sufficient scientific education. The Advisory Council of the Committee of the Privy Council was formed in July 1915 and the Department of Scientific and Industrial Research (DSIR) in December

²⁶³ The British Association presided over by Prof G. G. Henderson: F. H. Carr, “The Synthetic Chemical Industry” *Chemist & Druggist* 88.4 (9 September 1916): 45-7.

²⁶⁴ L. Haber, (1971): 241-45.

1916, based upon the model of the National Physical Laboratory.²⁶⁵ The Royal Society established the conjoint board of Scientific Societies in 1916.²⁶⁶ The common aim of these groups was to increase technical expertise related to science and particularly chemistry and its application to industry. The (DSIR) called for:

“a largely increased supply of competent researchers; secondly a hearty spirit of co-operating among all concerned, men of science, men of business, working men, professional men and scientific societies, universities and technical colleges, local authorities and Government departments”.²⁶⁷

A particular emphasis was placed on industries that had “become localised abroad and particularly in Germany” and concerns about the difficulties to be faced post-war unless there was growth and organisation of scientific resources.²⁶⁸ George Beilby²⁶⁹, a member of the Privy Council stated:

²⁶⁵ Sir Harold Melville, The DSIR: Does it Pay Off? (London: George Allen & Unwin, 1961): 26; Ian Varcoe, “Scientists, Government and Organised Research: the Early History of the D.S.I.R. 1914-16” Minerva 8 (1976): 192-217; I. Varcoe, Organising for Science in Britain: a Case Study of the Department for Scientific and Industrial Research (DSIR) 1916-64 (Oxford: University Press, 1974); R. McLeod, E. K. Andrews, “The Origins of the D. S. I. R. Reflections on Men and Ideas, 1915-6” Public Administration 48 (1970): 23-48; E. Hutchinson, “Scientists as an Inferior Class: The Early Years of the D.S.I.R.” Minerva 8 (1970): 396-411; J. D. Bernal, Science in History (London: C. A. Watts & Co., 1965); C. E. K. Mees, The Path of Science (Chichester: John Wiley, 1946); J. Jewkes, D. Sawers, R. Stillerman, The Sources of Invention (London: MacMillan, 1955); A. C. Seward (ed.), Science and the Nation (Cambridge: Cambridge University Press, 1971); A. Marwick, (1965) especially chapter 7.

²⁶⁶ Report of the Committee on the Position of Natural Science in the Educational System of Great Britain. (London: HMSO, 1918), Cd 9011: 53, 57, 64; David Layton, “Education in Institutionalised Societies” in A History of Technology, vol. 1, Trevor I. Williams (ed.), (Oxford: Clarendon Press, 1978); Ian Varcoe, “Cooperative Research Associations in British Industry” Minerva 19 (1981): 433-63; E. F. Armstrong, Chemistry in the 20th Century: an Account of the Achievement and Present State of Knowledge of Chemical Science (London: Ernest Benn, 1924): 88. V. E. Coslett (ed.), Scientific Research in Universities and Industry. A Report on the Conditions in Great Britain (London: Association of University Teachers, 1955).

²⁶⁷ R. C. Cochrane, Measures for Progress (Washington: National Bureau of Standards, 1966): 231, 559.

²⁶⁸ *Ibid.*

²⁶⁹ Beilby had been involved in the cyanide business and patented a method of making potassium cyanide used by Cassel; Judy Slinn, (1984): 61.

“The place of chemistry in the national life has been far more important than the majority of educated people have imagined, and this place bids fair to become of vastly increased importance in the near future. The special message for parents and teachers is, therefore, that trained chemists will, in the near future, be in increased demand for industrial and official positions”.²⁷⁰

The Government recognised that: “a special need exists at the present time for new machinery and for additional state assistance in order to promote and organise scientific research with a view, especially to its application to trade and industry”. The Haldane committee, which was established in 1908, was proposing to increase the funding of scientific research and training of chemists after the efforts of the British Association for the Advancement of Science.²⁷¹

At the Society of the Chemical Industry meeting in 1916 further points addressed by Francis Carr were education and training and he identified two classes of workers: technical and expert operatives:

“The first (class) consists of resourceful well-trained chemists directing on the spot, operatives of the second. He referred to the special qualifications of these first class men and said that in synthetic chemical manufacture and above all other branches of chemical manufacture men of this kind combining business and science are indispensable”.²⁷²

He suggested one or more technological colleges, with manufacturing capabilities so that chemists could spend a considerable time producing synthetic drugs under expert guidance, focusing on producing those required in small quantities of the sort not cost-effective for British industry to produce.

The college would have a large permanent staff and would be conducted along strict business lines. The aim would be to create realistic manufacturing conditions where students could work in chemical, physical and engineering laboratories, with drawing rooms, joiners and fitters shops and a plant generating steam, gas and electricity, all of which could be metered and expressed quantitatively so that students gained the value of

²⁷⁰ Alex Findlay, in R. B. Pilcher, F. Butler-Jones. What Industry Owes to Chemical Science (Cambridge: W. Heffer, 3rd edition 1945) Introduction: viii.

²⁷¹ D. Layton, Interpreters of Science: a History of the Association for Science Education (Bath: John Murray, 1984): 21.

raw materials, yields of reactions, the heat and power absorbed, the time and labour expended. Students would be given a commercial perspective and would undergo instruction in accountancy and costing. Students would spend time in the analytical laboratory in which intermediates and the final product were examined. They would have instruction in physical and electro-chemistry, applied mathematics, construction and design and preparation of steam joints, chemical engineering, machine drawing, repairs, use of special machinery and plant, stoking and engine driving, making steam joints and wood turning. These were the skills required to run a modern pharmaceutical business works. The second year would cover engineering including steam-raising and power production and analysis of waste and flue gases.²⁷³

The success or otherwise of the efforts to increase emphasis on chemical research will be dealt with in the subsequent chapter on post-War Britain, which will add the impact of tariff protection, the success of British dyestuffs and the exclusion of German drugs. In subsequent chapters I will examine how the interactions begun during the War became the models for further interactions between the pharmaceutical industry and the Government in both biological standardisation and clinical trials as British firms prepared further synthetic drugs.

The war marked a turning point for the standing of science, in relation to its potential importance in war as in peace and this was evident in the chemical and pharmaceutical industry.²⁷⁴ Companies rationalised the way in which they produced drugs.²⁷⁵ In doing so they created new challenges of how the model would be extended into peacetime and how new products arising would be tested.

4.10 The MRC Propose Clinical Testing

²⁷² Editorial, "Science, Education and Government" British Medical Journal (5 February 1916): 209-10.

²⁷³ F. H. Carr, "Synthetic Drug Industry" Chemist & Druggist (9 September 1916): 45-7.

²⁷⁴ S. M. H. Armitage, The Politics of Decontrol of Industry: Britain and the United States (London: Wadenfeld & Nicholson, 1969); P. B. Johnson, Land Fit for Heroes: The Planning of British Reconstruction 1916-9 (Chicago: Chicago University Press, 1968).

²⁷⁵ A. J. P. Taylor, (1988): 4-5, 49, 91, 176, 321, 371-6, 426; W. J. Reader, (1970): 132; L. F. Haber, (1971): 173.

The MRC recognised that having take up a central role in the testing of Salvarsan in order to ensure the quality and strength of British preparations, they needed to extend this role further by helping to convince conservative British physicians to use British synthetic drugs. Salvarsan was evaluated as part of a coordinated attack on Venereal disease. The Royal Commission raised the age of consent from 13 to 16 years and endorsed the conclusions of the Select Committee on Patent Medicines, that most treatments making unsubstantiated claims offered no benefit: it was important therefore to show that Salvarsan, a scientific drug endorsed by the MRC was effective.²⁷⁶ Editorials in the *British Medical Journal* were scathing in their contempt of efficacy figures generated in prisons, by the Poor law authorities and in voluntary hospitals. They called in particular for a record of how many times Salvarsan or its substitutes was provided at the public expense and urged “the use of modern scientific measures uniting the efforts of doctor and bacteriologist”. The aim was to show clearly the benefits as opposed to the “evil and unqualified treatment at the hands of chemists, herbalists and quack specialists”.²⁷⁷

The MRC had gained some experience of clinical evaluation by performing a small trial of bismuth iodide double salt of emetine at a military hospital for the treatment of amoebic dysentery and this became the standard therapy.²⁷⁸ Salvarsan was more complex as the drug was widely available, patients were widely scattered and recording of data was not as good. They tried to correlate clinical outcomes with laboratory results to assess whether there was a need to add to or modify the system of controls, appealing to members of the medical profession to “furnish it with accurate records of the results”.²⁷⁹

²⁷⁶ The Royal Commission on Venereal Diseases was appointed in November 1913 with the aim “to inquire into the prevalence of venereal diseases in the United Kingdom, their effects upon the health of the community, and the means by which those effects can be alleviated or prevented”. (HMSO: Cmnd. 8189, 1916)

²⁷⁷ “Royal Commission on Venereal Disease Regulations” *British Medical Journal* (11 March 1916): 380-6.

²⁷⁸ H. H. Dale Archives, Royal Society “NIMR”, 93HD 47.13.144.

²⁷⁹ “The Manufacture of Salvarsan Products in England and France” *British Medical Journal* (10 April 1915): 649; “British Made Salvarsan” *British Medical Journal* (17 April 1915): 689-690; J. E. R. McDonagh, “The Manufacture of Salvarsan Products in England and France” *British Medical Journal* (17 April 1915): 697; J. E. R. McDonagh, D. Watson, “The Manufacture of Salvarsan Products in England and France” *British Medical Journal* (24 April 1915): 742-3; “Ehrlich’s Recent Modification of Salvarsan” *British Medical Journal* (24 April 1915): 979; “The Manufacture of Salvarsan Products in England and

“The Committee venture to urge that members of the medical profession would be performing a service of national importance, in the present emergency, by keeping accurate records of cases in which the new preparations are used, and by placing such records at the disposal of the committee for their private information and guidance. Particular stress must be laid upon the desirability of recording in every case, the name of the preparation used and the serial number applied by the manufacturer to the particular batch employed together with such details as to dosage, the precautions taken to ensure purity of the water used and finally the results of the administration, both as regards therapeutic efficacy and the presence or absence of special incidental symptoms”.²⁸⁰

Some authors, less convinced, considered that efforts to produce drugs such as Salvarsan would be better spent preparing T.N.T. (trinitrotoluene) and they were concerned about toxicity due to the arsenic present in Salvarsan.²⁸¹ One of the army physicians, H. C. Lucey, based at the Royal Herbert Hospital, Woolwich wrote: “I believe Kharsivan to be every bit as potent as the original German preparation in the incidence of adverse reactions catalogued and the bactericidal power of the blood”.²⁸² The British Medical Association were clearly not convinced by British manufacturers when they stated that: “we have much to learn and a long way to travel before our chemists can put a beautiful packet of sodium salicylate at 3 shillings a pound on the market” (As the Germans could).²⁸³ Salvarsan was clearly important to the Army and reserves of drugs at Woolwich eventually included 250 million tablets.²⁸⁴ The MRC also offered support:

“the Committee are confident that so far as the strictest laboratory controls can ensure it, the profession and the public are now receiving from English and French sources compounds fully up to the standard of the best German supplies previously sold”.²⁸⁵

France” (26 June 1915): 1087; “British and French Salvarsan Products” British Medical Journal (26 June 1915): 1091.

²⁸⁰ “The Manufacture of Salvarsan Products in England and France” British Medical Journal (10 April 1915): 649.

²⁸¹ “The Chemical Constitution of Certain Proprietary Drugs” British Medical Journal (10 July 1915): 75.

²⁸² H. C. Lucey, RAMC, Royal Herbert Hospital, Woolwich, “British and French Salvarsan Products” British Medical Journal (10 July 1915): 75-76.

²⁸³ “Imported Synthetic Drugs” British Medical Journal (17 June 1916): 868.

²⁸⁴ Sir W. G. MacPherson, (1921).

²⁸⁵ “Manufacture of Salvarsan Products In England and France” British Medical Journal (26 June 1915): 1087.

But this summarised the key issue. MRC arguments were based on laboratory data rather than clinical outcomes. When the MRC announced their results they were strongly supportive for the British manufacturers efforts to manufacture synthetic Salvarsan:

“the Committee are satisfied that the products tested biologically under their direction were not inferior, in safety or in efficacy, to the original German preparations. It may be remarked here that the satisfactory results of clinical trials, as well as the results of laboratory tests for toxicity, were in the hands of the Committee before the issue of these products was authorised”.²⁸⁶

H. C. Lucey at the Royal Herbert Hospital, Woolwich recorded in detail the effects of a further 600 injections of Kharsivan in 1916.²⁸⁷ Studies of Kharsivan and Galyl were reported from France. Of 96 cases, 84 had no reactions, 11 only slight and one had a significant reaction.²⁸⁸

And yet there were concerns about safety and there was a second enquiry in Germany in 1917 on the safety of Salvarsan.²⁸⁹ Col. L. W. Harrison, of the Royal Army Medical Corps. (RAMC) reviewed over 40,000 cases treated in the Army and believed that Kharsivan, Salvarsan and Arsenobenzol were equally efficacious and safe.²⁹⁰ Major Lloyd Jones, (RAMC) performed tests on 200 patients. Of 1,320 injections, only 37% did not give an adverse reaction.²⁹¹ Haslar hospital produced data on 1833 injections of arsenicals, all of British manufacture.²⁹² It was against this background of continued

²⁸⁶ J. E. R. McDonagh, “Manufacture of Salvarsan Products in England and France” British Medical Journal (10 April 1915): 649-50.

²⁸⁷ H. C. Lucey, “The Therapeutic and Reaction Effects of Kharsivan” British Medical Journal (29 April 1916): 614-8.

²⁸⁸ “Treatment of Syphilis” British Medical Journal (1 January 1916): 16.

²⁸⁹ MRC Report of the Salvarsan Committee 66 II. “Toxic Effects Following the Employment of Arsenobenzol Preparations” (London: HMSO, 1922).

²⁹⁰ “Toxic Effects of Arsenobenzol Preparations” MRC Special Report Series 41; “Special Commission upon the Manufacture, Biological Testing of Salvarsan and its Substitutes”, MRC Special Report Series 44 (1919): 35.

²⁹¹ John Adam, “Salvarsan Treatment of Syphilis” British Medical Journal (17 February 1917): 234; another report of over 200 injections gave a more favourable reaction. “The Prophylaxis of Venereal Diseases” British Medical Journal (17 February 1917): 243-4.

²⁹² Sir Arthur May, “Medicine and the Sea Affair” British Medical Journal (28 April 1917): 533-5; of these 1522 were kharsivan, 55 Galyl and 256 arsenobenzolbillon.

scrutiny that a second MRC Salvarsan Committee chaired by Major Frederick Andrewes of St. Bartholomew's, London was set up at the end of 1917 to examine:

“manufacture, testing methods of administration and clinical effects of Salvarsan and the analogous group of antisyphilitic remedies”.²⁹³ The Army wanted Professor Gunn, Reader in Pharmacology at Oxford and Dr. Turner, Reader in Morbid Anatomy at the University of London to test the “chronic or ultimate effects [of Salvarsan] in experiments on animals”.²⁹⁴

When Arthur Ewins left the MRC, Dale had little help for the assay of Salvarsan and “with all too little likelihood at that stage of the war of finding anybody who would give me the kind of help which I required.” Help eventually materialised in the form of Miss Florence Durham, and the Belgian refugee, Mlle. Juliette Marchal but both eventually followed Dale to the NIMR.²⁹⁵

The MRC recognised the significance of the production of Salvarsan by British firms and they emphasised their own part in organising the effort:

“In this undertaking, in the emergency created by the war, a duty outside the strict limits of medical research, the committee are satisfied that they have assisted, not only in meeting an immediate national need, but in founding an industry which will be of increasing importance to the practice of medicine and to the health of the community as progressive effect is given to the recommendations of the Royal Commission on Venereal Diseases”.²⁹⁶

Thus, all advertising by patent medicine manufacturers for this disease was banned and therapy had to be administered by a General Practitioner, so discouraging concealment, continued spread of disease and self-treatment; a strong endorsement for ethical medicines over patent medicines.²⁹⁷ The Venereal Diseases Bill was passed on 25 May 1917, and

²⁹³ Major Frederick Andrewes (Chairman, Pathology Laboratory, St Bartholomew's), Surgeon-General Humphrey Rolleston of Cambridge, Colonel L.W. Harrison and Major C. J. White, both of the RAMC, Military Hospital, Rochester Row, F. J. H. Coutts, Professor W. Bulloch, of The London Hospital, J. W. McNee, University College Medical School, and Dr. H. H. Dale. MRC Salvarsan Committee Minutes, MB22, (14 February 1918): 1.

²⁹⁴ MRC Salvarsan Committee Minutes MB22 (14 February 1918): 1.

²⁹⁵ W.S. Feldberg, “Henry Hallett Dale 1875 – 1968” Biographical Memoirs of Fellows of the Royal Society 16 (1970): 107.

²⁹⁶ 5th MRC Annual Report in British Medical Journal (14 January 1922): 74.

²⁹⁷ “The Prophylaxis of Venereal Diseases” British Medical Journal (24 February 1917): 278-81; William Osler, “The Campaign against Venereal Disease” British Medical Journal (26 May 1917): 694-6.

centres were established across the country where people could be diagnosed and treated free of charge. It became a criminal offence knowingly to communicate the disease.²⁹⁸ Having recommended controlled therapy with arsenicals it became incumbent on the Government to ensure that Salvarsan and similar drugs were used safely.

4.11 The Second Salvarsan Committee.

The second Salvarsan Committee met every week from 14 February 1918 to the end of 1924 to examine “manufacture, testing, methods of administration and clinical effects of Salvarsan and the analogous group of antisyphilitic remedies”.²⁹⁹ Although this extends beyond the chronology of this chapter, their work followed from the war work on Salvarsan and so is included in this chapter. Their efforts can be divided into three main stages. Firstly, they asked for chemical standards on the assumption that toxicity would be related to the quality of each batch of drug. Then they collated data to assess side effects reported to them from the army and navy hospitals. Thirdly, they compared data on British preparations with the German originals and the French Galyl.³⁰⁰ From the outset they arranged planned to review Army and Navy records from Haslar and Rochester Row.³⁰¹

In defining standards, the Salvarsan Committee depended heavily upon the co-operation and expertise of scientists from pharmaceutical firms, especially Frank Pyman who had been responsible for its production at Burroughs Wellcome.³⁰² The works manager of Burroughs Wellcome, H. A. D. Jowett described the precautions taken in the synthesis of Salvarsan from arsenic.³⁰³ The process involved a complex series of reactions, purifications, analyses, crystallisations, and precipitations. The final product had to be protected from oxygen by sealing vials under sulphur dioxide gas. It was then

²⁹⁸ “Criminal Law Amendment Bill- The Treatment of Venereal Diseases” British Medical Journal (17 March 1917): 372-3.

²⁹⁹ Initial membership was the surgeon H³⁰⁰ MRC Salvarsan Committee Minutes MB22, (undated, February 1918): 2.

³⁰¹ MRC Salvarsan Committee Minutes MB22, (14 February 1918): 2.

³⁰² MRC Salvarsan Committee Minutes MB22, (5 March 1918): 3.

³⁰³ MRC Salvarsan Committee Minutes MB22, (22 March 1918): 5.

assayed both chemically and in a biological test. The MRC concluded: “the product seems uniform, the only marked variation is as to the result of the biological test”.³⁰⁴

The other commonly used Salvarsan preparation was May & Baker’s Novarsenobenzol-billon, so the Committee also checked the facilities of May & Baker at Dagenham. On 11 March 1918 the M&B pharmacist, Gilling, explained that the complete manufacture of Salvarsan had not yet been achieved by them in the U.K. as the intermediate ‘nitro’ compound was prepared by Poulenc Brothers, their French colleagues, and sent to them.³⁰⁵ In contrast to Burroughs Wellcome, May & Baker took no precautions to protect the product from air, but their pharmacist Gilling felt this was suitable if they did not take too long in the preparation and as long as materials remained dry.³⁰⁶

However, after one incident where a firm circumvented its testing procedures by using rejected batches of Salvarsan to prepare neosalvarsan without further testing, the Salvarsan Committee insisted that batch numbers appeared on commercial packages so that any problems could be traced back to the batch produced.³⁰⁷ The Committee were keen to produce a set of common standards of purity, but not to lay down standards that were too stringent for the British manufacturers. However, Jowett wanted the most stringent conditions so that only Burroughs Wellcome could meet them: the use of pure chemicals, re-crystallising intermediates, and assessment of the percentage concentrations of arsenic and of water in the preparations.³⁰⁸

Jowett emphasised the need for controls of vacuum drying, for complex solvents, filtration and precipitation and inert sealing of tubes of the final product. Standards of solubility and dissolution were also to be specified. He insisted that poor batches of Salvarsan should not be re-used to produce good batches of neosalvarsan and he cautioned that adding salt could unscrupulously lower the arsenic concentration, though this was not

³⁰⁴ MRC Salvarsan Committee Minutes MB22, (22 March 1918): 5.

³⁰⁵ For details on the agreement between Poulenc and May & Baker see Judy Slinn, (1984); MRC Salvarsan Committee Minutes MB22, (11 March 1918): 4.

³⁰⁶ MRC Salvarsan Committee Minutes MB22, (19 February 1919): 25.

³⁰⁷ MRC Salvarsan Committee Minutes MB22, (5 March 1919): 27; the novarsenobenzol preparation, glucarsenol was from the Anglo-French Drug Company.

³⁰⁸ MRC Salvarsan Committee Minutes MB22, (22 March 1919): 30.

permitted in his own company.³⁰⁹ During March 1919 the MRC visited the Burroughs Wellcome Works in order to see first-hand the progress made in preparing Salvarsan.³¹⁰ The MRC indirectly acknowledged Jowett's expert input, but only by writing that "the Committee are indebted to an outside authority for more detailed suggestions as to suitable standards for Salvarsan and neosalvarsan".³¹¹ They were cautious in specifying links with any given company.

Throughout these early developments the MRC staunchly defended the British products. The MRC Trench Fever Committee asked in 1918: "which of the present preparations most nearly approaches the original German preparation?" The Salvarsan Committee confidently replied that any might be used, such as Kharsivan, Arsenobillon, Diarsonal, or Salvarsan produced by May & Baker.³¹²

Henry Dale investigated Novarsenobillon and Neokharsivan in rabbits, in comparison with the original German Neo-salvarsan.³¹³ All three gave similar results and he concluded only that there was an "interesting comparative fatality".³¹⁴ The Committee wanted to compare the British and French drugs with Canadian and German drugs, which had been associated with jaundice.³¹⁵ However, in trying to obtain data from Army centres, they received variable feedback. Cherry Hinton reported several fatal cases, whereas another centre saw no jaundice from 108,000 injections.

The MRC hypothesis relating purity of the drugs to the safety profile gained further credence when Prof. W. Bulloch reported that a Committee of investigation in Germany had concluded that although Salvarsan passing animal tests produced jaundice, later batches passing even more stringent tests did not.³¹⁶ As a result the MRC applied their

³⁰⁹ MRC Salvarsan Committee Minutes MB22, (26 March 1919): 31; The Anglo French drug company applied to the M.R.C. to import Galyl with a lower arsenic content.

³¹⁰ G. E. Pearson, (1936), Typescript WF: 88/24:41d: 12.

³¹¹ MRC Salvarsan Committee Minutes MB22, (8 October 1919): 50.

³¹² MRC Salvarsan Committee Minutes MB22, (1 May 1918): 10.

³¹³ MRC Salvarsan Committee Minutes MB22, (17 April 1918): 9.

³¹⁴ MRC Salvarsan Committee Minutes MB22, (18 May 1918): 11.

³¹⁵ MRC Salvarsan Committee Minutes MB22, (31 May 1918): 12; (4 October 1918): 20; (4 December 1918): 21; (30 April 1919): 37.

³¹⁶ MRC Salvarsan Committee Minutes MB22, (15 May 1918): 11; (17 July 1918): 16.

strict guidelines to new products emerging from Germany such as silver Salvarsan.³¹⁷ Thus, whereas the initial aim of the MRC was to ensure that the purity, strength and safety of the British products were as good as those from Germany, as time moved on they effectively reversed the testing requirements, establishing a protectionist policy, and excluding foreign imports if not up to the newly established high standards. They tested Galyl, imported by the Anglo French drug company and Silver Salvarsan, and compounds '1495' and '1496' from Meister Lucius & Brüning, (Hoechst) of Germany, which were promoted as containing less arsenic.³¹⁸ There remained concerns about British Salvarsan, arising from deaths and adverse effects such as dermatitis and jaundice in British and allied hospitals, but these continued to be difficult to quantify under conditions of war.³¹⁹ In order to gain wider experience Dale corresponded with Dr Reid Hunt of Harvard University in Boston and compared his results in rats, using lower doses with his own studies in rabbits.³²⁰

The MRC had problems in getting the clinical data they needed to support their hypothesis. Civilian cases were inadequately reported; even though all deaths were followed up and investigated histologically and as agreed manufacturers were notified of the offending batch numbers.³²¹ Paul Fildes, the new Surgeon-General, responsible for summarising the Army experience with Salvarsan was unable to provide any comparative data, though he reported that the army in France was already using Silver Salvarsan.³²²

In private, the Salvarsan Committee acknowledged that it was impossible to properly define the relative therapeutic value from army returns, though the data did enable

³¹⁷ MRC Salvarsan Committee Minutes MB22, (18 December 1918): 22.

³¹⁸ MRC Salvarsan Committee Minutes MB22, (18 December 1918): 22.

³¹⁹ MRC. Salvarsan Committee Minutes MB 22, (14 February 1918): 1; MRC Report of the Salvarsan Committee 66 II. Toxic Effects Following the Employment of Arsenobenzol Preparations (London: H.M.S.O., 1922); "The Toxic Effects of Salvarsan", British Medical Journal (18 December 1920): 945; MRC Special Report Series 41 (1917) "Toxic Effects of Arseno-benzol Preparations in Surgery II, a Clinical Study of the Toxic Reactions Following the Intravenous Administration of '914'"; Lt. Col R. J. G. Parnell, P. Fildes, "Special Commission Upon the Manufacture, Biological Testing etc. of Salvarsan and its Substitutes" MRC Special Report Series 44 (1919).

³²⁰ MRC Salvarsan Committee Minutes MB22, (17 July 1918): 16, (24 July 1918): 17, (11 September 1918): 18.

³²¹ MRC Salvarsan Committee Minutes MB22, (17 January 1919): 23.

some comparison of relative toxic effects.³²³ Given their central role in evaluating Salvarsan, it was only natural that the MRC Salvarsan Committee would be asked searching questions. Walter Morley Fletcher answered one query with the opinion that “probably the safest is Hoechst's Neosalvarsan ('914') by syringe”. He also stated that:

“the Committee had come to the conclusion that there was no appreciable difference between the various neosalvarsan preparations and those from Britain, France and Canada seem equally efficacious with the original German Neosalvarsan, and not more likely to be followed by ill-effects”.³²⁴

Prof. Sims Woodhead investigated adverse reports, and Prof. W. Bulloch was asked to collect further statistics on '606' and '914' at the London Hospital. In contrast to Fletcher's public support for British drugs, the next meeting of the Committee agreed that it was not even possible to make an accurate statement about the numbers of patients treated with each preparation, let alone the percentage success rate, without which no 'statistical' comparisons were possible.³²⁵ The MRC again tried to distinguish what the reports of toxicity were due to: chemical impurities, oxidation of the drug or even due to the use of contaminated water. Yet again Fletcher re-emphasised to the committee that a report on the relative merits of British products compared with German products “would be a great help”.³²⁶ However the MRC struggled to piece together any kind of a report on the efficacy of Salvarsan from their diverse, incomplete, and primarily army sources. Instead they could only report on standardised nomenclature and chemical testing of the various preparations to control their sale.³²⁷ Given the exigencies of the period, it is perhaps not surprising that reliable retrospectively collected data was difficult to obtain. There were two issues, the lack of consistent data record forms and the way in which contemporary

³²² MRC Salvarsan Committee Minutes MB22, (17 January 1919): 23.

³²³ MRC Salvarsan Committee Minutes MB22, (26 February 1919): 26.

³²⁴ MRC Salvarsan Committee Minutes MB22, (19 March 1919): 29.

³²⁵ MRC Salvarsan Committee Minutes MB22, (19 March 1919): 29; (22 March 1919):

30.

³²⁶ MRC Salvarsan Committee Minutes MB22, (2 April 1919): 33.

³²⁷ MRC Salvarsan Committee Minutes MB22, (7 April 1919): 34.

data was collected with a strong emphasis on individual case histories.³²⁸ During the War the MRC were unable to impose a more systematic approach on the organisation and collection of medical data that they wanted. They routinely tested batches submitted by British firms, agreed licenses for importing firms and searched out foreign batches that were obviously inadequate or unsafe.

As a result of their problems, the Committee wished to make the control of these substances compulsory. Both '606' and '914' came under the heading of “arsenic and its medicinal preparations in part I of the Pharmacy Act of 1908” and had to be labelled as 'Poison'. However one Member of Parliament, in answer to questions asked:

“It was not clear who should take action to see to enforcement of the requirements or in what way these obligations would assist in obtaining proper tests or would prevent the sale of preparations not conforming. It might be desirable to empower some competent body to schedule certain drugs so that definite tests could be enforced”.³²⁹

This was the first suggestion of a national drug licensing system and the MRC were to be responsible for recommending licenses.

In February 1918, the Committee first discussed the possibility of Frank Pyman, helping them with safety studies. Pyman had departed Burroughs Wellcome to take up the post of Professor of Technological Chemistry in the University of Manchester and Head of the Department of Applied Chemistry. Pyman was willing to perform further tests on German substances on behalf of the MRC, but as late as February 1919 “his laboratory was not yet in order”.³³⁰

At the end of the War, George Barger left the MRC to take up the Chair of Chemistry in Relation to Medicine at the University of Edinburgh, but the MRC acquired his former colleague Harold King from Burroughs Wellcome as a replacement in 1919.

³²⁸ See U. Troehler, Quantification in British Medicine and Surgery 1750 – 1830, with Special Reference to its Introduction into Therapeutics. (University of London: PhD Thesis, 1978).

³²⁹ MRC Salvarsan Committee Minutes MB22, (11 April 1919): 35.

³³⁰ MRC Salvarsan Committee Minutes MB22, (11 April 1919): 35. The laboratory referred to must have been in the Department of Applied Chemistry in the College of Technology in Manchester where he was appointed Professor beginning on 1 March 1919: H. King. “Frank Lee Pyman” Biographical Memoirs of Fellows of the Royal Society 4 (1944): 687.

King studied the impurities contained in commercial preparations of Salvarsan and identified the main problematic component which was twice as toxic as Salvarsan itself.³³¹

When Salvarsan again became available from Germany post-war, the Salvarsan Committee suggested that Board of Trade licences should be amended to require the same biological tests and batch labelling for German Salvarsan derivatives, and the Board of Trade, MRC and Local Government Board met in May 1919 and agreed to require this before issuing import licences, effectively excluding many foreign preparations.³³² The Salvarsan Committee considered that importation of foreign drugs without testing “might lead to risk to the public and unfair competition with British manufacturers who are compelled to submit their products for testing”.³³³ If foreign preparations were to be excluded, there was a still greater need to prove the efficacy of British preparations.

There were two further disappointments for the MRC in their continued strive to collect clinical data to support their statements in support of British drugs. At the end of the war it was recommended that the cards of the military venereal disease clinics should be collected as they closed down, but again this decision came too late and the MRC found that many records had already been sent to the British Museum.³³⁴ Furthermore, Dale had to admit that animal tests failed to predict for problems in clinical use, and this recognition led the MRC to conclude that they definitely needed comparative clinical results.³³⁵

Fildes's paper summarising army data was still only in draft form in July 1919 and his findings were quite general: he stressed he was providing only results and not a guide to therapy.³³⁶ In contrast to the patchy and largely incomplete data available, the Committee had quite grandiose plans for analysis with the illness to be classed into one of 12 groups, with results subdivided by the brand of drugs (there were around 13), the number of

³³¹ MRC Salvarsan Committee Minutes MB22, (11 April 1919): 35; H. King, “Derivatives of Sulphur in Commercial Salvarsan” parts I and II. *J. Chemical Society* 119 (1921): 1107, 1415.

³³² MRC Salvarsan Committee Minutes MB22, (30 April 1919): 37; (28 May 1919): 40.

³³³ MRC Salvarsan Committee Minutes MB22, (4 February 1920): 52.

³³⁴ MRC Salvarsan Committee Minutes MB22, (2 July 1919): 43.

³³⁵ MRC Salvarsan Committee Minutes MB22, (8 July 1919): 44.

³³⁶ MRC Salvarsan Committee Minutes MB22, (23 July 1919): 46.

injections, the total dose, the amount of mercury contained, toxic effects, their duration, and clinical results.³³⁷

The MRC clearly set out to position itself through the Salvarsan Committee as a central source of independent knowledge of the new synthetic compounds, and as an arbiter of good professional standards. Their proposal for a centralised testing facility advising the Board of Trade placed them in a position whereby they became the focal point of requests for information on relative safety and activity of the drugs for which they had taken responsibility. In 1919 Dale created a National Laboratory for Biological Standards, analogous to the National Physical Laboratory to maintain standard samples of other drugs such as antitoxins, and more broadly to become the centre for maintaining standards.³³⁸ With the increasing workload Dale required a reliable assistant and on completion of his medical studies Joshua H. Burn, another ex- Burroughs Wellcome researcher rejoined him at the NIMR on 1 September 1920 and they were later supported by two technicians.³³⁹

Walter Fletcher wanted the MRC to be that central authoritative body and insisted that figures on Salvarsan had to be given as an incidence per thousand injections rather than just as the number of cases, but his Committee continued to find it impossible to raise such figures and as a result asked “if girls can do the work” at the MRC Statistical Department.³⁴⁰ Fletcher was particularly influenced by German reports that gave a definite air of precision e.g. 20 deaths after 225,000 injections.³⁴¹ Special interest groups in Germany used figures imaginatively to support their cases or to campaign against the new remedy, whether because of its high profits, because it was dangerous, because it was used for prostitutes or for anti-Semitic reasons, because of its association with Ehrlich, who was

³³⁷ MRC Salvarsan committee Minutes MB22, (26 November 1919): 51; “MRC Report on the ultimate results of the treatment of syphilis with arsenical compounds” (1919) (2): 867.

³³⁸ J. Austoker and L. Bryder, “The National Institute for Medical Research and Related Activities of the MRC” in J. Austoker and L. Bryder (eds.), (1989): 35-57.

³³⁹ MRC Minutes II, (7 July 1920): 72. He became a permanent member from 1 July 1921 at £500 rising by £25p.a. to £750; A. N. Richards and Dale on insulin and histamine also; E. Buelbring, J. M. Walker, “J. H. Burn”, (1981): 50; Dr Hine stayed for 6 months then went to St. Bart’s to be replaced by Mr H. C. Sayer, MRC Minutes II, (18 March 1921): 38; (22 July 1921): 127.

³⁴⁰ MRC Salvarsan Committee Minutes MB22, (10 March 1920): 54.

³⁴¹ MRC Salvarsan Committee Minutes MB22, (19 May 1920): 56.

a Jew. This air of accuracy had been seen in 1914, when it was reported that a total of 353 authorities had treated 74,018 patients with 92% cured. Further 'precise' German reports in 1917 showed that 254 authorities reported that 265,158 patients had received 1,268,946 injections.³⁴²

In marked contrast to the 'apparent' accuracy of reporting in Germany, it was impossible with the British data to classify even the administration method; though there was an impression that arsenobillon was losing its effectiveness.³⁴³ It also became clear that there were significant failings in the follow-up of patients.³⁴⁴ Any clinical suspicions that efficacy was decreasing presented a dilemma for the MRC after they had so vigorously supported the British drugs.³⁴⁵ Further concerns about the efficacy of British Drugs came after Dale's animal experiments in 1921, which showed May & Baker's Novarsenobenzolbillion and Burroughs Wellcome's Neokharsivan were less effective than Bayer's Neosalvarsan.³⁴⁶ They questioned Pearson and Jowett of Burroughs Wellcome, who frankly admitted that owing to problems of toxicity and solubility, the formulation had been changed. The MRC advised a return to the old form. In contrast, the May & Baker representatives Blenkinsopp, Haythornthwaite and Ewins had not made any recent changes so the deficiency of their product could not be explained.³⁴⁷

With growing questions about the efficacy and safety of British Salvarsan, the MRC faced a further dilemma in June 1921. The Minister of Health received an application from a German firm to market Silver Salvarsan at prices considerably lower than the British preparations. This was exactly what Carr had predicted would happen. The MRC Salvarsan Committee deliberated that: "on the grounds of economy it could be an advantage to approve it.... [But] it was felt that the position of the British manufacturer

³⁴² MRC Salvarsan Committee Minutes MB22, (21 July 1920): 59.

³⁴³ MRC Salvarsan Committee Minutes MB22, (29 September 1920): 61.

³⁴⁴ MRC Salvarsan Committee Minutes MB22, (19 January 1921): 64.

³⁴⁵ MRC Salvarsan Committee Minutes MB22, (1 December 1920): 63.

³⁴⁶ MRC Salvarsan Committee Minutes MB22, (18 February 1921): 67.

³⁴⁷ MRC Salvarsan Committee Minutes MB22 (3 March 1921): 69; Richard Blenkinsopp was the eldest son of William who died in 1916 who was one of several Blenkinsopp's that had managed the firm since a new partnership had been established in 1876. Richard trained in chemistry at the City & Guilds College in Kensington from 1898-1900: Judy Slinn, (1984): 82-31, 86, 91, 94.

should be born in mind”: a further example of their support for the British industry.³⁴⁸ In October of 1921 there was a further application for sulpharsenol, which therefore had to undergo Dale's animal experiments for approval.³⁴⁹

When the MRC Salvarsan report was finally published in 1922, it recognised that there were safety issues such as a small degree of liver-impairment. They arranged a grant so that Surgeon Lt. Commander W. J. Gerrard at Haslar could do experiments using the van den Bergh test to look for early signs of toxic jaundice.³⁵⁰ However “Salvarsan preparations were more efficacious than any other treatment. Deaths are far outweighed by those, which would occur with other methods”.³⁵¹ One of the report’s principal conclusions was that the “especially high incidence of jaundice in military hospitals, was very much rarer than on the continent, especially in Germany”, indicating that British and French preparations may have been better tolerated. It commented on “especially reliable army records” and that “less reliance can be placed on the records of civil venereal clinics”.³⁵² However, as I showed previously, and as the Salvarsan Committee meeting minutes continued to show, the MRC were unsure how good their data was to support the British industry. The attempts of the MRC Salvarsan committee to assess clinical efficacy quantitatively in patients was frustrating compared to their earlier work with antitoxins and vaccines, where a defined dose could be given to an animal and the degree of immunity conferred could be measured numerically and presented statistically. Also the collection of data was easier as the administration was centrally co-ordinated. In the case of Salvarsan the dose strengths varied, the preparations varied, the duration of treatment and follow up varied and the MRC had limited control over the quality of data collected.

³⁴⁸ MRC Salvarsan Committee Minutes MB22, (30 June 1921): 79.

³⁴⁹ MRC Salvarsan Committee Minutes MB22, (6 October 1921): 89.

³⁵⁰ P. Fildes, R. J.G. Parnell, “A Clinical Study of the Toxic Effects, which Follow the Intravenous Administration of ‘914’: MRC Special Report Series 41 “Report of the Salvarsan Committee” (London: HMSO, 1922); MRC Salvarsan Committee II (1922); “Toxic Effects Following the Employment of Arsenobenzol Preparations: Report of the Salvarsan Committee” British Medical Journal (29 July 1922): 184; MRC Minutes II, (17 November 1922): 383.

³⁵¹ “Toxic Effects Following the Employment of Arsenobenzol Preparations: Report of the Salvarsan Committee” British Medical Journal (29 July 1922): 184.

³⁵² *Ibid.*

Frustrated by the lack of progress the MRC provided grants to investigators in Liverpool for “statistics and clinical investigation of results of different forms of Salvarsan and mercurial treatments”. Investigators at St Bartholomew’s studied the effects on hepatic adequacy, and a group at The Royal Navy hospital at Haslar near Gosport were asked to study the early signs of toxic jaundice.³⁵³

Then along came another thorny challenge. J. E. R. McDonagh was a London physician with years of experience in treating syphilis cases with Salvarsan and similar drugs³⁵⁴; we met him previously as one of the doctors unconvinced by the MRC that the British substitutes were as good as their German originals. In reply to the Secretary of the NIMR, McDonagh explained that he had performed experiments and read all of the literature, including patents. He explained his concerns about comparing British and German preparations: “because they are chemically identical it does not follow that they are similar in other respects”; he gave the example that synthetic salicylic acid looks and acts differently to extracts and that adrenalin and suprarenin are diametrically opposed. He also explained that the patents were written in such a manner as to deceive – so how could British firms be sure they prepared the drug in the same way? He observed that the Salvarsan produced by the two British firms had a low yield, and this suggested to McDonagh a less complete linkage. He contended that the German drugs produced after 1912 were actually of better quality than when the patents were written. He dismissed the MRC biological controls as ‘valueless’; animals were not as sensitive as man. Furthermore, he argued that the toxic effect was very much greater in cats compared to dogs. He went on:

“I am fairly of the opinion from the several toxic effects I have seen following the use of the new products that the successful manufacture has not been solved and that the medical profession would be well advised to await the reports of clinicians before using the product”.³⁵⁵

McDonagh’s stark criticism awakened a flurry of correspondence and editorial comment in the *British Medical Journal* including a rebuttal; “he does not convince us that they are

³⁵³ MRC Minutes II, (28 February 1921): 28; (17 November 1922): 383.

³⁵⁴ J. E. R. McDonagh, Salvarsan in Syphilis and Allied Diseases (London: Hodder & Stoughton, 1912).

well founded.” Nobody understood what McDonagh meant when he wrote by his references to incomplete linkages and colloidal arsenic. The MRC conceded that Salvarsan should be highly reduced but they disagreed that there was a difference between natural and synthetic salicylic acid; or between adrenalin and synthetic Suprarenin.

To counter these arguments McDonagh gave an even more technical explanation as to why he believed the British products prepared in a different way might be more toxic. He pointed out that the amount of reduction required was not specified in the German patents and challenged the MRC; “why did Ehrlich deem it necessary to have the reports of certain medical men before allowing the drug to come upon the market?”. Ehrlich took the same position in 1912 with neosalvarsan, although he was fully aware on ‘*a priori*’ grounds that the preparation was less toxic than Salvarsan. From his own experience McDonagh reported 6 cases of exfoliative dermatitis and 2 cases of jaundice treated with the Burroughs Wellcome Kharsivan. One died and three lost all of their hair and all cases had hyperkeratosis of the nails. None had more than 2 injections and two had only one injection. One had dermatitis only a week after injection. In contrast he argued that he had given thousands of injections of German products in up to 16 doses and had only ever seen one case of dermatitis exfoliate.³⁵⁶ This round of correspondence in the *British Medical Journal* was acutely embarrassing for the MRC as it challenged their authority in several ways. Closer inspection of McDonagh’s career however shows that he claimed to have discovered Ferrivine and Intamine, the iron salt of sulphanilic acid, and a substituted derivative used for acute and chronic syphilis respectively, and perhaps this interest to criticise British Salvarsan. A more independent view from Prof Bayliss offered “a caution against exaggerated optimism – any reasonably safe therapeutic procedure will, in this

³⁵⁵ J. E. R. McDonagh, “The Manufacture of Salvarsan Products in England and France” *British Medical Journal* (17 April 1915): 697.

³⁵⁶ Quote from J. E. R. McDonagh, “The Manufacture of Salvarsan Products in England and France” *British Medical Journal* (17 April 1915): 697; further correspondence: J. E. R. McDonagh, David Watson, “The Manufacture of Salvarsan Products in England and France” *British Medical Journal* (24 April 1915): 742-3; “Editorial comment” *British Medical Journal* (24 April 1915): 697; “Parenchymatous Syphilis” *British Medical Journal* (30 January 1915): 198;

country secure an unbiased trial, especially if there is sound experimental evidence in its favour”.³⁵⁷

4.12 Conclusions.

The War marked a watershed in the rebirth of the British pharmaceutical industry. In 1920 an editorial in the *Pharmaceutical Journal* summarised that: “In Britain the manufacture of fine chemicals during the war was carried on under the most adverse conditions as to building plant, labour material and other factors. So that it is highly creditable that much good results were achieved”.³⁵⁸ Manufacturers from previously diverse backgrounds restructured to prepare synthetic German drugs and alkaloids. The Government supported the industry by legislation, through access to scarce commodities, and by helping to co-ordinate supplies of important chemical intermediates. Firms made use of the scarce chemical manufacturing resources and expanded production significantly, but sought reassurances that their investments would be secure. Hundreds of thousands of pounds (weight) of the anaesthetics were made; 1,080 million tablets of medicines; by 1916 a total of 66 million doses of quinine salts and by 1917 a monthly supply of 12,500 lb.³⁵⁹ After Burroughs Wellcome lost researchers to the MRC, they turned to them for assistance in the biological standardisation of Salvarsan. Thus, the MRC supported British synthetic drug production and became the arbiters of drug safety and extended their role to also arbitrate on drug efficacy, but found that their data collection methods were inadequate due to limited control over wartime data collection. They were determined to collate accurate data and established a second Salvarsan committee from 1918 to 1924, during which time the MRC established their own clinical research sites; these were to perform laboratory research, but also could be called upon for clinical research. This will be evaluated further in the next chapter.

³⁵⁷ J. E. R. McDonagh, “The Rationale and Practice of Chemotherapy” *British Medical Journal* (22 April 1916): 591-2 and (10 June 1916): 820-1. This report continued the debate that McDonagh had initiated in his first publication in April and was carried out at a meeting of the Dermatological Section of the Royal Society of Medicine.

³⁵⁸ “Chemical Industry in Germany and the United Kingdom” *Pharmaceutical Journal* 104 (21 February 1920): 162.

³⁵⁹ Major General Sir W. G. MacPherson, *History of the Great War* volume 1 (London: HMSO, 1921): 178-9.

CHAPTER FIVE: Post-War Problems, Patriotism and Protectionism: Industry -led Campaigns and the Rise of Francis Carr.

5.1 Introduction.

As a result of the War it was recognised that Britain was too reliant on Germany for drugs, dyes and chemicals, evident in the fact that many British firms manufactured German drugs in the special conditions of wartime. Carr addressed the Nottingham branch of the Society for the Chemical Industry in November 1918 and described that: “an industry that had been developing pre-war has grown to considerable proportions producing organics, antiseptics, sedatives and local anaesthetics and diuretics of English manufacture”.¹ However, pharmaceutical firms expected some form of protection from the return of German competition post-war, and the increasingly influential Association of British Chemical Manufacturers led these campaigns.

This chapter deals with the new challenges of peace: on the one hand export markets re-opened, on the other hand huge wartime sales to the armed forces disappeared. Markets were further compromised by the rapid return to productivity of the German industry and the reparations imposed on Germany. British firms had to address these short-term competitive problems, while establishing the longer-term supply of chemical engineers and clinical trialists. This chapter is the first of three chapters addressing the period 1921-31 both from the industry and the MRC perspective as they tried to exclude ‘unsafe’ foreign drugs, with a ‘protectionist’ policy - the requirement for biologically standardised drugs by the NIMR. Chapter 6 addresses the campaign for clinical trials, which is kept separate because it occurred in three main waves in 1922, 1926 and 1931. Chapter 7 is then a case study of post-war developments and strategic discussions that took place within these frameworks in the Scientific and Technical Committee (STC) at Burroughs Wellcome 1925-1939, and that chapter sets the scene and gives an industry insight for chapter 8 on the establishment and working of the Therapeutic Trials Committee from 1931-39, in which insights from the STC are continued through to 1939.

¹ Francis Carr to SCI, reported in Nottingham Journal, (October 1918) Carr Archives. 2130 B/CARR IV Press Cuttings: 6.

Post-war British pharmaceutical firms looked to the government for assistance and protection and were partially successful. Their initial gains, however, were temporary, resulting in a downturn in their business. Fortunately for British firms, new therapeutic opportunities allowed them to expand in new directions without directly having to challenge the increasing competition from the merger of several German firms. Nevertheless, British firms continued to manufacture some synthetic drugs - an important interwar development in Britain, which has been underestimated by historians.

5.2 Post-War Campaigns for the Protection of the Pharmaceutical Industry.

British companies took advantage of markets that opened up as a result of the ending of hostilities, leading to a boom period of 18 months as export restrictions were removed, but this only delayed the problems of over-capacity of pre-war standard drugs, ahead of an abrupt economic downturn, coinciding with the miners strike and rising unemployment.²

The end of the War rapidly decreased the demand for painkillers, antiseptics, vaccines, serums and anaesthetics.³ It also brought renewed competition from Germany in the production of synthetic drugs.⁴ Even to remain competitive with Merck and Schering in production of alkaloids required technological advances. The recommendations of the new British Pharmacopoeia of 1914, only partly implemented during the War, had the effect of replacing more alkaloids by pure active principles, some of which were synthetic.⁵ The market challenges were compounded by the surplus of German drugs as the Treaty of

² A. J. P. Taylor, English History 1914 - 1945 (Oxford: Clarendon Press, 1988): 142-5, 163; G. C. Allen, British Industries and their Organization (London: Longmans, 4th edition 1959).

³ In 1918 Burroughs Wellcome produced over one and a half million packs of sera and vaccines. H. J. Parish WF: 85/20:2.

⁴ From Germanin to Acylureidopenicillin: Research That Made History (Bayer: Leverkusen, 1980): 18.

⁵ Cantharides was replaced by cantharadine, coca by cocaine, jaborandi by pilocarpine and physostigmine by eserine. "B.P. 1914" British Medical Journal (10 October 1914): 634.

Versailles allowed the Reparations Committee to seize one half of German stocks held on 15 August 1919, and 25% of average monthly production up to 1 January 1925.⁶

The campaign for protection of the British pharmaceutical industry had begun during the War with the foundation of the ABCM in 1916. Just before this, in 1915, in his paper “The Manufacture of Organic Drugs Affected by the War” Francis Carr wrote:

“No longer can we be satisfied to be externally dependent for supplies of vital importance. It is our duty to admit frankly today that some form of protection is of vital necessity during the coming 10 years, while we develop a complete organisation and rectify educational shortcomings. Without this protection, what has already been achieved will rapidly and completely be devastated by competition from abroad. There can be no doubt that the industry unprotected would become the butt of heavy German artillery”.⁷

As a result of their poor competitiveness, the British pharmaceutical firms sought the same ten-year period of protection promised for dyestuffs from 15 May 1918, to allow a period of consolidation in order to establish more efficient drug production and research facilities. The British Dyestuffs Corporation was established in November 1918, bringing together most of the major British dye manufacturers.⁸ This offered the potential future benefits for pharmaceutical firms of better provision of chemical intermediates and solvents, which remained in limited supply as a result of the continued Trading with the Enemy Act and its German equivalent.⁹

In November of 1918 the Board of Trade issued a White Paper promising grants-in-aid for expansion and research, and this was officially announced as the Customs

⁶ A. J. P. Taylor, (1988): 127, 149. This was later modified in 1924 under the Dawes plan: L. F. Haber, The Chemical Industry 1900-1930 (Oxford: Clarendon Press, 1971): 248-9.

⁷ F. H. Carr, The British & Colonial Pharmacist (June 1915): 436-7.

⁸ “Scheme for the Allocation and Administration of the Funds Provided by Parliament for the Development of the Dye Industry by Means of Financial Assistance to Companies and Firms in Aid of Development, Extensions and Research” (London: H. M. S. O., 1918) Cmnd 9194; M. R. Fox, Dye-Makers of Great Britain 1856-1976 (Manchester: ICI plc. 1987): 55- 57, 60, 86, 156, 158, 168.

⁹ A. J. P. Taylor, (1988): 17 - 18; W. J. Reader, “British Dyestuffs: the Struggle for Survival 1919 –1926” Imperial Chemical Industries Ltd. A History: The Forerunners 1870 - 1926 volume 1(London: Oxford University Press, 1970): 425-445.

Consolidation Act (Dyestuffs: Prohibition of Imports Proclamation), which came into force on 24 February 1919 to begin the period of protection.¹⁰ This was a temporary measure, initially to the end of 1919, but with the suggestion of a ten-year extension.

5.3 The ABCM Mission to German Manufacturing Sites.

In 1915 William Tilden had described the organisation of German chemical companies. Management was by competent specialists, who were constantly on the lookout for new discoveries, and who had a large technical staff to make discoveries commercially viable, by securing cheap materials, improving processes and creating a demand. They had a legal staff, which patented all improvements and described them vaguely to prevent copying.¹¹ German companies influenced their Government on aspects of tax and freight costs and they had agencies spread around the world that encouraged an extensive credit system.¹² Little was known, however, about the way in which German firms structured their manufacturing capacity until the invasion and occupation of parts of Germany allowed a direct evaluation of German factories and processes. The first action organised by the ABCM in 1919 was the arrangement for a chemical mission to travel to Germany to evaluate what could be learned from the structure and workings of German pharmaceutical manufacturing plants.¹³

The ABCM party of 20 members plus 5 Government officials that visited Germany in May to June 1919 included Francis Carr of Boots, who had been responsible for the early British manufacture of Salvarsan at Burroughs Wellcome and of Flavine at Boots, and Ivan Levinstein of Levinstein's dye firm, who had taken over the Ellesmere Port factory to produce Novocaine and other German drugs. In June 1919 the ABCM reported on "the British Chemical Mission on Chemical Factories in the Occupied area of Germany." The aim of the visit was:

¹⁰ L. F. Haber, (1971): 173; W. J. Reader, (1970): 280.

¹¹ William A. Tilden, *The Supply of Chemicals to Britain and Her Dependencies*, in W. M. Gardner, *The British Coal Tar Industry: its Origin, Development and Decline* (London: Williams & Norgate, 1915): 315-334.

¹² F. H. Carr, "Synthetic Organic Drugs" *Chemist and Druggist* 88.4 (29 July 1916): 778-80; L. F. Haber, (1971): 129.

“Not so much to ascertain details as to temperatures, pressures and quantities of chemicals) used... (but) to determine the basic principles which must be adopted if British chemical manufacturers are to compete successfully with the established German undertakings”.¹⁴

The ABCM visited 39 works and found that German plants were designed to operate continuously in regular sequence, starting from initial reactions on upper floors down to crystallisation and packing on the lower floors. Large-scale operations could be operated independently of others - chemicals used once were recovered and reused. Equipment such as glassware, autoclaves, stirring and lifting machines were all of a much higher standard in Germany than in Britain. The ABCM also confirmed the greater commercial awareness, with a special development section within Bayer bringing together chemists, engineers and accountants.¹⁵ In the sales propaganda department of Bayer there were 70 graduates qualified in biology, pharmacology and chemistry who were active throughout Germany, divided into 12 districts, each including about 4 universities. Each one reported to Leverkusen, the head office, which produced propaganda. Free samples of drugs were given out, but not indiscriminately - only when asked for by doctors interested in a given subject.

The visits to German factories made the ABCM aware of what they were up against, not only regarding drugs but also key chemical intermediates. However, there were no factories in the occupied area that produced methanol (by wood distillation), formaldehyde or formic acid, although plants making acetic acid, sodium acetate, acetic anhydride, chloroacetic acid and alcohol were visited. The factories of Bayer at Elberfeld and Merck at Darmstadt were just outside the occupied area. Nevertheless, processes for the production of salicylic acid, sodium salicylate, phenacetin, antipyrin, Salvarsan and its

¹³ “Chemical Industry in Germany and the United Kingdom” Pharmaceutical Journal 104 (21 February 1920): 162.

¹⁴ Association of British Chemical Manufacturers, Report of the British Chemical Mission on Chemical Factories in the Occupied Area of Germany (London: ABCM, June 1919): 101.

¹⁵ Association of British Chemical Manufacturers, (1919): 14, 36, 101-3; J. F. Thorpe, in E. F. Armstrong (ed.), Chemistry in the Twentieth Century: An Account of the Achievement and the Present State of Knowledge of Chemical Science (London: HMSO, 1929), Cmnd. 3282: 315 ff.

derivatives, lactic acid, chloral, chloroform, cholic acid, opium alkaloids and cocaine hydrochloride were seen. The success of German firms was attributed to the scientific equipment and control, mass production, efficiency and sufficiency of plant, cooperation with other manufacturers in eliminating wasteful competition, while continuing to stimulate the introduction of new methods and new products. Laboratories were divided into research for new products and separate sections for technological research directed at improvement and control of processes, especially the intermediate stages of new drug manufacture. The laboratories had a high percentage of trained specialists: at Boehringer, where opiates were prepared, 10% were chemists. Some manufacture was restricted to large capacity firms for efficiency. Examples given included the production of 2 tons per day of glacial acetic acid at Knapsack, 20 tons a month of antipyrin at Hoechst, and the small but specialized works of Boehringer produced 40-80 oz. of cocaine hydrochloride per day, 80 tons a month of tartaric acid and 3 tons a day of lactic acid. Important by-products were recovered during manufacture: in the case of antipyrin these were benzene, sodium bromide, and sodium acetate and in the case of Salvarsan these were ether and methyl alcohol.¹⁶

German firms dealt directly with customers rather than through wholesalers and agents: "They seem to have possessed a unique capacity to excite, and involving ordinary people in their affairs. In Germany the whole community takes interest in the chemical industry and this is perhaps one of the predominating factors in promoting the welfare of that industry".¹⁷

The ABCM recognised that:

"British chemical manufacturers must not only possess the necessary financial means, but must be willing to spend freely large sums of money in extending the scientific side of their activities. Libraries and laboratories must be fitted up or extended, a staff of chemists trained for the supervision of different processes, and adequate buildings and plant erected in order to compete with foreign countries."

¹⁶ Association of British Chemical Manufacturers, (June 1919): 101- 103.

¹⁷ Quoted in Lee Niedrighaus Davis, The Corporate Alchemists: the Power and Problems of the Chemical Industry (London: Temple Smith, 1984): 56.

And “It is evident that British chemical manufacturers will not be able to compete successfully with the German industry until some such cooperation has been effected”.¹⁸

The ABCM stated that:

“It is of importance that chemical engineers in this country should devote their attention to the question of being able to supply standard plant, such as tile-lined iron vessels as used for corrosive acids, etc., autoclaves, stills, a variety of enamel ware, earthenware and filtering apparatus quickly and economically”

(and) “to equip their works on these [German] lines, British chemical manufacturers will require a large supply of well trained chemists who are not only able but willing to specialise in the particular branch”¹⁹.

German factories were “in splendid conditions with a large and highly trained force of employees, and moreover with additional opportunities for increasing their production by utilizing the extra equipment added for war material production” described as “ a dangerous factor in the struggle for commercial supremacy”.²⁰ The clear messages taken home were the need for better organisation of facilities, and greater efficiency of manufacture. In short there was a significant role to be played by chemical engineers. While Levinstein returned primarily to dyestuffs manufacture, Francis Carr, as one of these rare chemical engineers took up the gauntlet to campaign for better training of this particular type of chemist for the pharmaceutical industry and this will be addressed later, but towards the end of 1919 a more immediate challenge threatened the British pharmaceutical manufacturers.

5.4 The Sankey Judgment and its Consequences.

The protection initially afforded to British manufacturers, restricting dye imports was foiled when Lord Justice Sankey confirmed on 17 December 1919 that the Dyestuffs Prohibition of Imports Proclamation set up to offer protection was illegal. It had been based on the 1876 Customs Consolidation Act, which prohibited “arms, ammunition, gunpowder and any other goods”. Following German protestations Sankey ruled that law did not give the Government the power to invoke restriction on the trade of dyes, so he had

¹⁸ Association of British Chemical Manufacturers, (1919): 103.

¹⁹ Association of British Chemical Manufacturers, (1919): 102-103.

²⁰ “German Poison Gas Factories” Chemist & Druggist 91.3 (28 June 1919): 55.

no option but to allow German imports.²¹ This judgment quickly led to “the swamping of the market with German drugs”.²² At the annual dinner of the Chemical Industry Club in 1920, Lord Moulton recounted: “We are at this present at a crisis of our history. If England does not realise that it must be a great chemical nation, its future is gone”.²³

Immediately after the Sankey judgment, British firms campaigned for further protection in the short term. Firms represented by the Salicylic Acid Association clearly realised that they could only succeed in the long term if prices came down due to efficiencies and they became more competitive rather than just relying on protection. However, they needed some protection to get time to develop this efficiency of production.²⁴ The Society of Dyers and Colourists lobbied for extended protection of the dyestuffs industry, suggesting that the Germans had too easily circumvented the 1907 Patent Act (discussed previously), and that the British dye and related chemical industries were of key strategic importance. They suggested that tariff protection would allow British firms time to establish chemical plants and research facilities and to become competitive.

Protection was eventually granted for dyes in 1920 in the form of the Board of Trade Dyestuffs (Import Regulations) Act, which came into operation on 15 January 1921.²⁵ Immediately the ABCM lobbied for an extension of the protection to include “synthetic organic chemicals, analytical reagents, all other fine chemicals except sulphate of quinine, except of vegetable origins or from fermentation processes”.²⁶

²¹ “Society of the Chemical Industry” Chemist & Druggist 93.3 (11 December 1920): 57; S. Miall, History of the British Chemical Industry (London: Ernest Benn Ltd, 1931): 95-96; M. R. Fox, (1967): 56 – 60 (quote), 85, 89; W. J. Reader, (1970): 280, 430-1, 439.

²² Editorial, “The Fine Chemical Industry” British Medical Journal (22 January 1921): 133.

²³ The quote is from “Warfare and the Dye Industry” Chemist & Druggist 93.3 (27 November 1920): 92. Moulton died the following year, “Lord Moulton of Bank” British Medical Journal (19 March 1921): 433.

²⁴ F. H. Carr, “Society of Chemical Industry” Chemist & Druggist 93.1 (17 July 1920) at 4th ABCM.

²⁵ M. R. Fox, (1987): 60.

²⁶ J. Davidson Pratt, “The Economics of the Fine Chemical Industry” Chemistry and Industry (20 January 1951): 38.

Lobbying from the Institute of Chemistry also began in 1920, with Francis Carr, now at British Drug Houses, once more involved supporting legislation to protect the manufacture of chemicals and chemical glassware as key industries. Carr emphasised the social benefits of chemistry, the raising of the skills of the country, and its strategic importance, not only in the production of fine chemicals and drugs but also T.N.T. and poisonous gases. He urged that England should be a great manufacturing nation and a shopkeeper. He particularly pointed to protectionism in Germany and America and the effect on prices such as the extortionately high price for saccharin.²⁷ He discussed the necessity of retaining the hold on organics and also referred to important new developments of novel hormone extracts such as thyroxin in 1918²⁸

Charles Hill, Chairman of BDH. emphasised that the industry wanted protection for analytical and research reagents, pharmaceuticals and photographic materials, arguing that “the expansion of an organic chemical industry is intimately associated with developments in biochemistry or therapeutics”.²⁹ The Key Industries Act was extended eventually to pharmaceuticals as the Safeguarding of Industry Act in 1921, and levied a tariff of 33.3% on imports. Pearson of Burroughs Wellcome wrote to the *Times* about his firm’s approval of the Safeguarding of Industry Act though the rate of tax was less than he had hoped for. He claimed:

“The adverse conditions which he foresaw in 1918 have since become realities and the competition from Germany and other countries is now such that unless the S.C.I. obtains some assistance at some time, this country will sink back into the condition that it was in before the war – in the event of another war, this country will again be dependent for our supplies of vital chemicals on foreign and possibly hostile nations”.

He referred to the recent case of the closure of 14 manufacturers of chemical glassware in this country and 6,000 employees being given 7 days notice.³⁰ Samuel Rideal, Fellow at

²⁷ Notes handwritten by Carr in preparation for a lecture - Files of Francis Howard Carr, B.CARR. at the Imperial Institute, London 2131 B/CARR III, 1920

²⁸ “Dyestuffs (Import Regulation) Bill” Chemist & Druggist 93.3 (11 December 1920): 58-9.

²⁹ C. A. Hill, (Society of the Chemical Industry) “The Fine Chemical Industry” British Medical Journal (22 January 1921): 133.

³⁰ “Industrial Protection” Chemist & Druggist 94.2 (9 April 1921): 33-34.

UCH wrote in the preface to Barrowcliff and Carr's book, *Organic Medicinal Chemicals* published in 1921: "Creditable though the accomplishments, British manufacture is not especially cost-effective".³¹ Carr gave a presentation in London in February 1921 entitled "Industrial research – importance against future attack by a foreign power" in which he emphasised that it was only by the alliance of chemical research that we could hope to meet effectively the flood of German competition.³²

Some wartime (and earlier) problems remained. The Government still demanded the payment of what manufacturers considered to be excessive duty to be paid on industrial alcohol, though its availability in Britain was at least guaranteed by mergers to form the Distillers Company immediately post-war and by the 'Pure Methylated Spirits' regulation of 1921.³³ Capital grants, building materials and fuel remained in short supply. The situation worsened in 1921 when there was a national trading loss of £204,159. After depreciation and tax refunds the losses were in excess of £1 million on sales, which were a quarter of the 1920 level.³⁴

The *Economist* described 1921 as "one of the worst years of depression since industrial revolution".³⁵ For the British pharmaceutical industry to survive it had to increase the efficiency of its process chemistry of large-scale production to be competitive or it had to change from imitation to innovation. George Pearson of Burroughs Wellcome commented that British firms "had the capacity to become a major manufacturer of synthetic drugs if given the chance to develop its industry".³⁶

In a British Science Guild booklet prepared in 1921 Carr wrote that:

³¹ S. Rideal, preface in M. Barrowcliff, F. H. Carr, Industrial Research: Organic Medicinal Chemicals (London: Ballière, Tindall & Cox, 1921).

³² F. H. Carr, "Industrial Research- Importance Against Future Attacks by a Foreign Power" Chemical Age (12 February 1921)- summary of paper is in the Carr Archive at Imperial Institute, London. 2131 B/CARR 2 IV Press cuttings: 7

³³ E. F. Armstrong, (1924): 20.

³⁴ L. F. Haber, (1971): 247.

³⁵ A. J. P Taylor, (1988): 144, 163.

³⁶ "Industrial Protection" Chemist & Druggist 94.2 (9 April 1921): 33-34.

“Future progress lies in extending the use in our industry, in closest possible relationship with that carried out in academic institutions and under the aegis of the M.R.C and secondly by finding employment for greater numbers of scientifically trained staffs and workers to whom is given responsibility and a living interest is the work they are performing”.³⁷

Britain also sought novel ways of excluding German drugs; the 1921 British Pharmaceutical Conference executive committee continued the process of defining essential drugs and included the pharmaceutical manufacturers, Charles Hill of BDH and E. T. Neathercott³⁸ of Savory & Moore, while the research subcommittee included both Fred Gamble of Allen & Hanbury’s and Charles Hill.³⁹ In 1922 the ABCM took this a step further, producing a list of over 2,000 fine chemicals already manufactured in Britain, emphasising that we “ought to be independent of foreign supplies”.⁴⁰

Stanley Baldwin took up this campaign in October 1922 as he felt that Britain could only fight unemployment with protection, which became one of the key election issues. However, the election of December 1923 went against protection.⁴¹ Nevertheless, the change had been dramatic, as the Key Industry Act at least gave companies the confidence to forge ahead producing German – style drugs. The Society of Public Analysts, including Carr, campaigned for more stringent tests before drugs were sold, and they met with the Retail Pharmacists Union represented by Frederick Gamble of Allen & Hanbury’s at the Institute of Chemistry on 12th June 1923 to discuss the Sale of Foods and Drugs Act.⁴² Gamble sent a letter to the Minister of Health about the variable analysis of prescribed medicines.⁴³ By the time of their 1923 annual report, the increasingly influential ABCM had expanded to represent 150 firms, and produced a directory in French, Spanish,

³⁷ F. H. Carr, British Science Guild booklet, 1921 in the Carr archives 2130 B/CARR, Imperial Institute, London page 77.

³⁸ G. E. Pearson, WF: E2PF YL Box 23: 28.

³⁹ “Government Chemistry” Chemist & Druggist 95.2 (5 November 1921): 59

⁴⁰ “British Fine Chemicals” British Medical Journal (22 April 1922): 666.

⁴¹ A. J. P. Taylor, English History 1914 - 1945 (Oxford: Clarendon Press, 1988): 206, 208, 220-1.

⁴² “Sale of Food and Drugs Act” Chemist & Druggist 99.1 (4 August 1923): 183-184.

⁴³ “The Conference Past and Present” Chemist & Druggist 99.1 (28 July 1923): 129-133.

Portuguese, Italian and German. They claimed: “We can produce irrefutable data that the Key Industry duty has been instrumental in promoting the development of this important key industry”.⁴⁴ An editorial in *Chemist & Druggist* agreed that manufacturers had been “assisted in a small way by the Act”.⁴⁵

A pattern can be seen emerging which paralleled the continued actions of the government in their campaigns against patent medicines and in their quest for biological standardisation of drugs that could not be assayed by chemical means. If the German drugs could not be excluded by tariffs, then they could be excluded by raising the barriers to marketing them, namely, requiring further chemical and biological tests and ultimately clinical trials. Standardisation with checking of purity became important tools in excluding substandard foreign preparations.

The debates around Protection within the pharmaceutical firms mirrored those in wider political circles. Three elections between October 1922 and October 1924 were fought on these issues.⁴⁶ At the end of 1923, just before another general election, Charles Hill wrote in a letter to the Times:

“It is well that candidates of whatever political party and every voter should understand the position. Circumstances have conspired to minimise the usefulness of the Safeguarding of Industry Act. The country overflowed with stocks of foreign chemicals brought in immediately prior to the Act coming into force. The depressed currency made the 33.3% duty of little avail”.⁴⁷

Charles Hill considered that it was essential to maintain the Act on the statute and if it was dropped or replaced by some other protection “would mean giving back to Germany the supremacy in the fine chemical industry which she possessed before the war”.⁴⁸ The aim

⁴⁴ “ABCM” *British Medical Journal* (9 June 1923): 1003.

⁴⁵ “The Fine Chemicals Market” *Chemist & Druggist* 99.2 (3 November 1923): 621.

⁴⁶ A. J. P. Taylor, (1988): 195, 197, 206-7, 230.

⁴⁷ *The Times* (27 November 1927). The letter also appeared in C. A. Hill, “Fine Chemical Industry Outlook” *Chemist & Druggist* 99.2 (1 December 1923): 751.

⁴⁸ *Ibid.*

was to extend the duration of the provisions of the Safeguarding Industries Act, which was due to lapse on 19th August 1924.⁴⁹

The ABCM and SCI collaborated closely throughout this period and many of the committee members were common to both Societies. Edward Frankland Armstrong, who spoke at the ABCM annual meeting in July 1924, also chaired the SCI meeting and discussed the possibility of sharing the same building for the Chemical Society, Society for the Chemical Industry, Association of British Chemical Manufacturers, Institute of Chemical Engineers and Institute of Chemistry, thus cementing their collaboration.⁵⁰

5.5 British Pharmaceutical Firms Post-War.

Falling sales and the associated excess capacity brought a decreasing return on the British pharmaceutical firms' expanded fixed assets. Small, geographically isolated firms, dependent on others for intermediates were a feature of many British industries in the inter-war period.⁵¹ A specific example of this had been cited in the ABCM document in 1919. In Britain a mixture of gas companies, dye firms, fine chemical manufacturers and others used low efficiency methods to make salicylic acid. Because of the decreasing market and increased competition from Germany, British firms had rapidly to rationalise their production and decide which of several paths to follow. The SCI meeting on 17 September 1921 discussed synthetic ways of making natural products as one possible way forward.⁵²

For firms such as Burroughs Wellcome, Boots, British Drug Houses and May & Baker that had prepared synthetic drugs, even if only to a limited degree, the choice was most difficult. They could return to their large ranges of simple drugs, or, having invested in expensive manufacturing plant, could attempt further production of a narrower range of

⁴⁹ "Westminster Wisdom – Safeguarding Industry, Therapeutic Substances Bill" Chemist & Druggist 100.2 (12 April 1924): 526.

⁵⁰ "The Association of British Chemical Manufacturers" Chemist & Druggist 101.1 (26 July 1924): 124.

⁵¹ T. H. Burnham, G. D. Hoskins, Iron and Steel in Britain (London: Allen & Unwin, 1943): 149 – 190.

⁵² "Society of the Chemical Industry" Chemist & Druggist 95.2: (17 September 1921) 42-43.

more complex synthetic drugs like Salvarsan, with higher profit margins, but in competition with German firms. In practice most compromised and continued producing biological drugs as new opportunities arose in the field. The firm of Evans Sons, Lescher and Webb, which had prepared some synthetics, decided instead to concentrate on physiological standardisation of natural extracts and also continued to prepare vaccines and antitoxins at their Biological Institute in association with the physiologist Charles Sherrington of Liverpool (and later Oxford),⁵³ and at their fine chemicals department, established in 1916 at Runcorn in Cheshire.⁵⁴

I will now describe the size of British firms and especially their laboratory staff, and how firms acted differently and this background will aid an understanding of the interactions with the MRC Therapeutic Trials Committee as will be described in the final chapter. The strategic dilemmas faced by Burroughs Wellcome are discussed in greater detail in the next chapter, as direct evidence is available from the minutes of their Scientific and Technical Committee (STC).

5.5.1 May & Baker: May & Baker produced fine chemicals and inorganics such as lithium before the War. Their general manager, William Blenkinsopp's son Richard, was well suited to weigh up the possibilities as he had studied chemistry at the City & Guilds College in South Kensington. His father had built up an informal relationship with Poulenc of France from 1909, which was formalised in September 1916 after Poulenc received a license to prepare Salvarsan derivatives. May & Baker bought a factory at Bell Lane, Wandsworth and acquired Arthur Ewins, the ex- Burroughs Wellcome chemist from the MRC as chief manufacturing chemist. Ewins appointed George Newberry, a graduate of the Royal College of Science, who helped during the war and joined permanently in March 1918, and Capt. R. W. E. Stickings, a graduate of Kings College was appointed Works manager. In Slinn's account she found that few records survived to document wartime

⁵³ E. G. T. Liddell, "Charles Scott Sherrington" Obituary Notices of Fellows of the Royal Society 8 (1952): 241-70; M. W. Weatherall, Gentlemen, Scientists, and Doctors: Medicine at Cambridge 1800-1940 (Cambridge: Boydell Press, 2000): 139, 170, 173, 221.

⁵⁴ The Story of Evans Medical Supplies 1809-1959 (Liverpool and London: Evans Medical Supplies, 1959): Dr. H. Wolferstan Thomas, their first Director, first described the value of Atoxyl for trypanosomiasis while working at the school of Tropical medicine in Liverpool. C. Turner (ed.), Gold on the Green: Fifty Glaxo Years at Greenford, (Greenford: Glaxo, 1985).

difficulties. May & Baker did well out of the war. Their net profits rose from a steady £6-7,000 pre-war to a peak of £209,000 in 1916. However, with the death of the General Manager in 1918 they were cautious in extending the lease of the factory, with the option to purchase it for £25,000 by the end of 1922. May & Baker struggled and made a trading loss of £10,888 in 1921 compared with a profit of £31,606 the previous year and turnover fell to its lowest level in 1922.⁵⁵ In the period from 1923, Poulenc arranged to purchase shares in May & Baker and in 1927 the firm effectively became a subsidiary of the French firm and the following year Poulenc merged with the Société Chimique des Usines du Rhône. Thus, although May & Baker appeared to fail to invest and commit strongly to synthetics, they acquired experience of synthetic drugs by their merger.⁵⁶ In addition to Ewins there were only three other chemists at M & B until 1925.⁵⁷ In 1924 Dr T. B. Maxwell joined M & B as an assistant manager. By 1927 May & Baker expanded their research facilities and employed four chemists and two pharmacists. Harry James Barber joined as a research chemist in 1927 and became production manager from 1929-1934.⁵⁸

5.5.2 Boots: Having lost Francis Carr in 1920, Boots regressed into their old production methods. After the war Jesse Boot, suffering from arthritis, decided to sell his company to the American-based United Drug Company in 1920. During the 1921 Miners strike, many manufacturing processes were shut down and only a skeleton staff worked in the chemical department at Boots with only 3-4 chemists, including Dr. J. Marshall and H. H. L. Levene, who played prominent roles in the inter-war period.⁵⁹ Jesse Boot, in a manner similar to Henry Wellcome, made huge philanthropic payments towards the establishment of the

⁵⁵ Judy Slinn, (1984): 95-96; G. Tweedale, At the Sign of the Plough: Allen & Hanbury's and the British Pharmaceutical Industry 1715-1990 (London: Murray, 1990): 125; C. Turner (ed.), (1985): 14.

⁵⁶ J. Slinn, (1984): 99-126.

⁵⁷ J. Slinn, (1984): 100 - 101.

⁵⁸ H. J. Barber, Historical Aspects of Chemotherapy: Six Essays (May & Baker, 1978).

⁵⁹ W. H. Sims "Notes" (8 November 1963): 2; Dr. J. Marshall retired in 1950 and Mr. H. H. L. Levene retired in the 1960's; Carr's departure is discussed in S. Chapman, Jesse Boot of Boots the Chemist: A Study in Business History (London: Hodder & Stoughton, 1974): 127.

University College of Nottingham, while his retail firm expanded further in the hands of his son John. Boots did however extend their manufacturing capacity to prepare insulin.

Many chemicals were made in small quantities and were sold to the photographic industry, but this became unprofitable after the removal of import duties and Boots began screening of new chemicals again in 1923, no doubt stimulated by the success of insulin and arsphenamine (Stabilarsan). Insulin was produced from June 1923, after Dr. Marshall visited Toronto, and arsphenamine was licensed from an American university. As both were injected, Boots had to master new techniques such as sterile manufacture. In order to achieve this, bacteriological and pharmacological laboratories were founded.⁶⁰ However the laboratories were small and John Boot, son of the founder took up the challenge to develop a new site at Bulwell just outside Nottingham early in 1927⁶¹ allowing a significant expansion, as they began to make their own process chemicals such as the oxidising agents sodium and potassium dichromate. Dr. Frank Lee Pyman, who had been at Burroughs Wellcome until 1914, and then Professor of Technological Chemistry at the University of Manchester, joined Boots in July 1927 as Director of Research, bringing with him five postgraduate chemists, taking the total up to nine.⁶² Pyman directed synthetic work on some glyoxalines, soluble glycerophosphate salts and a series of antiseptics. C. E. Coulthard, and J. Marshall supported Pyman in developing a homologous series of phenols, leading to the description of n-amyl-meta- cresol as an antiseptic.⁶³ During 1927 Boots produced saccharin, finely- divided bismuth (Bismostab), potassium iodide, Glauber's salt, sulphostab, quinine salts, hexylresorcinol, aspirin, chloroform, acriflavine, insulin and liver extract, dimethyl sulphate, butyl chloral hydrate, benzyl chloride, phthalic anhydride, and

⁶⁰ J. Slinn, (1984): 95-110.

⁶¹ Christopher Weir, Jesse Boot of Nottingham. Founder of the Boots Company (Nottingham: The Boots Company, 1994).

⁶² Leonard Anderson of Boots fine chemical department recommended Pyman as the best research chemist in the country after Sir Robert Robinson. Pyman was initially involved in determining the structures of natural agents, mostly alkaloids and hormonal extracts; H. King, "Frank Lee Pyman, 1882- 1944" Obituary Notices of Fellows of the Royal Society 4 (1944): 681- 697.

⁶³ F. L. Pyman, C. E. Coulthard, J. Marshall, "The Variation of Phenol Coefficients in Homologous Series of Phenols" J. Chem. Soc. (1930): 280.

vanillin. It was through work on patents for hexylresorcinol and preparation of alkyl phenols that amylmetacresol was discovered, extending Boots main interest in antiseptics.⁶⁴

5.5.3 Howard's: Howard's produced tablets of alkaloids and established a research department in 1919, hiring Dr. John William Blagden from C. F. Boehringer & Sons of Mannheim. David Howard was a chemist, who like William Perkin had trained under August Wilhelm Hofmann at the Royal College of Chemistry in London.⁶⁵

5.5.4 Glaxo: In the early post war period only Allen and Hanbury's and Glaxo were added to those who began to produce drugs.⁶⁶ The company later known as Glaxo started as Nathan's. They had originated from a New Zealand firm that had imported dairy produce and took their new name from their milk substitute advertised as: "Glaxo builds bonnie babies".⁶⁷ Nathan's (Glaxo) grew in niche markets through dramatically increased export sales of nutritional products, and dried milk substitutes and had a large range of malted products due to concerns over tuberculosis- infected natural milk.⁶⁸ However, they incorporated scientific thinking into promotional material:

"Biologists have shown that sunlight acts as effectively as cod liver oil in respect to the cure and prevention of tuberculosis and rickets and it increases phosphorus and calcium content. Milk of perfect composition can be produced only by cows which are properly sunlit and feeding green grass, itself the product of sunlight. Such milk is brought to this country in the form of Glaxo dried milk".⁶⁹

Glaxo had a turnover of only £½ m in 1918 and they were just beginning to develop pharmaceuticals simply by adding vitamins to their milk products. Sales increased up to 1921 before falling back between 1921 and 1925.⁷⁰ Their early laboratory research began

⁶⁴ S. A. B. Kipping, Chemistry and Industry (25 February 1963): 303-4.

⁶⁵ A.W. Slater, Howard's Chemical Manufacturers 1797-1837: a Study in Business History, (University of London, M.Sc 1956); Blagden had been interred during the war; Howard's 1797-1947 (London: Howard's, 1947).

⁶⁶ R. P. T. Davenport-Hines and Judy Slinn, Glaxo: A History to 1962 (Cambridge: Cambridge University Press, 1992): 68- 134; G. Tweedale, (1990).

⁶⁷ C. Turner (ed.), (1985): 17; R. P. T. Davenport-Hines, J. Slinn, (1992): 29, 33.

⁶⁸ G. Tweedale, (1990): 91-97, 127,157, 182,184.

⁶⁹ Advert "Sunlight in Milk" Chemist & Druggist 100.1 (1924): 126.

⁷⁰ R. P. T. Davenport-Hines, J. Slinn, (1992): 46, 99.

when they hired a 17-year-old man called Ted Farmer, who would play an important role in their laboratory. They also hired an experienced analyst, Norman Radcliffe, and in January 1920 they took on the Cambridge graduate, Alfred Louis Bacharach, from the analytical laboratories at Burroughs Wellcome and G. P. Dodds from the Oxford public analysts' laboratory. Glaxo took on Harry Jephcott, a young man with a Pharmaceutical Society diploma and a first class degree in chemistry.⁷¹ Together this small team began to investigate the vitamin content of their milk products under various conditions. Davenport-Hines and Slinn gave a detailed account of the early work on vitamins in their Glaxo history.⁷² Diseases due to diet deficiencies were recognised by Bland-Sutton in 1889 and Casimir Funk of the Lister Institute coined the term vitamin(e) in 1912. Rickets was known to be due to a fat-free diet and cod liver oil was beneficial.⁷³

Bacharach and Harry Jephcott discovered that their dried milk was deficient in fat-soluble vitamins, performing studies in animals after the firm was granted a Home Office license. Bacharach was a member of the Society of Public Analysts from 1919 and presented data on vitamins at several of their meetings.⁷⁴ Harry Jephcott, visiting an International Dairy Congress in Washington D.C. in 1923, took the chance to visit the Johns Hopkins Hospital in Baltimore where Prof. Elmer V. McCollum claimed to have identified the anti-rachitic factor, which he called vitamin D, and in 1924 negotiated with Columbia University a process for extracting vitamin D, with which Glaxo fortified their milk products 1,000 fold.

They then produced their first pharmaceutical Ostelin D in August 1924, the earliest standardised vitamin concentrate on the British market, with an activity 2,000 times that of cod liver oil. It was recommended by the *Lancet* and soon replaced cod liver oil as a therapy for rickets, though cod liver oil remained useful as it also contained vitamin A and

⁷¹ R. P. T. Davenport-Hines, J. Slinn, (1992), 47,49-50,64,66-7,71,87,97,114,124, 157-8; C. Turner (ed.), Gold on the Green. 50 Years of Glaxo at Greenford (Greenford: Glaxo Pharmaceuticals Ltd., 1985): 58-59.

⁷² R. P. T. Davenport-Hines, J Slinn, (1992): 68-97.

⁷³ F. G. Hopkins, "The Present Position of the Vitamin Problem. (II) Rickets" British Medical Journal (27 October 1923): 748-50.

⁷⁴ R. P. T. Davenport-Hines, J Slinn, (1992): 72-73; A. L. Bacharach, "Nutrition" in Royal Institute of Chemistry, What Industry Owes to Chemical Science (Cambridge: W. Heffer, 1945): 10-12.

iodine. In 1924 an American researcher, Harry Steenbock discovered that irradiation increased the yield of the anti-rachitic factor from various oils and he patented this process, securing royalties for the University of Wisconsin. Many firms paid to acquire the rights to this discovery, including Abbott laboratories, Mead Johnson, Parke Davis, E. R. Squibb and Winthrop Medical Co., which forced Glaxo to do the same, and they prepared their first irradiated ergosterol in 1929.⁷⁵

Bacharach brought much to Glaxo including statistical analysis of biological results and colorimetric assays utilising new ultraviolet spectrophotometers, and by 1929 Harry Jephcott was a Director.⁷⁶ Glaxo sales suffered in the post-war depression and their profits reached their lowest point in 1932 before recovering again.⁷⁷

5.5.5 Allen & Hanbury's: Geoffrey Tweedale contributed a history of Allen & Hanbury's from which I can summarise the interwar developments.⁷⁸ Reginald Hanbury, like his grandfather Cornelius qualified as a surgeon and led the surgical instruments division. The firm had grown significantly from a staff of 20 in 1850 to 500 in 1915. Turnover doubled during the war to reach £1m, although they were left with a damaged factory at Bethnal Green. They relied heavily on the milk and malted food business, but this placed them in a position to take advantage of the discovery of vitamins, which were added to their existing products. Much of their other products arose from processing raw materials into fine chemicals. Allen & Hanbury's were a small family run firm at the start of the war, having just had the setback of the deaths of Cornelius Hanbury in 1916 and their chemist William Ralph Dodd died in 1917. Despite their long history Allen & Hanbury's turnover only reached £1 million in 1920 with over 50% due to its milk and food products, despite a tenfold rise since 1913. They failed to pay a dividend in 1919 for the first time and profits of £93,129 had to be set against the loss of their Russian factory as a consequence of the revolution, and their Bethnal Green site, damaged by bombs had to be rebuilt.⁷⁹ They had

⁷⁵ R. P. T Davenport-Hines, J Slinn, (1992): 75- 79; Dale notes, "NIMR". (5 May 1950) at the Royal Society, HD 47.13.144 under 'Vitamin D'.

⁷⁶ C. Turner (ed.), (1985): 18.

⁷⁷ R. P. T. Davenport-Hines, J Slinn, (1992): 47, 66, 71-2.

⁷⁸ G. Tweedale, (1990): 115-59.

⁷⁹ G. Tweedale, (1990): 123, 248; L. F. Haber, (1971): 251

their own expert science graduate in chemical analysis, Norman Evers, who joined the firm in 1912, having been a public analyst in Birmingham. He had trained at the Institute of Chemistry and received his degree from Kings College, London.⁸⁰ In 1922 the Dangerous Drugs Act necessitated the employment of trained and qualified men and increased the use of analytical methods. Separate analytical, research, bacteriological and experimental manufacturing divisions were established at Allen & Hanbury's along the Burroughs Wellcome lines to check the purity of purchased materials. They also established research, bacteriological and experimental manufacturing divisions. The laboratories occupied 120 by 40 feet of the top floor of the Bethnal Green building. The Director of the laboratories was Norman Evers, supported by 7 chemists and a number of assistants. According to Tweeddale's account:

“in the research and experimental research laboratories work is carried out with an eye to the future: new preparations are made in small batches with the object of discovering how best they can be manufactured on a large scale: old methods of manufacture are examined in the light of recent knowledge: investigations are made upon vexed and troublesome problems in chemistry, pharmacy and pharmacology, and new manufacturing plant is tested”.⁸¹

As described previously, Allen & Hanbury's played a significant role in the British manufacture of insulin and established a large manufacturing unit at Graham Street, under the direction of Francis Carr of British Drug Houses, their collaborative partner, and insulin contributed significantly to profits. Glaxo grew as a major competitor in the milk business and especially after adding vitamins to its products from 1924, a technique in which A&H followed from 1928. A & H were being marginalised in their previously strongest area and therefore sought new channels, but had to do with declining income.

5.5.6 British Drug Houses: Before the war British Drug Houses offered purified drugs in different forms.⁸² Their chairman, Charles A. Hill, had been a contemporary of Francis

⁸⁰ Norman Evers, G. D. Elsdon, (of Allen & Hanbury's), "The Analysis of Drugs and Chemicals" (London: Charles & Griffen Co., 1919); N. Evers, Chemistry of Drugs (London: Ernest Benn Ltd, second edition 1933); Evers became Director of Research at Allen & Hanbury's from 1922, remaining there until 1952."Norman Evers" Chemistry and Industry (25 October 1952): 1060.

⁸¹ G. Tweeddale, (1990): 127.

⁸² Chemists & Druggist 85.1 (29 August 1914), near p. 51 adverts.

Carr at the Pharmaceutical Society and a campaigner for pure and standardised drugs. At the end of the War he turned to his friend for advice on how British Drug Houses could enter the synthetic drug area. Carr first visited BDH in November 1919.⁸³ He submitted a detailed memorandum of recommendations for the planned reorganisation of the firm's research including staffing details, amounts of drugs to be made and intermediates and equipment to be purchased.⁸⁴

They moved forward ambitiously. Francis Carr was asked to give an opinion of what would be required to set up a modern plant for BDH. In a memo written to Hill in November 1919, Carr promised that: "with first class equipment, given time any chemical can be produced". He estimated that:

"A reasonable target for a chemist working with two boys would be to make 15 chemical preparations in a year on a scale of 20 kg. With four such chemists and assistants the 60 preparations would probably be accompanied by 40 intermediates and others could be purchased from dyestuffs firms. Capital of around £8,000 would be tied up in stocks and that £3,200 would be set aside for purchases of intermediates. The wages for the boys would be £2 per week together with the chemist's salary bill of £1,432. In order to attract a suitable technical director would require a further £500 p.a. A further £2,500 would be needed for the purchase of materials such as reaction vessels, autoclaves, mechanical stirrers, vats and filters".⁸⁵

However, instead he recommended developing boldly, investing £0.25m and building a small- scale laboratory and control facilities, removing the steam plants to a site with rail and canal connections, a dumping ground and cheap power. The site chosen was at Graham Street in London.⁸⁶ When asked if he could fill the role of Director, he was also bold in his own suggested salary:

⁸³ Pharmaceutical Journal 104 (14 February 1920). The text of the speech is in Carr's archives, (8 July 1919), Imperial Institute.

⁸⁴ F. H. Carr to C. A. Hill, (19 November 1919), B.CARR at Imperial Institute-personal notes of Francis Howard Carr.

⁸⁵ F. H. Carr to C. A. Hill, (23 November 1919): B.CARR at Imperial Institute-personal notes of Francis Howard Carr.

⁸⁶ He later confirmed they did spend £1/4m. in "Chemistry in the Progress of Medicine" British Medical Journal (6 August 1927): 233-4.

"My services might be dear, even £2,000, and disproportionate to other Directors. Given a suitable field I am confident of being able to make myself worth over £2,000.... and with first class equipment any chemical could be produced and the delivery time depended on the scale of the operation".⁸⁷

This was a fantastic sum at the time and it allowed him to move house to Hampstead and educate his two daughters. His other conditions included the control of manufacturing and powers of appointment and dismissal.⁸⁸ Carr would have a lot to live up to and he did. BDH decided to expand and aim for synthetic drugs with Francis Carr driving them forward. The BDH laboratories doubled their size and they acquired Curling, Wyman and J. Warren who employed 30 trained chemists and about 40 pharmacists in a payroll of over 1,200.⁸⁹

Carr contributed to the production of thyroxin and also insulin, as discussed previously. He also led the efforts to prepare preparations of the new vitamins and following his discovery of a means of estimating the strength of vitamin A by a colour reaction using a tintometer, he gave keynote lectures reviewing developments in preparation of vitamins.⁹⁰

In summary British firms followed different tracks after the War, but the common theme was to develop novel differentiated drugs. Some did this by using vitamins, particularly Glaxo and Allen & Hanbury's, and some did so by focusing on hormones and gland extracts. The only firm to significantly enter into synthetic drug manufacture was British Drug Houses, but they too developed their infrastructure based upon large-scale production of hormones and Allen & Hanbury's learned a great deal by collaborating with them. Boots and May & Baker turned increasingly to chemistry in the later interwar period.

⁸⁷ F. H. Carr Archive 2130 B/CARR IV Press cuttings: 41. F. Carr to C. A. Hill, "re: Research Chemists." (23 November 1923).

⁸⁸ Chemist & Druggist 92.1 (14 February 1920): 57. At this time M.R.C. researchers typically received £400 - £500 per annum.

⁸⁹ "The British Drug Houses Ltd." Chemist & Druggist (20 February 1926): 254; "Still Progressing" Chemist & Druggist (5 July 1919): 46.

⁹⁰ F. H. Carr, "Vitamins" Pharmaceutical Journal (18 December 1926): 729-34.

5.6 Protecting the British Public: The MRC and National Institute of Medical Research- Biological Standardisation and Government Legislation of Drugs.

We have seen how the Government tried to offer assistance to British pharmaceutical firms in the form of capital grants during the war and tariff protection post-war. The Government also expressed concerns about the growing sales of patent medicines to a gullible public, and the biologicals, trusted by doctors as being of reliable strengths and yet capable of causing serious harm. I have described previously how the BMA brought the patent medicine issue to a head with their publications *Secret Remedies* and *More Secret Remedies*. The latest British Pharmacopoeia had been published after the outbreak of the war, and it had not been possible to focus on these issues until the end of hostilities. The wartime legislation of the Venereal Diseases Act began this process and was aimed at the most flagrant breaches, such as quack claims to treat syphilis. A committee for the “Control of Patent Medicines” was also announced following to the recommendations of the Select Committee on patent medicines of 1914 to focus on legislation on the composition of patent medicines, their advertising of claims and whether they contravened the Poisons Act. The stance taken fitted in well with the stringent efforts to prove that British made Salvarsan was a valid therapy.⁹¹

When the Ministry of Health was established in 1920, the government immediately took a more active role in the Health of the Nation and the control of drugs. A committee was established “to consider and advise on the legislative measures to be taken for the effective control of the quality and authenticity of each therapeutic substance offered for sale to the public as cannot be tested adequately by direct chemical means”.⁹² The government also enacted the Dangerous Drugs Act in 1920 to specifically control the sale of narcotics such as opium and heroin.⁹³ Addison sought to continue protection of

⁹¹ “Ministry of Health Enquiry. Select Committee 1914” Chemist & Druggist 92.3 (1 May 1920): 83.

⁹² “The Control of Therapeutic Substances Not Amenable to Chemical Analysis” British Medical Journal (5 March 1921): 357-58.

⁹³ “Dangerous Drugs Act 1920” British Medical Journal (15 January 1921): 96; S. W. F. Holloway, Royal Pharmaceutical Society of Great Britain 1841-1941: a Political & Social History (London: The Pharmaceutical Press, 1991): 392-5.

abrogated foreign patents under the Defence of the Realm Act in order to maintain drug synthesis by British firms.⁹⁴

Viscount Astor explained during the second reading of the proposed Proprietary Medicines Bill in 1920 that there had been compromises, but “all we were trying to do was protect the life and health of the people”.⁹⁵ The issues were the unreliable content of some drugs, the fact that self-prescribing led to delays in seeking medical consultation, and that some medications were advertised as curing all manner of diseases, some of which were considered incurable; in short, dealing with the issue of reliability of claims made by manufacturers.

One way of protecting the British public would be to exclude foreign drugs. The Society of the Chemical Industry, appealed to the medical profession to use British rather than foreign drugs:

“We do not advertise to the public, nor 'prescribe', nor in any way trespass on the rightful province of the medical practitioner; on the contrary, we rely on the position that the chemist, so far as the medical use of chemicals is concerned, is the handmaid of the medical man, and we might add, rather bluntly, we do not recommend foreign medical men and health resorts. Why should the medical man recommend foreign pharmaceutical preparations? The scientific staffs in our laboratories welcome suggestions from medical men, and will carry out investigations to elucidate problems connected with chemistry, *materia medica* and the like, which may prove of assistance in the art of healing”.⁹⁶

In a follow –up letter, the ABCM described how, at the request of the Secretary of State, firms had extended their research and their manufacturing plant in order to secure the products of science for the war effort. They wrote:

⁹⁴ MRC Salvarsan Committee Minutes MB22, (18 February 1920): 53; Maisie Fletcher, *The Bright Countenance: a Personal Biography of Walter Morley Fletcher* (London: Hodder & Stoughton, 1957): 320. On Addison, see “Works of the Ministry of Health” *British Medical Journal* (24 July 1921): 135.

⁹⁵ “The Proprietary Medicines Bill” *British Medical Journal* (7 August 1920): 214-9.

⁹⁶ “British Chemical Industries” *British Medical Journal* (5 March 1921): 347.

“We have received from a number of old-established British firms more particularly concerned with the production of drugs, an appeal to medical men of the British Empire to support British industry”.⁹⁷

In his 1921 address as President of the Society of the Chemical Industry, Sir William Jackson Pope⁹⁸ of Cambridge University called upon

“The Chemical Society, The Society of the Chemical Industry, and the Institute of Chemistry ... with perhaps the newly founded ABCM to set up a watchful and alert joint council, with directions to consider national questions in which any of the various interests of chemistry are concerned, and to make such representations to our administrators as would voice the corporate view of the whole body”.⁹⁹

Following this combined lobbying the Key Industries Bill was passed and came into operation on 1 October 1921. It imposed a duty on imports of all synthetic organic agents, and around seven thousand defined fine chemicals as well as dyestuffs, optical glass, wireless parts, laboratory wares, tungsten and fermented chemicals for a five year term. It was:

“An act to impose duties of customs on certain goods with a view to the safeguarding certain special industries and the safeguarding of employment in industries in the UK against the effects of depreciation of foreign currencies, and the disposal of imported goods at prices below the cost of production”.¹⁰⁰

The imposition of tariffs in Britain polarised the British pharmaceutical industry. The British Chemical Trade Association, whose members sold all types of drugs, was opposed to the Key Industry Bill as it decreased their overall trading, many of their proprietary

⁹⁷ “The Position of the Fine Chemical Industry” British Medical Journal (16 February, 1921): 315; the quote is from “British Chemical Industries” British Medical Journal (5 March 1921) 347.

⁹⁸ Pope had a background similar to Francis Carr. He had been an Assistant Professor at the Central Technical Institution in London, then from 1897 Head of Chemistry at Goldsmiths College, from 1901-08 Professor of Chemistry at the Municipal College of Science & Technology in Manchester and from 1908 Professor at Cambridge. He was President of the SCI 1920-1, C. S. Gibson, “William Jackson Pope” Obituary Notices of Fellows of the Royal Society 3 (1941): 290 –324.

⁹⁹ Sir William Jackson Pope, “The Chemists Part in Therapeutic Progress” J. Soc. Chem. Ind. (15 September 1922).

¹⁰⁰ Quoted from “Safeguarding of Industry Act” Chemist & Druggist 95.2 (10 September 1921): 38-40; See also “The Key Industry Bill” Chemist & Druggist 95.2 (24 September 1921): 57-69; “Medicinal Chemicals” Chemist & Druggist 95.2 (12 November 1921): 62-63.

medicines being of foreign origin.¹⁰¹ But Stanley Baldwin, who the following year would have to handle the controversy around the bill in office at the Board of Trade, “pointed out that the experience of war years showed the great danger of dependence upon foreign sources”.¹⁰² The ethical pharmaceutical companies acclaimed the tariffs, which protected their production of high value products. As a direct result, in November 1921, Evans Sons, Lescher & Webb completely relinquished their trade in proprietary medicines in favour of ethical medicines.¹⁰³

However, protection in the form of tariffs was not enough to shield the British pharmaceutical industry as it struggled through the economic recession of the 1920's and found it increasingly difficult to export drugs.¹⁰⁴ Even after the passing of the Key Industries schedule of the Safeguarding of Industries Act in 1921, it was clear that many hospitals were still using continental remedies and: “that owing to the duty now imposed would have to pay more”.¹⁰⁵ The reasons ranged from ignorance that the products were German, through the use of trade names and purchases from wholesalers, to reluctance on the part of the end user to accept that the British product was as good as that produced in Germany.

At the end of the War the greater role of government in organising and setting national priorities for science was confirmed.¹⁰⁶ The MRC were placed under the Privy

¹⁰¹ “Safeguarding of Industry Act” Chemist & Druggist 95.2 (24 September 1921): 57.

¹⁰² Dr. Murray, question to the Board of Trade, “Medicinal Chemicals” Chemist & Druggist 95.2 (12 November 1921): 62-63.

¹⁰³ “The Relinquishment” Chemist & Druggist 95.2 (5 November 1921): 57.

¹⁰⁴ Overseas trade began to improve between July and September 1921, Chemist & Druggist 95.1 (15 June 1921): 51.

¹⁰⁵ Dr. Murray “Medicinal Chemicals” Chemist & Druggist 95.2 (12 November 1921): 62-63.

¹⁰⁶ Report of the Machinery of Government Committee, iv, Cd 9230, (London: H.M.S.O., 1918); H. Himsworth, The Development and Organisation of Scientific Knowledge (London: Heinemann, 1970); A. Landsborough Thompson, Half a Century of Medical Research, vol 1. Origins and Policy of the Medical Research Council UK (London: HMSO, 1973): 36-8.

Council, rather than reporting to the Minister of Health.¹⁰⁷ The connection between the original Medical Research Committee and National Insurance funding ceased on 31 March 1920, offering greater independence, and re-establishment as the Medical Research Council. (I continue to use the abbreviation MRC for convenience)¹⁰⁸ Having been temporarily displaced during the War, the MRC established the National Institute of Medical Research (NIMR) at the site of the old Mount Vernon Hospital (Hampstead) with departments of Bacteriology and Experimental Pathology, Biochemistry and Pharmacology, Applied Physiology, and Statistics. A formal Director of the Institute was not announced, but Dale chaired the Committee of departmental directors and was finally appointed as the first Director in 1928.¹⁰⁹

Henry Dale had already been much influenced by his visit to the laboratory of Paul Ehrlich in 1903-04 a year prior to joining Burroughs Wellcome previously. He wrote: “I came away with my store of ideas, and my repertory of ways to approach problems greatly enriched”.¹¹⁰ Central to Ehrlich’s thinking was that isolated active substances should be biologically standardised. I previously described how the Pharmacopoeia Committee of 1909 had first addressed the standardisation of biological drugs, and the General Medical Council approached the Government about legislation as early as 1909 with the concurrence of responsible drug manufacturers.¹¹¹ Dale had explored these approaches at

¹⁰⁷ The first meeting of the MRC took place on 7 July 1920, MRC Council Minutes II, (1920): 41; “The Proposed Ministry of Health” British Medical Journal (21 April 1917): 517-18.

¹⁰⁸ “Medical Research Council” British Medical Journal (27 March 1920): 447. The new Committee included Viscount Goschen C.B.E., Mr William Graham, MP for Edinburgh Central, Hon. E.F.L. Wood MP of Ripon, C.J. Bond, F.R.C.S., Consultant Surgeon, Leicester Royal Infirmary; William Bulloch MD, FRS, Professor of Bacteriology at London Hospital, T. J. Elliott, FRS Physician at UCH, Henry Head MD, FRS, formerly physician to the London hospital, F. Gowland Hopkins FRS, Prof. of Biochemistry, University of Cambridge, Major-General Sir W. B. Leischman, MB, FRS, Director of Pathology in the Army and Dr Noel Paton, MD, FRS, Prof. of Physiology, University of Glasgow. British Medical Journal (10 April 1920): 510-11.

¹⁰⁹ W. S. Feldberg, “Henry Hallett Dale 1875 – 1968” Biographical Memoirs of Fellows of the Royal Society 16 (1970): 116.

¹¹⁰ W. S. Feldberg, “Henry Hallett Dale” (1970): 116.

¹¹¹ “Biological Standards and the Therapeutic Substances Bill” British Medical Journal Suppl. (12 September 1925).

Burroughs Wellcome, achieving the post of Director after Dowson was sacked due to poorly standardised biological drugs. All countries had been dependent on Paul Ehrlich's Institute for Experimental Therapy for standardisation of biological drugs until August 1914.¹¹² The lack of an enforceable biological standard at the outbreak of the war left Britain behind Germany and America as the only great nation with no such system. Dale addressed this during the war with his work on the standardisation of Salvarsan, and recruited former colleagues from Burroughs Wellcome, including George Barger and Arthur J. Ewins. However, Ewins was poached by the Managing Director of May & Baker in 1917 and Barger accepted a Chair at Edinburgh University towards the end of the War, leaving Dale with limited support and relying on trusting the firms to do their own testing. This was not a sound basis for the scrutiny of drugs, especially those of foreign origin. Ewins replacement was also secured from Burroughs Wellcome; on 30 May 1919 Harold King, an organic chemist from the WCRL rejoined Dale at the MRC and his permanent appointment at the NIMR was confirmed in March 1922.¹¹³

It was Dale's initiative that led to the appointment of a Government Committee on Biological Standardisation as announced by Addison. He was instrumental in writing the section of the MRC report of 1919-20 suggesting that there should be more research on standards of biological preparations and sera, and that submitted drugs should be tested against defined standards, rather than relying on testing by the companies themselves.¹¹⁴ In

¹¹² MRC Minutes II, (16 December 1921): 181.

¹¹³ Harold King had studied chemistry under K. J. P. Orton at University College, Bangor, graduating with first class honours. He joined the WPRL in 1911 and also worked in the Experimental laboratory at the Works, and during the War he manufactured salicylic acid. "Staff Records", WF: Box 25; King was appointed at a salary of £800, increasing to £900. MRC Minutes II, (24 March 1922): 266 and MRC Minutes II, (27 November 1923): 161; Sir Charles Harrington, "Harold King 1881-1957" Biographical Memoirs of Fellows of the Royal Society 2 (1937): 157-171. "Harold King, Obituary" The Times (18 February 1957); He was the only full-timer at the NIMR until a separate department was established in 1927; NIMR early history, 1968, Dale Archives 93 HD.143.11.

¹¹⁴ "MRC Report 1919-20" British Medical Journal (10 April 1920): 510-511.

April 1920 Addison appointed a committee to consider new legislation and administrative measures to deal with standards for:¹¹⁵

- a) A group of 'biologic products' as described in the U.S. regulations of 1919 i.e. vaccines and antitoxins.
- b) Potent synthetics e.g. Salvarsan and its analogues, ordinary drugs e.g. digitalis, strophanthus, ergot, cannabis indica and pituitary gland.¹¹⁶

Dale established a Committee on Biological Standards and Assay “to coordinate research on determination and maintenance of biological standards,”¹¹⁷ which included Prof. William Bulloch, Professor of Bacteriology of the London Hospital, Prof. George Dreyer of the Dunn School of Pathology in Oxford, C. J. Martin of the Lister Institute and MRC Secretary, Walter M. Fletcher. The Committee awarded grants to researchers standardising biological drugs.¹¹⁸

The principal centre for biological standardisation became the Department of Biochemistry and Pharmacology at the NIMR led by Dale and he attracted several more former Burroughs Wellcome colleagues including Joshua Burn, who joined him in July 1921.¹¹⁹ In 1920 just before their own reorganisation, the MRC had offered a grant of £600 to Burn for studies of biological standards.¹²⁰ By 1920 he had served in the army

¹¹⁵ The advisory committee consisted of Sir George Newman, Chairman, Ministry of Health, Mr. John Jeffrey, Scottish Board of Health, Sir Thomas Houston, Minister of Home Affairs, Northern Ireland, Dr. Henry Dale of the MRC; Sir Nestor Tizzard, G.M.C., Dr. C. U. Hawthorne, B.M.A., Dr. J. H. Burn, Pharmaceutical Society and Prof. J. F. Tucker, Institute of Chemistry. Edmund White and F. W. Gamble were appointed as witnesses; “Therapeutic Substances Bill” Chemist & Druggist 99.1 (4 August 1923): 183.

¹¹⁶ “Report of the Departmental Committee on Control of Certain Therapeutic Substances” (London: HMSO, 1921); “The Control of Therapeutic Substances not Amenable to Chemical Analysis” British Medical Journal (5 March 1921): 357-8.

¹¹⁷ MRC Minutes II, (7 July 1920): 82, 101.

¹¹⁸ MRC Minutes II, (15 October 1920): 138; (10 December 1920): 192.

¹¹⁹ Burn was appointed to the staff from July 1921 at an initial salary of £500 p.a. MRC Council Minutes II, (18 March 1921): 105.

¹²⁰ MRC Council Minutes II, (20 March 1920): 72.

and completed a medical degree in Cambridge.¹²¹ In 1921 Percival Hartley was recruited from Burroughs Wellcome to the NIMR as Director of Biological Standards. Hartley has not been described previously because he only joined Burroughs Wellcome in 1919, working on diphtheria antitoxin for 2 years. He had a first class degree from The Yorkshire College of the Victoria University (later Leeds University), studying and researching organic chemistry under J. B. Cohen, and after a brief period in Oxford, he was at the Lister Institute in 1906-08, and then performed research and lectured in physiology at St. Thomas' Hospital in London. Hartley then performed research in India from 1909, returning to the Lister in 1913, where he worked with Dale until his war posting abroad with the RAMC in 1915.¹²² Dale also secured another former Burroughs Wellcome colleague, Dr. Patrick P. Laidlaw to run the NIMR bacteriology department in December 1921. Dale then secured Harold W. Dudley, a chemist who had been working in Dakin's laboratory in New York.

The first work on biological standards at the NIMR was to characterise extracts of posterior pituitary lobe, a gland found at the base of the brain, and of nearsphenamine, another arsenical for treating syphilis. Just prior to the War, Dale had described the stimulatory action of pituitary extracts on the uterus and such extracts had been used to control contractions during childbirth. In May 1921 the Obstetric Section of the Royal Society of Medicine established a Committee, including Dale to evaluate its use.¹²³ Assays performed against standards by Burn showed very variable strengths of the different manufacturers' brands of pituitary extract and sometimes this variability led to uterine rupture.¹²⁴ The committee agreed that it was important to have the right strength of preparation: "a remedy of great value when accurately used, may when inaccurately

¹²¹ A. S. Milton, "Burn Oxford for a Start" Brit. J. Pharmacology 119 (1996): 1293-9.

¹²² H. H. Dale, "Percival Hartley, 1881-1857" Biographical Memoirs of Fellows of the Royal Society 3: 81-100; "P. Hartley, Obituary", The Times (18 February 1957), HD 38.16.16; "Sir Percival Hartley, Obituary" British Medical Journal (23 February 1957) 466.

¹²³ MRC Minutes II, (27 May 1921): 78; W. S. Feldberg, "Henry Hallett Dale" (1970): 120.

¹²⁴ J. H. Burn, H. H. Dale, "Standardisation of Pituitary Extract" British Medical Journal (2 December 1922): 1087; "On the Physiological Standardisation of Extracts of the Posterior Lobe of the Pituitary Body" MRC Reports on Biological Standards Special Reports Series 69.

employed, produce dangerous and even fatal consequences”.¹²⁵ Other tests performed by the MRC showed that biological extracts such as strophanthin, the cardiac glycoside extracted from the seeds of *Strophanthus gratus*, by Thomas Fraser in Edinburgh,¹²⁶ (and previously used by Indians for poison arrows) also varied in strength by up to 80 – fold.¹²⁷

As a result of these very variable findings and with the MRC obtaining the patent rights to insulin from the University of Toronto, (of which more in the next chapter), Dale campaigned for laws to give the NIMR the authority to control biological standards and therapeutic substances by licensing of manufacturers, inspection of plant, premises and processes and testing marketed products.¹²⁸ One plan was to license foreign firms to ensure each consignment attained the required standards. However, Addison recognised that it was not practicable and that the “MRC should supervise whatever tests required”.¹²⁹

Dale was keen to extend the requirement for standardisation to other biological drugs and to create a system of International standards. Dr. Thorvald Madsen, Director of the State Serum Institute in Copenhagen, who had recently become the President of the Health Committee of the League of Nations, arranged a meeting in London on 12 December, 1921 to discuss the possibility of creating an internationally recognised centre from which reference samples of all antitoxin sera could be distributed.¹³⁰ The first

¹²⁵ “Standardisation of Pituitary Extract” British Medical Journal (2 December 1922): 1087.

¹²⁶ “The Late T. R. Fraser” Chemist & Druggist 92.1 (17 January 1920): 65.

¹²⁷ Report on Biological Standards. Pituitary Extracts. I. Pituitary Extracts Special Report Series 69 (London: HMSO, 1922); J. H. Burn, J. W. Trevan, “The Standard for the Biological Assay of Strophanthus” Pharmaceutical Journal (1928): 117: 439; J. H. Burn, U. J. Grewal “The Strength of the Tincture of Strophanthus B.P. and of Samples of Strophanthus Related to the Internal Standard Ouabain” Quart. J. Pharmacology 2 (1921): 1; W. Sneader, Drug Discovery: the Evolution of Modern Medicines, (London: John Wiley, 1985): 138.

¹²⁸ Report of Departmental Commission on Control of certain Therapeutic Substances, Ministry of Health (London: HMSO, 1921)

¹²⁹ “Standardisation of Serums etc.” British Medical Journal (12 March 1921): 399.

¹³⁰ A. A. Miles, “Biological Standards” British Med. Bull. 7 (1951): 283; E. Buelbring, J. M. Walker, “Joshua Harold Burn (1892-1981)” Biographical Memoirs of Fellows of the Royal Society (1981): 45-89.

International standards were agreed between France, the USA, Germany and Britain for diphtheria and tetanus antitoxins at a conference in Paris in 1922.¹³¹

Early in 1922 the MRC created a series of subcommittees to establish standards for various biological drugs and sera, including anti-tuberculosis, anti-meningococcal and anti-pneumococcal sera, anti-dysenteric fever and a fourth for anti-diphtheric and anti-tetanic sera. R. A. O'Brien of Burroughs Wellcome was included in the last two committees.¹³² Leonard Colebrook¹³³ of the NIMR staff, who was a member of the anti-meningococcal and anti-pneumococcal team, was seconded to work and lecture at Sir Almroth Wright's unit at St. Mary's for two years to learn more about vaccines.¹³⁴

Following the revelations of several antitoxins and sera of variable strength and especially the implication that these were mostly of 'foreign' origin, the Therapeutic Substances Acts were drafted to make it obligatory for samples to be tested. It was also recognised that the ultimate way in which to standardise a biological extract was as stated in the MRC Report of 1922:

"The absence of official standards of value and authenticity for drugs of this kind and for numerous biological preparations, such as serums and the like used in general practice has been publicly denounced as discreditable to our national position in the world of science and a source of grave danger to the community. It would be a great advantage if a stable chemical substance could be prepared of known chemical composition which acted on the uterus in the same way as the pituitary extract".¹³⁵

¹³¹ MRC Council Minutes (1922.): 385; Dale chaired a meeting in Geneva. International standards were adopted for pituitary (posterior lobe) extract, neoursphenamine, digitalis and insulin. Standards at League of Nations; H. H. Dale Archives, Royal Society, 93 HD 143.3.

¹³² MRC Minutes II, (20 January 1922): 189.

¹³³ C. L. Oakley, "Leonard Colebrook" Biographical Memoirs of Fellows of the Royal Society 17 (1971): 91-138.

¹³⁴ MRC Minutes II, (24 March 1922): 272; (22 February 1924): 116; Z. Cope, Almroth Wright, Founder of Modern Vaccine Therapy (London: Nelson, 1966).

¹³⁵ Report on Biological Standards. Pituitary Extracts. I. Pituitary Extracts MRC Special Report Series 69 (London: HMSO, 1922); British Medical Journal (2 December 1922): 1087.

Meanwhile the Therapeutic Substances Act targeted towards foreign drugs was still being guided through parliament. A statement from discussions in the House of Lords in August 1923 emphasised that:

“It is essential that doctors when writing prescriptions should be sure that the patient will have what he intends him to have” with the aim “to ensure that the standard of goods coming in ... should be as high as the articles which we ourselves manufacture in this country”.¹³⁶

In fact some groups such as the North British Branch of the Pharmaceutical Society saw “no reason to think that the present methods by which these substances are produced and placed at the disposal of the medical profession and pharmacists gave any occasion to fear that adequate precautions were not taken to protect the public intent”.¹³⁷ Yet by 1924 the MRC was overrun with assays to perform and from 17 July 1924 the Insurance Commission agreed to allow a trial period of around 2 months, during which British manufacturers were allowed to perform their own tests on the insulin, which they were then producing, with control batches being sent to the NIMR. A small amount of US insulin was imported but the US tests were trusted.

A row occurred between the MRC and the Canadians over the standard units of insulin after the latter group changed them. Dale chaired a heated debate at a meeting in Edinburgh in 1923 about whether to use rat or mouse units, and eventually the MRC definition was upheld.

The much-debated Therapeutic Substances Bill was further delayed in 1924 by the attention focused upon the economy. The Bill recommended that substances that could not be tested chemically should be supervised under a committee of the Privy Council assisted by an advisory committee: “It is recognised that the MRC which already possesses the requisite organisation, should be responsible for this central laboratory.”

Ethical manufacturers sought to collaborate with the MRC to define standards for biologicals, to further distinguish their ethical drugs from patent and proprietary medicines and to be able to export drugs to America and Europe, where tight laws on biological

¹³⁶ “Therapeutic Substances Bill” Chemist & Druggist 99.1 (4 August 1923): 198.

¹³⁷ “Therapeutic Substances” Chemist & Druggist 100.2 (19 April 1924): 568.

standardisation of biological products already existed.¹³⁸ The MRC was to act as a regulator and protector to prevent the sale in Britain of products, which had already failed tests in other countries, including Germany.¹³⁹ They were particularly concerned about the toxicity of the arsenobenzols.¹⁴⁰

In order to relieve the already overworked laboratories of the NIMR it was proposed at the end of 1924 that the Pharmaceutical Society would establish a laboratory if the Therapeutic Substances Act became law.¹⁴¹ Dale and Fletcher supported the Therapeutic Substances Act, which was passed on 23 June 1925, to mark the beginning of formalised State monitoring of drugs. It covered substances that could not be chemically analysed and needed indirect tests i.e. vaccines, sera, toxins, antitoxins, antigens, Salvarsan, insulin, and pituitary lobe extracts.¹⁴² Like the American guidelines, it asked for manufacturers to keep records of distribution of batches. Dale was opposed to a clause in the guidelines allowing individual doctors to be able to import. He was concerned that “unscrupulous foreign manufacturers might use their machinery to get objectionable substances into the country”.¹⁴³

In parallel, the General Medical Council (GMC) invited additions and amendments to the British Pharmacopoeia, following suggestions from Professors of Pharmacology and Materia Medica, pointing out previous defects that needed to be remedied. The MRC

¹³⁸ B. G. Rosenkrantz, Public Health and the State (Cambridge Mass; 1972): 123-6; J. Liebenau, Medical Science and Medical Industry: Changing Views in Massachusetts 1842-1936, the Formation of the American Pharmaceutical Industry (Basingstoke: Macmillan, 1987): 325 ff, 396.

¹³⁹ Of 75 remedies analyzed earlier, as many as 48 were dangerous to life and 11 more were injurious. “Secret Remedies and the German Medical Press” British Medical Journal, (30 April 1921): 649.

¹⁴⁰ In March 1924 Harrison visited the Pasteur Institute to discuss an observed decrease of the efficacy of Stovarsol; MRC Salvarsan File MB22, (6 March 1924): 89

¹⁴¹ MRC Minutes II, (24 October 1924): 136; “Biological Standards, Therapeutic Substances Bill” British Medical Journal (7 August 1925), suppl. and (12 August 1925): 105.

¹⁴² “Therapeutic Substances Bill” British Medical Journal (1925): 176, 234, 273; Dale Archives, 93 HD 21.2; 93 HD 126.

¹⁴³ “Therapeutic Substances Regulations”, Dale Archives 93 HD 21.2.126) 1925.

established a subcommittee involving Elliott, Wallace, Dale and Fletcher, which met with the GMC to review these therapeutic guidelines.¹⁴⁴ Dale continued to push for International Standards and a further meeting took place in 1925.¹⁴⁵

Joshua Burn was appointed Director of the Laboratory at the Pharmaceutical Society on 24 October 1925, which became operational at the start of 1926.¹⁴⁶ Rather than just perform routine tests, he explored the reasons for their variation and recognised that differences were not only due to variation in the mechanism of extraction, but also an inherent biological variability of action and response. Burn wrote:

“The surprising fact was established that the dose per bodyweight required to produce oestrus in 50% of ovariectomised mice was the same as for rats, when results were expressed as a mean effect in a group of animals and a revolution of thinking was required before it was realised that all responses must be taken into account including the odd ones and that the correct response was the mean of all these varying responses”.¹⁴⁷

In December 1926, the numerical methods applied to biological standardisation were strengthened further by the appointment of John Henry Gaddum, another former Burroughs Wellcome man, to the biochemistry and pharmacology section of the NIMR. Gaddum had qualified at Cambridge in Mathematics and Medicine and studied in the famous physiology department, and then at UCH, London. Gaddum then worked under J. W. Trevan at the Wellcome Research Laboratories from January 1925.¹⁴⁸

Burn collaborated closely with Trevan and recognised that a mathematical model could be developed to understand the statistics of biological variation. He proposed that differences of strength in animal tests were due to the inherent variability of the animals or

¹⁴⁴ MRC Minutes II (16 October 1925): 151; MRC Minutes II (29 January 1926): 11 (5 March 1926): 32 and (28 May 1926): 94.

¹⁴⁵ International Congress of Biological Standards, Dale Archives, 93 HD 146.4 II.

¹⁴⁶ Burn tested manufactured drugs with his colleagues Dr. Katherine Coward and H. W. Ling, who began as a boy with Dale. His appointment was discussed in the MRC Minutes II (1924): 136. Burn built up a department between 1926 and September 1937, which led the world in biological standardisation.

¹⁴⁷ “The Variation in the Unit of the Oestrus Producing Hormone”, J. H. Burn, K. H. Howard, *Journal of Physiology* (London) 63 (1927): 270.

¹⁴⁸ W. Feldberg, “John Henry Gaddum 1900-1965” *Biographical Memoirs of Fellows of the Royal Society* 13 (1967): 57-77.

organs, and these also varied from day to day in the same animals, forming the basis for always needing to compare the results against a known standard.¹⁴⁹ Both the MRC and the Pharmaceutical Society adopted Burn and Trevan's revolutionary concepts as they fitted into their own schemes of independent testing and the development of internationally defined standards.¹⁵⁰

Just ahead of the 1927 Therapeutic Substances Act, Norman Evers gave a presentation to the Royal Society of Arts on "Chemistry and the Supply of Drugs" in which he emphasized the growing influence of chemical approaches to drug development. Whereas at the end of the nineteenth century there was little standardisation, a firm now producing 1,000 drugs needed to have checks in place:

"The medical profession must be protected and the public must be protected against the introduction of new drugs with exaggerated statements of efficacy. The literature of synthetic drug manufactures of these times indeed remind one of rose catalogues rather than scientific productions in the unstinted praise".¹⁵¹

Chemistry now contributed to the isolation of the active principles of natural drugs, the elucidation of the constitution of natural drugs, the synthesis of natural drugs, the modification of the structure to change the physiological action, preparation of pure supplies of inorganic drugs, the preparation of drugs in a form suitable for administration and analytical controls. A new department was established at the Pharmaceutical Society for testing vitamins from August 1927.¹⁵² Despite the establishment of formalised testing, the Therapeutic Substances Act could only prevent overt malpractice and carelessness. Subsequently there were minor changes to the Therapeutic Substances Act from 21st

¹⁴⁹ The statistical methods in J. K. Trevan's paper were discussed extensively with Dale prior to publication and were routinely applied to the testing of the potency of vitamins, digitalis, cocaine, and dysentery toxin to establish dose- response curves; "Statistical Methods for Estimation of Biological Variations in Toxicity Determination", Proceedings of the Royal Society (Biology) 101 (1927): 483-512.

¹⁵⁰ They also had a great influence upon the thinking of other MRC statisticians such as Gaddum and especially Austin Bradford Hill, who was to play a major role in developing clinical trials methodology. A. B. Hill personal communications, including 6 October 1988.

¹⁵¹ N. Evers, "Chemistry in the Supply of Drugs", Pharmaceutical Journal 106.1 (12 February 1927): 164-66.

¹⁵² "Standardisation of remedies", Lancet (10 March 1928): 508.

February 1927, and effective from 6 February 1928. These covered practicalities, such as more detailed conditions concerning the type of containers and the labeling, including the date of manufacture, potency, and likely date of expiry. Both the proprietary and scientific name had to be given on the label. There were new rules concerning the need for adequate staff, premises and plant, proper housing of animals, and keeping records of batches of drugs prepared and tested.¹⁵³ The law stated that new samples had to be forwarded to the MRC for testing and no materials could be sold after reaching their expiry date. Resales were prohibited in the same containers and details of the purity and microbiological content had to be established.¹⁵⁴

Marked variation of strengths of strophanthin and pituitary extract remained an issue in 1928-9, yet the number of firm's products being tested was still limited.¹⁵⁵ The Annual Report of the Pharmacological Laboratories of the Pharmaceutical Society for 1929 showed that only 153 samples were assayed, and the majority of the tests were done on four of the most difficult medicines to standardise but also the most important.¹⁵⁶

The publication "*Methods of Biological Assay*", by J. H. Burn in 1928 began to be referred to as 'the bible' for biological standardisation.¹⁵⁷ In 1930 Burn summarised the principles of biological standardisation: "the tests must be comparative, and they must be based on a quantitative determination of the animal variation"... "these principles have been

¹⁵³ "Therapeutic Substances Regulations" (21 February 1927) (31 May 1927); Dale Archives 93HD Box 21.2 126-147 (1925-62).

¹⁵⁴ "Therapeutic Substances Act" British Medical Journal (16 April 1927): 737; "The Testing of Therapeutic Substances" Chemist & Druggist (23 April 1927): 499-502.

¹⁵⁵ U. G. Bijlsma, J. H. Burn, J. H. Gaddum, "A Comparison of the Oxytocic Pressor and Anti-Diuretic Activities of Commercial Samples of Pituitary Extract" Quarterly Journal of Physiology 1 (1928): 494.

¹⁵⁶ Tests were performed on pituitary extract 46, digitalis 39, squill 30, ergot 23, strophanthus 6, ovarian extract 3, insulin 2, and others 4: also on new growth factors, vitamin A 39, vitamin B1 and B2 18, vitamin C 3, vitamin D 72, and others 4., Report of the Pharmacological Laboratories of the Pharmaceutical Society (1929).

¹⁵⁷ Prof. H. R. Hausler (who had worked at NIMR) to H. H. Dale, (21 December 1945), Dale Archives, HD38.16; J. H. Burn, Methods of Biological Standardisation (Oxford: Oxford University Press, 1937).

shown to be capable of transforming the whole subject from the plane of an insidious means of self-discipline to that of a well-ordered and progressive science”¹⁵⁸.

Due to the practical impossibility of maintaining overseas standards for each medicine, instead the importer was licensed, and in 1930 six licenses were cancelled.¹⁵⁹ Regional medical officers collected 555 suspicious samples, of which 44 were of below-strength diphtheria antitoxin and two 'foreign' preparations were withdrawn. Three samples of vaccine lymph were withdrawn because of concerns about sterility, and after further problems of sterility the Therapeutic Substances (Catgut) regulations of January 1930 were introduced because of the use of unsterilised catgut in surgery, and a consolidated set of Regulations was issued in 1931 with added guidelines standardising gas gangrene antitoxin.¹⁶⁰

The work on biological standardisation reflected a continuity of operation including Dale, Brown, Burn, Gaddum, Trevan and Underhill.¹⁶¹ Eventually the Pharmaceutical Society Laboratories became part of the College of Pharmacy, with Burn becoming the first Prof. of Pharmacology and subsequently in 1933, Dean of the College of Pharmacy, renamed the School of Pharmacy of London University in 1937. In 1937 he succeeded Gunn at Oxford, remaining there until his retirement in 1959.¹⁶²

In conclusion, in the decade after the War, first the MRC and then also the Pharmaceutical Society established laboratories for the routine testing of biological

¹⁵⁸ J. H. Burn, “The Errors of Biological Assay” Physiological Reviews 10 (1930): 146-61.

¹⁵⁹ “Difficulty Regarding Adopting Standards of Products from Overseas- License the Importer not the Manufacturer” British Medical Journal (27 June 1931): 588.

¹⁶⁰ There were specific guidelines for vaccines of antityphoid, anti-TAB (typhoid and paratyphoid), TABC (typhoid, paratyphoid and cholera), plague, dysentery, whooping cough, tuberculosis, the Schick test (toxin and control), diphtheria prophylactic, tuberculin, tubercle vaccine, diphtheria antitoxin, and tetanus, arsenobenzenes, novarsenobenzene and Sulpharsan. “State Control of Therapeutic Substances” British Medical Journal (27 June 1931): 588; The MRC tested over 300 kinds of catgut, vaccine lymph, antisera for toxin of *B. welchii*, antidysentary serum, strophanthus tinctures and every batch of arsenobenzenes: MRC Report Series 1929-30 (London: HMSO, 1930); British Medical Journal (14 March 1931): 446-8; Dale Archives, 93 HD 21.2.128-9.

¹⁶¹ Quart. J. Med (1932) 5: 33.

¹⁶² A. S. Milton, “Burn Oxford for a Start” Brit. J. Pharmacology 119 (1996): 1293-9.

substances. The staff involved, many from Burroughs Wellcome, also performed research on the fundamental principles of biological variation, and played an important role in establishing the Therapeutic Substances Acts. Thus a series of measures were being put in place to protect the British public from unscrupulous patent medicines, from inadequately controlled pharmacopoeial drugs and from unstandardised biologicals, particularly from abroad. These measures also protected the developing British pharmaceutical industry and British science.

5.7 Chemical Workers in Britain; Francis Carr and Chemical Engineering.

Some of the longer – term problems for the British pharmaceutical industry that were described in chapter 4 had begun to be addressed, but much more needed to be done. The introduction of scientifically – trained politicians such as Albert Mond,¹⁶³ chairman of Brunner Mond, into the Government in 1916 had helped to draw attention to the urgent need for technically trained process chemists, and plant managers. There had been a clear movement during the war to recognise the importance of science, with the creation of the DSIR and a Committee on the Neglect of Science, formed in May 1916.¹⁶⁴

Experience in some 'unit processes' had been gained in the Ordnance factories, laid out in a rational manner, with organised materials handling, standard vessels, and efficient production, but most chemists had no previous experience of preparing highly purified sterile synthetic drugs on a manufacturing scale. The pharmaceutical industry needed chemical engineers who could not only perform chemical synthesis, but also had the engineering skills required to scale - up to manufacturing capacity.¹⁶⁵ J. Lewskovitsch,

¹⁶³ Albert Mond was the chairman of Brunner Mond from 1894-1916, retiring in 1923. J. Chem. Soc. (1931) II: 3324 – 39; W. J. Reader, (1970): 482-3.

¹⁶⁴ D. S. L Cardwell, The Organisation of Science in England (London: Heinemann, 2nd edition 1972).

¹⁶⁵ L. F. Haber, (1971): 359.

who acted as a consultant to Burroughs Wellcome, had used the term ‘chemical engineer’ in Britain as early as 1906 but such chemists were rarities.¹⁶⁶

By the time that Carr joined British Drug Houses in 1920 he was one of the most important chemical engineers in the country. The four presidents of the Chemical Society, Institute of Chemistry, Society of the Chemical Industry and Pharmaceutical Society selected Carr to give the prestigious lecture commemorating the work of E. F. Harrison at the British Pharmaceutical Conference in July 1919.¹⁶⁷ Shortly afterwards, he was awarded a C.B.E. for his wartime drug productions. In 1921 he captured this experience by publishing an important text on organic medicinal chemicals, which detailed methods of production of many new drugs.¹⁶⁸ Carr developed a special interest in the training of chemists and gave a lecture on the subject to the Society of the Chemical Industry in 1921. In his keynote address on the subject of postgraduate training, for the opening of Imperial College of Science and Technology, Carr acknowledged that a strong alliance between universities and industry was essential.¹⁶⁹ The number of chemists entering manufacturing firms was insufficient for a growing industry, requiring process control, research and analysis.¹⁷⁰ Carr played an active role on the committees of various chemical societies and used this platform to campaign for better training of chemists and for chemical engineering

¹⁶⁶ J. Lewskovitsch to F. B. Power, (9 August 1906), WF: 88/94:41.

¹⁶⁷ “Harrison Memorial Lecture” Pharmaceutical Journal 103 (July 1919): 34, 53.

¹⁶⁸ Marmaduke Barrowcliff and Francis H. Carr, (1921).

¹⁶⁹ F. H. Carr, “Postgraduate Training in Industrial Chemistry”, J. Society of the Chemical Industry (16 May 1921- from a transcript at 2130 B/ CARR F. H. 6 at Imperial College. Several hundred thousand pounds was still needed to equip the Department of Chemical Technology of Imperial College. The South Kensington site incorporated the Royal College of Science, the Royal College of Mines, and the City and Guilds Institute Central Technical College, leading to the founding of Imperial College in 1908. D. S. L. Cardwell, 2nd edition 1972): 197-8, 228.

¹⁷⁰ Report of the UGC, (London: HMSO, 1921), Cmd 1163: 12: M. Sanderson, The Universities and British Industry 1850-1970 (London: Routledge & Kegan Paul, 1972).

to be afforded academic status.¹⁷¹ The first chair in chemical engineering was assigned in 1923 at University College London.¹⁷²

The largest laboratory in Britain was that of the British Dyestuffs Corporation (BDC), which had a research staff of around 150 by January 1923, but this still compared with over 1,000 in the largest German conglomerate.¹⁷³ British dye firms had not taken up the challenge to invest for the future. BDC's research staff actually fell from 50 to 30 over the period 1920-1923 and was 19 in 1924.¹⁷⁴

Carr was part of a group advocating the union of chemistry with chemical engineering as an academic discipline. Carr felt that a three-year academic course did not adequately qualify a chemist for practice and that a further post-graduate year was required. Trained chemists needed to know how to react if chemical reactions proceeded along unexpected lines. They needed to increase yields, and reduce labour costs, suggest appropriate materials, understand thermodynamics, chemical kinetics, fuel economy, construction of plant, and engineering. These requirements were especially acute in the pharmaceutical industry, where continuous production processes could not be used, so fine chemicals tended to be batch-processed. Quite small changes of conditions could result in large changes of yields, and hence costs. In addition, the modern manufacturing chemist needed to learn some aspects of management, costing and accountancy. Carr had a strong platform for his case as his fame spread internationally following his large-scale production of insulin, making Britain self-sufficient in 1923 (discussed in chapter 6).¹⁷⁵

¹⁷¹ F. H. Carr archives at Imperial College, London B. Carr FH 6; notes made by A. E. Guenther after a conversation with F. H. Carr, Winter 1966-7.

¹⁷² D. B. Keyes, "History and Philosophy of Chemical Engineering Education", Chemical Engineering Progress 49 (1952): 635; G. G. Haselden, Chemical Engineering and its Educational Challenge (Leeds: Leeds University Press, 1961); W. F. Furter (ed.), History of Chemical Engineering (Washington: American Chemical Society, 1980).

¹⁷³ M. R. Fox, (1967).

¹⁷⁴ L. F. Haber, (1971): 355.

¹⁷⁵ The Chemical Age (24 April 1926): 405; Natal Mercury (30 June 1927); Daily News (5 July 1927), Columbia, Ceylon. Cuttings and notes from Carr Archives at Imperial College, 2130 B/CARR IV; "Insulin and its Manufacture" Royal Society of Arts (26 February 1927): 263.

Ivan Levinstein recognised similar requirements for dyestuffs chemists, saying it required 5 years training plus 2 years acquaintance in order to be fully functional.¹⁷⁶ He required competent works managers with knowledge of science, engineering, and quantitative thinking on questions of energy and he was loath to take on foreign chemists instead of our own.¹⁷⁷ However, British university chemists contributed mostly to theoretical rather than the more urgently needed practical knowledge.¹⁷⁸

Carr, already an examiner at London University, fought long and hard against the closure of Finsbury Technical College under Sir William J. Pope, after it was announced in May 1924 that it would close in July 1926.¹⁷⁹ In October 1926 Carr was elected President of the Society of the Pharmaceutical Industry, and gave his inaugural address to the Annual meeting in Manchester:

“The engineer who has an adequate perception of the niceties of the requirements from the chemists angle of vision is as rare as the Dodo and a chemist with sufficient knowledge is rare. Chemists blame engineers, plant makers and process workers”.¹⁸⁰

There was an abundance of chemists, but a lack of trained engineers. The Institute of Chemistry held engineering examinations from 1926, so progress began to be made, but for a long time the main method of gaining experienced staff for the immediate future was to train them on the job or poach experienced staff from another firm. Such had been the case with Carr himself.

“In order that an industry may obtain practical value for scientific research, it is absolutely necessary for at least an adequate proportion of those who occupy responsible positions in the industry to have a scientific habit of mind - their

¹⁷⁶ “Society of the Chemical Industry” Chemist & Druggist 93.3 (11 December 1920): 57.

¹⁷⁷ M. R. Fox, (1987): 29-34.

¹⁷⁸ E. F. Armstrong, (1924): 16, 95.

¹⁷⁹ The Financial News (17 June 1926) in Carr Archives; F. H. Carr letter to The Times (5 December 1925).

¹⁸⁰ 2130 B/CARR handwritten notes of Francis Howard Carr, Imperial College, 1926

minds should be receptive of the results of such research and alert to its practical bearings”.¹⁸¹

Reports on the relationship between technical education and the requirements of trade and industry emerged in 1925 and 1927 but it was the “Report of the Committee on Trade and Industry” in 1929, which recognised “education as a factor in industrial and commercial efficiency”.¹⁸²

5.8 Post –War Germany and Other Foreign Competition.

Post - war it was hoped that competition in drug production from defeated Germany would be reduced. Instead German dye and chemical manufacturers expanded their activities into photographic materials and especially pharmaceuticals.¹⁸³ Germany lost colonies that had provided medicinal plants, leading her firms to focus even more towards synthetic drugs as higher value products with less competition.¹⁸⁴ With favourable exchange rates, lower wage costs, longer working hours, much greater economies of scale, and royalties from British firms producing their drugs, Germany was able to offer very low prices for chemicals and dyes. Its “enormous engine of commercial warfare”, created for the War, increased its efficiency still further.¹⁸⁵ German firms initially priced their products artificially low, created a monopoly and then increased prices. They became even more dominant when they gained windfall overseas profits during the runaway inflation of 1921 to 1923, which allowed them to easily pay off their borrowings and plant expenses with

¹⁸¹ Final Report of the Committee on Industry and Trade (London: H.M.S.O., 1928) Cmnd. 3282: 217 - 218.

¹⁸² E. Moonman, Reluctant Partnerships (London: Victor Gollenz, 1971): 66.

¹⁸³ W. J. Reader, (1970): 317.

¹⁸⁴ Sir William Pope, “The Manufacture of Chemical Products”, Society of the Chemical Industry meeting. Chemist & Druggist 95.2 (17 September 1921): 42-43.

¹⁸⁵ “Report of the Alien Property Custodian” J. Industrial Engineering Chemicals (April 1919): 335; G. Stopler, K. Haueser, K. Borchardt, translated by T. Stolper, The German Economy: 1870 to the Present (London: Weidenfeld & Nicholson, 1967): 34- 35.

worthless Reich Marks.¹⁸⁶ A major concern was that political chaos of runaway inflation in Germany would lead to rises in prices of certain drugs such as Aspirin by forcing some of the smaller firms out of business.¹⁸⁷ Recollections of the period were; a “rapid recovery of the German chemical industry”.¹⁸⁸

From the German perspective: “Der Krieg war zwar offiziell beendet, wurde aber in anderer form weiter geführt”.¹⁸⁹ Overproduction post-war led to an expansion of cartels. In 1905, Germany had 23 chemistry and dye cartels including 7 in pharmaceuticals; by 1923 there were 93 cartels in place.¹⁹⁰ In retaliation, the ABCM initially offered a range of drugs “at or below costs”, but could not compete on prices in the longer term.¹⁹¹ Extending the wartime mergers between German firms, in 1923 J. D. Riedel took over E. D. de Haen, a firm that specialised in fine chemicals, and Schering merged with Kahlbaum and became part of a large chemical conglomerate, Kokswerke and Gemische Fabriken. The Germans tried to extend their influence further at the start of 1925 by asking the three major Swiss firms, CIBA, Geigy and Sandoz to exchange shares with them.¹⁹² As will be described later this was not the end of the merger activity, which came to a head in 1926.

A further threat to British firms came from American firms establishing offices in Britain. Parke Davis had been established in London since 1891, and was followed by

¹⁸⁶ Exchange rates are quoted in L. F. Haber, (1971). The value of the mark fell from 20/£ in 1900 to a worthless 4.2 bn. marks/\$ by 1923; W. J. Reader, (1970): 444. The Act was passed at 240M/£ but by October 1921, 240M were worth 6s 8d (one third).

¹⁸⁷ “The Fine Chemical Market” Chemist & Druggist 99.2 (3 November 1923): 621; P. Frankland, “The Chemical Industries of Germany” in W. M. Gardner, (1915): 379-388.

¹⁸⁸ “German Trade and the Mark” Chemist & Druggist 95.2 (8 October 1921): 56-57.

¹⁸⁹ With the war over it was carried on in another form. (My translation.) H. Tammen, Die IG Farbenindustrie Aktiengesellschaft, 1925-33. Ein Chemiekonzern in der Weimar Republik (Berlin: T.O.M., 1978): 15.

¹⁹⁰ A. Arora, R. Landau, N. Rosenberg (eds.), Chemicals and Long-Term Growth: Insights From the Chemical Industry (New York: J. Wiley, 1998): 56.

¹⁹¹ Editorial, “The Fine Chemical Market” Chemist & Druggist 93.2 (11 December 1920): 64-65.

¹⁹² L. F. Haber, (1971): 274-5.

Abbott in 1915, as they sought increased export markets.¹⁹³ J. Wyeth & Brothers established their own firm in Havant in 1926, Sharp & Dohme in Hoddesdon in 1927, W. R. Warner in Eastleigh in 1932, Eli Lilly in Basingstoke in 1934. Smith Kline & French established a sales base here through Menley James. However, even in 1936 SKF's "research and development department consisted of eight people with a budget of \$70,000, while the firm employed about 180 and had sales of \$8-9m".¹⁹⁴ Of the Swiss firms, Roche were established in Welwyn in 1908, CIBA in Horsham in 1919, Sandoz in London and Bradford in 1921 and Geigy, in Manchester, but not until 1940.¹⁹⁵

As the British chemical and dye industry came under growing pressure from Germany, BDC began to discuss market shares with I.G. Farben as "no one else could make dyestuffs, so cheaply, so plentifully, nor had the sales and technical backup".¹⁹⁶ Had BDC accepted their terms, then IG would have dominated the manufacture of chemical intermediates in the United Kingdom but the British government blocked this.¹⁹⁷ However, in November 1923 the Government sold shares in BDC allowing reorganisation under a new chairman, Lord Ashfield (Sir Albert Stanley) who was joined on the Board by Alfred Mond and Dr. E. F. Armstrong.¹⁹⁸

Towards the end of 1924 the Labour Government was considering withdrawal from its association with the British Dyestuffs Corporation, but McDonald's Government fell in October before a decision on market shares was agreed.¹⁹⁹ Labour ministers were opposed to such an agreement but were divided on how to reorganise BDC until late in 1925. Baldwin recommended selling BDC and using the proceeds of the sale to develop, through

¹⁹³ Journal of the Society of the Chemical Industry (1915): 151; "Medicines, Drugs and Preparations" Chemist & Druggist 85.2 (3 October 1914): 46; L. F. Haber, (1971): 123.

¹⁹⁴ John F. Marion, The Fine Old House, Smith Kline Corporations First 150 Years, (Philadelphia: Smith, Kline, 1980): 130.

¹⁹⁵ Allan Duckworth, "Rise of the Pharmaceutical Industry" Chemist & Druggist 156 (10 November 1959): 127 – 139.

¹⁹⁶ This refers to the 'Little IG' merger of 1916, W. J. Reader, (1970): 51-2.

¹⁹⁷ L. F. Haber, (1971): 274.

¹⁹⁸ W. J. Reader, (1970): 444-7.

¹⁹⁹ K. Middlemass, J. Barnes, Baldwin: a Biography (London: C. Tinkling & Co., 1969): 313-6.

the DSIR, facilities for pursuing chemical investigations not necessarily to the making of drugs, but of value to the fighting services and to the chemical industry generally to ensure that Britain was self-sufficient in important chemical intermediates.²⁰⁰

By 1925, in addition to the dye firms, there were 1219 establishments in Germany with 24,000 employees in pharmaceuticals, dominated by Merck and the other five largest firms. The chemical industry was going through a very serious time and in the first 5 months of the year imports into America doubled.²⁰¹ Britain returned to the Gold standard with interest set at pre-war rates, making British exports expensive. In the summer of 1925 Edward Frankland Armstrong told the ABCM annual meeting: “The penetration of the Germans into matters chemical was even wider, more rapid and more serious today than it was in 1914”.²⁰²

The threat to the British industry increased in September 1925 with the announcement of the planned mergers of the major German synthetic dye producers, who already dominated the synthetic pharmaceuticals industry.²⁰³ In contrast, the British chemical and dyestuffs industries remained widely fragmented. In his Streatfield Memorial lecture of 3 December 1925 Francis Carr discussed the 'scientific basis of industry' and urged closer collaboration in Britain.²⁰⁴ By 1926 the German mergers were completed

²⁰⁰ PRO, CAB/24/165 Report of the BDC, 26 July 1924: 5; CAB/ 24/ 175 Report by Chairman of Committee on Civil Research, (16 October 1925) P2.

²⁰¹ “ABCM 9th Annual meeting” Chemist & Druggist 103.1 (25 July 1925): 105; the same pattern was reported by the Society for the Chemical industry, Chemist & Druggist 102.1 (6 June 1925): 803.

²⁰² “ABCM, 9th Annual Meeting” Chemist & Druggist 103.1 (25 July 1925): 105.

²⁰³ By 1925 British exports were only 84% of 1913 levels and imports were 120%, A. J. P Taylor, (1988): 238. A change in German law in 1923 encouraged mergers. The original Dreibund of BASF, Bayer, and AGFA amalgamated with the Hoechst group on 18 August 1916. In 1925 they added Kalle, Cassella, Griesheim-Elektron and Weiler-ter Meer to become the fourth largest firm in the world after General Motors, U.S. Steel, and Standard Oil, with a annual turnover of £20 m; I. G. comprised 48% of the German chemical industry and 66% of its profits; Peter Hayes, IG Farben in the Nazi Era: The Nascent Concern 1860-1933 (Cambridge: Cambridge University Press, 1987); L. F. Haber, (1971): 123, and Chapter 10: 279-91.

²⁰⁴ F. H. Carr archives at Imperial College, London B. Carr FH 6; notes made by A. E. Guenther after a conversation with F. H. Carr, Winter 1966-7; F. H. Carr, “Streatfield Memorial Lecture” Chemist & Druggist 103.3 (3 December 1925): 829.

creating an extended Interessengemeinschaft, known as I.G. Farben, employing 7,200 and with a turnover of £50m that threatened to engulf British industry.²⁰⁵ The merger allowed the rationalisation of purchasing, patents, research, and sales with central offices in Leverkusen. The three pharmaceutical firms Merck, C. F. Boehringer, and Knoll also formed their own separate 'Interessengemeinschaft' in Germany.²⁰⁶

In response, 1926 also brought momentous changes in the British chemical and pharmaceutical industry. Management of the British pharmaceutical firms changed as the organisations themselves became more complex.²⁰⁷ At the start of 1926, BDH were wound up with a capital of £100m to protect their name, and the next week were re-established as BDH plc.²⁰⁸ Sir Alfred Mond combined the British chemical industries, Brunner Mond, Nobel, United Alkali and the British Dyes Corporation to form Imperial Chemical Industries (ICI), announced publicly on 26th October 1926.²⁰⁹ Thus “an all-embracing nationwide chemical trust was created in Britain” and “combined all the most important chemical branches”.²¹⁰ Sir Alfred Mond’s political career had ended with the fall of the coalition government in 1922; he lost his seat in 1923 and took over as Chairman of Brunner Mond.²¹¹

Another way in which competition was eliminated after the mergers was through a series of further agreements on market share between IG Farben, ICI and Du Pont.²¹² Similar mergers occurred in the USA where DuPont and Allied Chemical combined in

²⁰⁵ M. R. Fox, (1987): 169-71.

²⁰⁶ L. F. Haber, (1971): 289.

²⁰⁷ A. J. Levine, Industrial Retardation in Britain 1880-1974 (London: Weidenfeld and Nicholson, 1967): 53.

²⁰⁸ “The British Drug Houses Ltd” Chemist & Druggist 104.1 (20 February 1926): 254

²⁰⁹ In 1926 ICI was about the same size as I.G.Farben with a market capitalisation of about £56.8 m.; L. F. Haber, (1971): 291 ff., 302; W.J. Reader, especially chapter 19 “The foundation of ICI” (1970). The amalgamation of 45 small firms to form the United Alkali Co. began this process in 1890 and Brunner Mond acquired firms between 1917-1920; S. Miall, (1931): 61.

²¹⁰ A. Arora, R. Landau, N. Rosenberg (eds.), (1998): 241, 245.

²¹¹ W. J. Reader, (1970): 220-1, 371; On Mond see A. J. P. Taylor, (1988): 249.

²¹² H. Tammen, (1978): 19.

1926,²¹³ and in France where Rhône Poulenc and the Société Chimique des Usines du Rhône, combined in 1928²¹⁴

Arnold Renshaw M.D. of the Laboratory of Applied Physiology and Preventative Medicine in Manchester wrote that the: “recent merging of the outstanding British chemical companies into a single organisation is hailed by scientific men as one of the greatest steps towards the economic prosperity of the chemical industry.” He felt that the new company of ICI could restore 'national honour' and that there was now no longer an obstacle to competing with German rivals so that:

“Whilst congratulating the German investigators upon their achievement in the introduction of drugs of the type of Salvarsan and Bayer 205, we may envy the facilities and resources upon which they are able to draw”²¹⁵

By this he meant that Britain would no longer be dependent on Germany for chemical intermediates, and this would benefit the pharmaceutical industry. There was still a lot of progress to be made in establishing research and manufacturing capacity on the German lines.

5.9 Conclusions.

During the 1920's, British firms that had embarked on drug synthesis began to produce simple organic chemicals. Many of the new compounds were variants on new agents appearing elsewhere. The Dangerous Substances Act of 1922 mandated the employment of trained staff to deal with poisons and other dangerous drugs and this further stimulated the development of laboratories. Processes and manufacturing capacity were improved: an example of a small stepwise improvement was the preparation of beta-eucaine (Benzamine) rather than the naturally occurring alpha-eucaine. This may not seem an exciting development but the new preparation was important at the time because it was far

²¹³ G. D. Taylor, DuPont and the International Chemical Industry (Boston, Mass: Twayne, 1984); W. H. A. Carr, W. H. Alexander, The DuPonts of Delaware (London: Muller, 1965).

²¹⁴ Judy Slinn, A History of May & Baker 1834 - 1984 (Cambridge: Hobson's Ltd., 1984): 99.

²¹⁵ A. Renshaw, “Chemical Research in Britain” British Medical Journal (6 November 1926): 857.

less irritant and toxic than the parent substance.²¹⁶ Similarly at Boots, after the chemical department was expanded in 1929, work on hexylresorcinol led to the significantly improved antiseptic, amylmetacresol and several further derivatives, which were more soluble and better tolerated.²¹⁷ Several companies expanded their facilities to produce insulin, vitamins and hormones.

During the period under review there were many such advances but previously historians have concentrated only on major developments, concerning themselves with drugs such as insulin or penicillin, which have made a more lasting impression and which are better documented. In his thesis Robson went as far as denigrating chemists with their “obsession with obscure technical details of little overall importance”.²¹⁸ Contemporary writers did not see the interwar period as the 'barren period' ascribed by later authors.²¹⁹

Whereas in other industries the Wartime collaboration between Government and industry was ‘transitory’, I argue that this remained fruitful in the case of the pharmaceutical industry and that the relationship continued in the interwar period, forming a solid foundation for production of drugs in World War Two.²²⁰

Protectionist measures were recognised as only stopgaps until the availability of chemical engineers and chemical intermediates improved, and until firms developed more innovative drugs and better collaboration with the medical profession. British firms faced difficult choices in the interwar period. Those that had invested in extending their manufacturing capacity were especially vulnerable. There was no way that they could compete with Germany on price and efficiency of production. However, in order to survive, British companies had to make profits in the contemporary austere financial climate. Being in no position to rely entirely upon synthetic chemistry, they continued to

²¹⁶ J. Chem. Soc. 125 (1924): 46.

²¹⁷ S. A. B. Kipping, Chemistry and Industry (25 February 1963): 303-4.

²¹⁸ M. Robson, The Pharmaceutical Industry in Britain and France 1919-1939: (London: PhD, June 1989): 7.

²¹⁹ “Scientific and Industrial Problems of Hormones” British Medical Journal (24 July 1926): 167.

²²⁰ J. V. Pickstone, Ways of Knowing. A New History of Science, Technology and Medicine (Manchester: Manchester University Press, 2000): 164.

produce biologically standardised hormones and vitamins, inorganic drugs, and alkaloids and their synthetic efforts were primarily those, which Carr proposed, of gradual improvements of methodology for purifying the active principles in better yields. While this chapter showed that in general British pharmaceutical firms expanded their chemistry efforts, further support is given in the chapter on Burroughs Wellcome and their Scientific and Technical Committee, which examines in more detail the dilemmas caused by the alternative potential strategies.

The dearth of chemists in the respective companies up to 1927 may explain the apparent lack of innovations by Boots, May & Baker, Evans and Burroughs Wellcome in this period, although another strong reason was the success of the organotherapies and hormones, which offered an alternative to direct competition with Germany. Furthermore, several of these companies suffered the loss of key members of staff.

Nevertheless, significant improvements had emerged in the British pharmaceutical industry from 1922 and 1926 such that by 1931 Miall could describe the “Cooperation, which is taking place between the chemist and biologist, the chemist and physicist and between the chemist and engineer”.²²¹

Soon after the TTC was announced, Dr Percival Hartley, ex- Burroughs Wellcome and by now Head of the Standards Division of the National Institute of Medical Research recounted the “difficulty in applying standards of products from overseas” in a paper on ‘State Control of Therapeutic Substances’ to the Annual meeting of the Fever hospitals group in June 1931. With limited resources to check samples, a high proportion of biological drugs had been either contaminated or under strength and potencies varied widely, pointing to a need for new chemical drugs to be tested clinically.²²² These comments reflected an ongoing suspicion about the potency of foreign drugs.

The government assisted British firms by first excluding and then raising tariffs against imports and then required chemical or biological standardisation. According to their rhetoric, seemingly backed up by the figures they produced, the main problem was with

²²¹ S. Miall, History of the British Chemical Industry (London: Ernest Benn Ltd., 1931): 237.

²²² P. Hartley, “State Control of Therapeutic Substances” British Medical Journal (20 June 1931): 1072.

foreign drugs. Much of the initial expertise at the MRC came from Burroughs Wellcome and they continued to secure staff from Burroughs Wellcome such that concerns were raised at one stage.

However, based upon the close collaboration of Burroughs Wellcome with the MRC, Britain emerged from a position of weakness to take a significant international lead in biological standardisation. The Therapeutic Substances Act confirmed the important central role of the MRC and later the Pharmaceutical Society headed by J. H. Burn in drug standardisation and helped to protect Britain from importation of drugs that had not been tested. By 1928 Dale, by now the overall Director of the NIMR, and Fletcher were increasingly influential in deciding the fate of medicines, and both were invited to sit on the Pharmacopoeia Commission.²²³ The MRC had become a powerful central body for the evaluation of novel medicines. However there was as yet no formal means of having drugs tested in clinical trials and this had been an issue for British firms for many years.

In chapter 8 I will explore how Dale and Fletcher were also influential in assisting firms to arrange for the clinical testing of new drugs and suggest that to some degree this became a further barrier to the importation of foreign drugs. Clinical testing could be done in Germany but British physicians would be more likely to use a medicine if it had the approval of the MRC.

²²³ MRC Minutes III, (22 June 1928): 83.

CHAPTER SIX: The Campaign for Clinical Trials.

“Interesting new compounds are discovered. Interesting new drugs are developed”.¹

6.1 Introduction.

This is the second chapter of three covering the period 1919-1931. Chapter 5 dealt with the general problems faced by the pharmaceutical industry in the interwar period, Chapter 7 is a case study of Burroughs Wellcome strategy in this period. This chapter deals with the specific problem of how British firms campaigned to get their new drugs tested clinically. Having collaborated closely with the pharmaceutical industry during the war, particularly regarding Salvarsan, the MRC became the focus of medical research in Britain, developing a series of clinical research centres linked to patient care, and established themselves as arbiters of drug quality. After the War, with the establishment of the NIMR at Hampstead in 1919, the role of the MRC in the standardisation of novel medicines was formalised, to ensure that drugs could be used reliably with known potency (chapter 5). In addition to biological standardisation of drugs, the MRC clinically evaluated some new drugs, first retrospectively and then prospectively and shaped the regulatory framework. At the end of the War the work of the second Salvarsan Committee continued as described in Chapter 4. From their first meeting of the Medical Research Council in July 1920, Fletcher introduced the concept of small, specialised coordinating sub-committees, which recommended research grants to individuals and institutions, and which oversaw research studies.² They were also the means by which the MRC considered small clinical studies of any promising new agents, usually arising from academia.³

¹ William Osler, (1849-1919) “Aequanimitas”, 1900 quoted from C. D. Leake, An Historical Account of Pharmacology to the Twentieth Century (University of California: Springfield, Illinois; C. C. Thomas, 1975): 2.

² W. M. Fletcher to Sir George Newman, Chief Medical Officer at the Ministry of Health, (7 May 1918), MRC 1381/1.

³ MRC Minutes II, (7 July 1920), “Committee on Biological Standards”: 82; “Committee on Cinchona Derivatives and Malaria”: 83; “Committee on Rickets”: 84; “Committee on Accessory Food Factors”: 85.

Pharmaceutical firms had previously tried with limited success to organise their own clinical trials. At Burroughs Wellcome, both WPRL and WCRL scientists tried to establish clinical trials of novel extracts and when available, the publications supported commercial activity.⁴ When they had limited clinical data, as was the case with their throat Tabloids, all they could say was that: “Sir Morrell MacKenzie likes the idea” or that their malt extract was “submitted to many therapists and a general opinion has been expressed”.⁵ During the War the MRC tested not only Salvarsan, but also some other products that showed potential benefits for the troops, but they emphasised that their interests were scientific rather than supporting firms. One example was the testing of ‘collosol cocaine’ on behalf of Crookes Collosols Ltd. Dale wrote: “it is important that this statement should not be misunderstood as indicating that the MRC, or any members of their staff, undertake the examination of proprietary medicines at the request of makers”.⁶ Firms saw a chance to collaborate with the MRC through the sub-committees to perform clinical trials of their new drugs. However, ultimately these arrangements were too specific and limited and the pharmaceutical firms continued to campaign for a system of testing drugs until the creation of the Therapeutic Trials Committee in 1931.

6.2 The MRC and Clinical Research Centres.

Following their initial wartime research efforts, the MRC established a network of centres to encourage the development of academic clinical researchers with laboratory research and access to patient beds. The network of clinical research centres was wider than previously described by Joan Austoker, who examined the role of Walter Morley Fletcher and the origins of a research policy.⁷ Similarly, Christopher Booth based his conclusions that the academic clinical research base was quite limited by reviewing only

⁴ A total of 58 cases of constipation treated with Cascara Tabloids with success in 44. Chemist & Druggist 39 (1891): 554 – cutting in WF: 89/29: 7.

⁵ Chemist & Druggist 39 (1891): 134-39, 625, cuttings found in WF: 89/29: 7.

⁶ British Medical Journal (1917) ii: 710.

⁷ J. Austoker, “Walter Morley Fletcher and the Origins of a Basic Biomedical Research Policy” in J. Austoker and L. Bryder (eds.), Historical Perspectives on the Role of the MRC (Oxford: Oxford University Press, 1989): 23 – 33.

summaries of the MRC annual reports.⁸ The biography of Walter Morley Fletcher and the MRC histories are also instructive⁹, but the MRC Minutes document fully the level of support given and identify further centres. Steve Sturdy studied the development of clinical science in detail, particularly Edward Mellanby's department at Sheffield.¹⁰ More recently Helen Valier examined research in Manchester¹¹ and Malcolm Nicolson in Glasgow.¹²

Post war, the research activities financially supported by the MRC expanded to include cerebrospinal fever, influenza, pneumonia, rheumatic fever, venereal disease, child life problems, growth disorders, accessory food factors, disorders of the cardiovascular system, biochemistry, chemotherapy, and status lymphaticus.¹³ Wartime interests in septic shock, wounds and trench fever were continued.¹⁴ The MRC performed work on typhoid and paratyphoid vaccines and on tropical diseases including bilharzia and cholera.

⁸ C. C. Booth, "Clinical Research" in J. Austoker and L. Bryder (eds.), (1989): 205-241.

⁹ Maisie Fletcher, The Bright Countenance: a Personal Biography of Walter Morley Fletcher (London: Hodder and Stoughton, 1957); A. Landsborough Thompson, Half a Century of Medical Research, volume 1. Origins and Policy of the Medical Research Council (London: HMSO, 1973); A. Landsborough Thompson, Half a Century of Medical Research volume II. The Programme of the Medical Research Council UK (London: HMSO, 1975).

¹⁰ S. Sturdy, "Medical Chemistry and Clinical Medicine: Academics and the Scientisation of Medical Practice in Britain 1900-1925" in Ilana Löwy (ed.), Medicine and Change: Historical and Sociological Studies of Medical Innovation, Colloquia INSERM 220 (Montrouge: John L Furstadt, 1993): 371-394; S. Sturdy, "The Political Economy of Scientific Medicine: Science, Education and the Transformation of Medical Practice in Sheffield 1890-1922" Medical History 36.2 (1992): 125-39.

¹¹ Helen Kathryn Valier, (University of Manchester: PhD thesis, 2002) The Politics of Scientific Medicine in Manchester c 1900 – 1960.

¹² D. Smith, M. Nicolson, "Paton, Cathcart and Findlay: a Conservative Stance in Scottish Nutrition" Soc Hist. Med. Bull 40.6 (1987): 45-47; D. F. Smith, M. Nicolson, "Chemical Physiology versus Biochemistry, the Clinic versus the Laboratory. The Glaswegian Opposition to Edward Mellanby's Theory of Rickets" Proc. Roy. Coll. Physicians Edinburgh 19.1 (1989): 51-60.

¹³ Review of MRC Minutes I-II, (1920-27).

¹⁴ "Shock: its Nature and Prevention" British Medical Journal 1917 (2): 771-3. The researchers involved included Prof. F. Bainbridge, Prof. W.M. Bayliss, Prof. W. B. Cannon, Dale, Elliott, Capt. John Fraser, C. S. Sherrington, E. H. Starling, and Col. Cuthbert Wallace.

Professor Warrington Yorke was responsible for research at the Tropical Research Unit in Liverpool.¹⁵

The MRC gained some further limited experience in performing clinical trials of various potential treatments suggested by physicians. In 1921 they tested a Swiss specific treatment for tuberculosis.¹⁶ In reviewing the literature Wilkinson showed that one doctor, A. H. Croucher of Eastbourne, who claimed he had used the method since 1896 gave the MRC a clear insight into how he thought it should be studied in clinical trials.

“I personally welcome any fair and open trial of any method of specific treatment, which is most surely the method of the future. But it must be a real trial of the relative merits of our system by competent judges who have made themselves authorities by work and not by official position”.¹⁷

Croucher argued that he had set down the requirements for a trial design as early as 1912. He stated that the remedy should be the only remedy used in treatment:

“It should be exploited in a consecutive series of cases of all kinds (not merely especially selected cases) and all the cases fully treated should be published. After treatment the cases should be carefully watched and examined for at least three or four years before a final judgment is given upon the value of the remedy. The results should be arranged in these groups or better, as in my own records in five groups, according to the character and degree of the changes in the lungs”.¹⁸

In fact the questions about the Spahlinger treatment remained and the MRC were asked by a group of MPs for a statement on its merits and although they referred the question to the Tuberculosis Committee, in truth they had no conclusive data.¹⁹ As I will demonstrate such elaborate clinical trials remained only a theoretical concept for a long time. British

¹⁵ MRC Minutes III, (26 April 1929): 69. Also Bengel laboratories, a subsidiary of British Drug Houses provided £2,000 towards new laboratories for the Manchester University Medical School. *Times* (12 July 1929); “Toxicological Effects Following the Employment of Arsenobenzol Preparations” *MRC Special Reports Series* (London: HMSO, 1920) 66; J. Austoker and L. Bryder (eds.), (1989): 110 – 11, 117, 120.

¹⁶ “The Spahlinger Treatment for Consumption” *British Medical Journal* (5 March 1921): 360; “Spahlinger Treatment” *British Medical Journal* (2 May 1921): 683.

¹⁷ W. C. Wilkinson, “The Search for a Specific Treatment for Tuberculosis” *British Medical Journal* (26 February 1921): 308.

¹⁸ *Ibid.*

¹⁹ MRC Minutes II, (16 October 1925): 178.

firms simply wanted a quick ratification in simple studies and in small groups of patients so that they could sell their products and the MRC appeared to have the infrastructure to achieve this.

Although the MRC established a central role in clinical research, there were some opponents. Austoker discussed the ‘battleground’ between the Royal Colleges and the emerging specialities in the inter-war period. Lords Moynihan and Dawson, representing the Royal Colleges of Surgeons and Physicians respectively, saw the MRC as a threat to their central control and were concerned at seeing a divergence between research and medical and surgical practice. They felt that physicians rather than scientists should direct research and they saw some of the research sponsored by the MRC as lacking clinical relevance. However, Fletcher’s view that “A committee of eminent clinicians...will...be perfectly useless as well as highly embarrassing in directing clinical research” antagonised his opponents.²⁰ Lord Moynihan made a series of comments: “physiologists could not introduce new medicines” and they were “aloof from medicine”.²¹ Moynihan and Dawson both saw science as a part of the routine daily practice, whereas Fletcher divorced science to the laboratories for later application in medicine. In 1920 Moynihan had pushed for research relevant to surgery and chided the MRC for a lack of clinicians on their Council, and yet the main Committee members included Sir Thomas Clifford Allbutt, the Consultant surgeon C. J. Bond, who was a Fellow of the Royal College of Surgeons and Consultant at Leicester Royal Infirmary, plus T. R. Elliott of UCH, F. R. Fraser of St. Bart’s, and Dr W. W. S. Topley of Charing Cross.²²

Fletcher wanted to encourage MRC research in all branches of medicine, but this also brought conflict with the physicians and surgeons treating cancer, whose research was already funded by the Imperial Cancer Research Fund, established in 1902 - though the

²⁰ W. M. Fletcher to F. G. Hopkins, (12 April 1923), MRC 1383: I.

²¹ W. M. Fletcher, “The Science of Medicine” *Lancet* (11 October 1930): 779-85.

²² MRC Minutes II, (7 July 1920): 114 and 116 and (28 January, 1927): 17.

Council did study the effects of Radium. In 1923 a further funding body, the British Empire Cancer Campaign was set up, to work without conflict.²³

Fletcher invited Dawson to join the MRC Committee in 1931, though this did not stop further outbursts.²⁴ A clinical committee including Dawson, Trotter, Edward Mellanby and Lewis was appointed to advise the Council regarding clinical research.²⁵ Dawson was influential and had been President of the Royal Society of Medicine and he became President of the BMA in 1932.

Fletcher funded an internationally renowned research network of physicians, physiologists, bacteriologists and surgeons, many arising from Cambridge and University College Hospital, but also other major London hospitals such as St. Bartholomew's, and St. Thomas' as well as Sheffield, Manchester and Glasgow.²⁶ The network expanded as investigators moved from UCH and Cambridge to establish research centres elsewhere.

In 1919 St. Bartholomew's was the first to appoint a Professor of Medicine, Archibald Garrod, though he moved to Oxford to succeed Sir William Osler. Francis Richard Fraser was appointed Prof. of Medicine at St Bartholomew's in 1920, where the MRC already supported C. H. Andrewes and E. A. Carmichael, respectively the future Directors of the Common Cold Unit in Salisbury and a research unit at the National Hospital in Queen's Square, and Mr F. H. K. Green.²⁷

²³ J. Austoker, *A History of the ICRF* Chapter 3, (1902-86), (Oxford: Oxford University Press, 1988); D. Cantor, "The MRC's Support for Experimental Radiology During the Inter-War Years" in J. Austoker and L. Bryder (eds.), (1989): 181 – 204.

²⁴ J. Austoker, "Walter Morley Fletcher and the Origins of a Basic Biomedical Research Policy" in J. Austoker and L. Bryder (eds.), (1989): 23-33.

²⁵ MRC Minutes III, (21 October 1932): 160.

²⁶ Walter Morley Fletcher's papers may be found at the Wellcome historical library PP/WMF; Maisie Fletcher, (1957): 30; A. Landsborough Thompson, (1975); Richard Glazebrook, *Science and Industry: the Place of Cambridge in any Scheme for Their Combination* (Cambridge: Cambridge University Press, 1971).

²⁷ Fraser trained at Cambridge then Edinburgh, Rockefeller and Columbia University, S. Sturdy in Ilana Löwy (ed.), (1993): 371-394; C. C. Booth in J. Austoker and L. Bryder (eds.), (1989): 211; MRC Minutes II, (22 October 1926): 181; MRC Minutes III, (23 November 1928): 167.

Thomas Lewis was funded by the MRC and became the first full-time chair and Director of Clinical Research at the Department of Clinical Research and Experimental Therapeutics at UCH in 1920.²⁸ Col. T. R. Elliott, its new Professor of Medicine collaborated with Dale during his time at Burroughs Wellcome and the MRC.²⁹ Dale wrote “T. R. Elliott, Thomas Lewis and Wilfred Trotter were giants of UCH” where the “first tentative essays were being made in the application of scientific methods to clinical problems”.³⁰ Elliott “demonstrated that an academic unit, combining teaching, research and care of patients, could actually be made to work”.³¹ Arthur Robertson Cushny was Professor of Pharmacology at UCH, and later continued his structure-activity studies in Edinburgh.³²

Sir Arthur Ellis,³³ the first Professor of Medicine at The London Hospital, was supported, as was work at St. Thomas’s in London and at the Research Institute set up by Sir James MacKenzie; in 1922 at the Department of Therapeutics at Edinburgh and run by

²⁸ Lewis’ salary rose to £2,000 MRC Minutes, (30 January, 1925): 11; He studied atropine for atrial fibrillation and quinidine, MRC Report 110 (1922); W. R. Merrington, UCH and its Medical School: a History (London: Heinemann, 1976): 118, 192; MRC Report 1920-1 (London: HMSO, 1922): 23-28; Arthur Holman, Sir Thomas Lewis, Pioneer Cardiologist and Clinical Scientist (Godalming: Springer Verlag, 1986); C.C. Booth in J. Austoker and L. Bryder (eds.), (1989): 208-210.

²⁹ Elliott performed research on adrenaline, W. R. Merrington, (1976): 85-6, 118, 125-126; Thomas Renton Elliott, GC/42 Therapeutic Trials Committee Correspondence Files 13/1, 13/2; Sir William Grant MacPherson, Sir Wilmot Parker Herringham, T. R. Elliott, Sir Andrew Balfour (eds.), History of the Great War volume 1 “Medical Services, Diseases of the War” (London: HMSO, 1922-3); Sir Henry Dale, “Thomas Renton Elliott” Biographical Memoirs of Fellows of the Royal Society 7 (1961): 53 –74; “T. R. Elliott, Obituary” Lancet (11 March 1961): 567-68.

³⁰ 93 HD Box 36.4.31.

³¹ “T. R. Elliott Obituary” British Medical Journal (11 March 1961): 752-4.

³² A. R. Cushny papers, Wellcome Institute PR/ARC; James Coleman, The Hammersmith 1935-1985. The First 50 Years of the Royal Postgraduate Medical School at Hammersmith Hospital (London: M & P Press, 1985); J. Parascandola, “Arthur Cushny, Optical Isomerism, and the Mechanism of Drug Action” J. Hist. Biol. (1975) 8: 145- 65; H. MacGillivray, “A Personal Biography of Arthur Robertson Cushny, 1866 – 1926” Annual Rev. Pharmacology. (1968): 1 –24.

³³ A. Landsborough Thompson, (1975): 27.

Prof. J. C. Meakins.³⁴ Edinburgh was also the new home of the former Burroughs Wellcome chemist and botanist, George Barger, who took up the first Chair of Chemistry in relation to medicine in 1919 and held it for 18 years.

Fletcher also developed international connections at meetings such as the International Red Cross Meeting in Geneva in July 1920.³⁵ This led to funding from the Carnegie, Dunn and Rockefeller Institutes.³⁶ Lewis was also involved in negotiating the Rockefeller grants for UCH.³⁷ With funding from the Sir William Dunn and Rockefeller trustees, further grants were awarded by a sub-committee involving C. H. Andrewes (who joined the pathology and bacteriology department of the NIMR in 1926), Thomas Elliott, Frederick Hopkins and the surgeon, Cuthbert Wallace, (later chairman of the Radiology Commission).³⁸ Booth also identified the Welsh National School of Medicine in Cardiff as an important centre.³⁹

Two further researchers, who had collaborated with Lewis, moved to Cambridge. The pathologist, Alan N. Drury,⁴⁰ had been supported at University College and his

³⁴ MRC Minutes II, (24 March 1922): 250; (4 May 1923): 63.

³⁵ Fletcher met Flexner, Roux, Calmette, Bernard, Bordet and Madsen and traveled to the U.S.A. on several occasions, visiting McGill University: Maisie Fletcher, (1957).

³⁶ E. R. Brown, Rockefeller Medicine Men: Medicine and Capitalism in America (Berkeley: University of California Press, 1979); Maisie Fletcher, (1957): 30,147,197; "Mr. Rockefeller and Medical Research" British Medical Journal (1917): 130; R. E. Kohler, "Walter Fletcher, F. G. Hopkins and the Dunn Institute of Biochemistry: a Case Study in the Patronage of Science" (1978) Isis 69: 301, 331-55; W. H. Schneider, Rockefeller Philanthropy and Modern Biomedicine. International Initiatives from World War 1 to the Cold War (Bloomington: Indiana University Press, 2002).

³⁷ W. R. Merrington, (1976): 123; Abraham Flexner, Medical Education in the United States and Canada (New York: Carnegie Foundation, 1910): 116.

³⁸ MRC Minutes II, (20 July 1923): 91; (17 July 1925); D. Cantor in J. Austoker and L. Bryder (eds.), (1989): 199.

³⁹ Helen Kathryn Valier, (University of Manchester: PhD thesis, 2002) The Politics of Scientific Medicine in Manchester c 1900 – 1960: 168; C. C. Booth in J. Austoker and L. Bryder (eds.), (1989): 205.

⁴⁰ Drury joined the scientific staff on a salary of £850, MRC Minutes III, (25 January 1925): 8., and later transferred work from UCH to Cambridge, MRC Minutes III, (24 June 1927): 106.

funding continued at the Department of Pathology at the University of Cambridge.⁴¹ R. T. Grant was appointed to the Department of Experimental Medicine on 11 May 1928, but he left for Cambridge in October 1928 (and subsequently headed the new clinical research unit at Guy's Hospital, the first to emerge directly from Lewis' department.⁴² In Manchester, E. J. Wayne⁴³ worked on the metabolism of insulin.⁴⁴ George W. Pickering received support at St. Thomas's and was later Professor of Medicine at St. Mary's then Regius Professor of Medicine at Oxford. The MRC also supported George Dreyer at the Dunn School of Pathology in Oxford, working on bacterial diseases including his 'Diapylite vaccine' for Tuberculosis.⁴⁵

From Cambridge, Fletcher knew Charles Sherrington who became Professor of Physiology at Oxford. Archibald. V. Hill, a physiologist was Fletcher's own student at Cambridge from 1909 before he went to Manchester. The MRC provided a grant for J. B. Bateman to work under Prof. A.V. Hill later at UCH⁴⁶ and to Henry. Stanley Raper (ex-Leeds) and John Beresford Leathes (ex- Sheffield, ex-Toronto) as Professors of Physiology in Manchester, after Hill went to UCH.⁴⁷

These were the men who were to be central in the clinical testing of new drugs. The MRC research at the Central Research Institute, Mount Vernon, Hampstead was

⁴¹ MRC Minutes III, (24 June 1927): 106.

⁴² MRC Minutes III, (26 October 1928): 129; C. C. Booth in J. Austoker and L. Bryder (eds.), (1989): 220, 226, 234.

⁴³ "Edward J. Wayne, Obituary" *Lancet* (13 October 1990): 932. Wayne obtained his degree in chemistry at Leeds before studying medicine, and he later moved to the University of Manchester and received an MRC grant of £125 to work on fat and carbohydrate metabolism and insulin, MRC Minutes II, (1 May 1925): 87. He joined Lewis' department in 1931 then went to Sheffield as Prof. of Pharmacology, and then on to Glasgow. E. J. Wayne was later Professor of Medicine at St Mary's then Regius Professor at Oxford. He was a member of the MRC and chaired the BPC.

⁴⁴ MRC Minutes II, (22 October 1926): 181.

⁴⁵ Papers by L. Bryder and J. Austoker in J. Austoker and L. Bryder (eds.), (1989): 10, 46, 53, 63.

⁴⁶ Mark Weatherall, *Gentlemen, Scientists and Doctors: Medicine at Cambridge 1800-1940*. (Cambridge: Boydell Press, 2000).

⁴⁷ MRC Minutes II, (1 January 1920): 42.

closely linked to bacteriology through Almroth Wright and Leonard Colebrook, both of whom had collaborated in clinical trials with the War Office. The MRC supported beds for Wright at St Mary's Hospital. Leonard Colebrook followed up his vaccine work with further MRC studies on puerperal fever at a new building at Queen Charlotte's Hospital.⁴⁸ He joined the MRC Committee in November 1930.⁴⁹ Biochemistry and pharmacology at the NIMR were under Henry Dale who was appointed Director on 1 June 1928.⁵⁰

The MRC established sub-committees for the study of rickets, (including Hopkins, Paton, and Edward Mellanby)⁵¹, a haemoglobin committee (Joshua H. Burn,⁵² D. Murray Lyon of Edinburgh Infirmary),⁵³ an anaesthetics committee (including Prof. H. B. Dixon from the University of Manchester),⁵⁴ a committee on Cinchona derivatives and malaria (including Dale, A. Balfour, Col. S. J. James, Major H. W. Acton), and a Yellow Fever committee.

Although Fletcher fought against the establishment of the British Empire Cancer campaign, Gowland Hopkins and C. J. Bond were part of the Ministry of Health Departmental Committee on Cancer.⁵⁵

⁴⁸ MRC Minutes III, (11 April 1930): 49.

⁴⁹ MRC Minutes III, (28 November 1930): 179.

⁵⁰ M.R.C Minutes III, (2 March 1928): 59

⁵¹ MRC Minutes II, (24 March 1922): 243.

⁵² MRC Minutes II, (1 May 1925): 87.

⁵³ MRC Minutes II, (4 May 1923): 63. Murray Lyon was sponsored by the MRC in 1927. He was the first to give synthetic thyroxin to a patient, M. Weatherall, In Search of a Cure: A History of Pharmaceutical Discovery (Oxford: Oxford University Press, 1990): 89.

⁵⁴ MRC Minutes II, (29 January 1926): 8.

⁵⁵ MRC Minutes II, (19 October 1923): 101; (12 December 1923): 150; both were on the MRC; MRC Minutes II, (10 April 1920): 510-11. On the BECC see J. Austoker in J. Austoker and L. Bryder, (eds.), (1989): 29.

Frederick Gowland Hopkins,⁵⁶ chaired an Accessory Food Factors Committee, established jointly with the Lister Institute in 1918, including Harriette Chick, Jack Drummond at University College Hospital⁵⁷, the biochemist Arthur Harden⁵⁸ and Edward Mellanby (who we met previously in a temporary laboratory role at Burroughs Wellcome with his brother John).⁵⁹ From 1923 Edward Mellanby was Professor of Pharmacology at Sheffield, and then UCH.⁶⁰ The MRC also supported further nutritional research by Noel Paton, Regius Professor of Physiology at the University of Glasgow.⁶¹ A more general Nutrition committee⁶² was set up in 1929 with Prof. Edward Provan Cathcart⁶³ (chairman), John Boyd Orr, and continued support from Hopkins, Drummond and Chick. The MRC statistician, Major Greenwood, Professor of Epidemiology and Vital Statistics

⁵⁶ H. Kamminga, "F. G. Hopkins and the Unification of Biochemistry" Trends In Biological Sciences (22 May 1997): 184-7; H. Kamminga, M. W. Weatherall, "The Making of a Biochemist (I) Frederick Gowland Hopkins' Construction of Dynamic Biochemistry" Medical History 40 (1996): 269-292; M. W. Weatherall, H. Kamminga, "Making of a Biochemist (II) The Construction of Frederick Gowland Hopkins' Reputation" Medical History 40 (1996): 415 – 436; F. G. Hopkins, "The Practical Importance of Vitamines" British Medical Journal (26 April 1919): 507-10; J. Needham, E. Baldwin (eds.), Hopkins and Biochemistry 1861-1947: Papers Concerning Sir Frederick Gowland Hopkins, FRS. (Cambridge: W. Heffer & Sons, 1949): 5; MRC Minutes II, (9 September 1920): 113.

⁵⁷ F. G. Young, "Jack Cecil Drummond" Obituary Notices of Fellows of the Royal Society 9 (1954): 99 – 129; Walter Sneader, Drug Discovery: the Evolution of Modern Medicines (London: John Wiley, 1985): 227 – 247.

⁵⁸ F. G. Hopkins and Charles Martin, "Arthur Harden" Biographical Memoirs of Fellows of the Royal Society (1942) 4: 3-14.

⁵⁹ R. P. T. Davenport-Hines, J. Slinn, (1992): 75.

⁶⁰ Sir Henry Dale, "Edward Mellanby" Obituary Notices of Fellows of the Royal Society 1 (1955): 193 – 222.

⁶¹ MRC Minutes II, (12 January 1923): 3.

⁶² MRC Minutes III, (24 May 1929): 90; for an account of its work see C. Petty, "Primary Research and Public Health: the Prioritisation of Nutrition Research in Inter-war Britain" in J. Austoker and L. Bryder (eds.), (1989): 83 - 108.

⁶³ G. M. Wishart, "Edward Provan Cathcart" Obituary Notices of Fellows of the Royal Society 9 (1954): 33 - 53. Cathcart as Chairman of the Committee on Quantitative Problems of Human Nutrition carried out several nutritional surveys on behalf of the MRC between 19226 – 1932.

at the London School of Hygiene and Tropical Medicine was added to this team⁶⁴, and he was chair of the Ministry of Health's Advisory Committee on Nutrition from 1931-4.⁶⁵ The Sex Hormones Committee included Dr. F. H. A. Marshall (chair), Dr. V. Korenchevsky at the Lister Institute, and Dr. A. J. Parkes of the NIMR.⁶⁶

In addition to establishing committees, the MRC funded further research: Warrington Yorke's⁶⁷ colleagues, Dr. A. Adams and Dr. F. Murgatroyd to study anti-malarial remedies and potential trypanocides; Prof A. E. Boycott and Prof. F. J. Browne at UCH to study the bacteriology of puerperal infection;⁶⁸ Dr. J. F. Wilkinson at Manchester Royal Infirmary for chemical work on pernicious anaemia;⁶⁹ Prof. W. W. C. Topley of the University of Manchester⁷⁰ (later Professor of Bacteriology at the London School of Hygiene and Tropical Medicine) and Prof. Henry Stanley Raper, Professor of Physiology at Manchester University received funding for work for the anaesthetics committee,⁷¹ Prof. Edward Charles Dodds⁷² at the Middlesex hospital for work on testicular hormones; Dr. R. Cruickshank at the University of Glasgow for serum treatment of pneumonia⁷³ and Dr Derek N. Dunlop of Edinburgh work on metabolism;⁷⁴ Prof. J. C. Meakins at the University of Edinburgh was given two grants to support Drs. J. S. Murray and C. G. Lambie (from March 1923) and Prof. R. T. Leiper performed studies on immunity of

⁶⁴ J. Austoker and L. Bryder (eds.), (1989): 52, 99, 107; L. Hogben, "Major Greenwood" Biographical Memoirs of Fellows of the Royal Society (1950) 7: 137-154.

⁶⁵ MRC Minutes II, (22 February 1924): 111; C. Petty, in J. Austoker and L. Bryder (eds.), (1989): 83- 108.

⁶⁶ The Sex Hormones CIBA Handbook 4 (Horsham: CIBA, 4th edition, reprinted 1954).

⁶⁷ C. M. Wenyon, "Warrington Yorke" Biographical Memoirs of Fellows of the Royal Society (1944) 4: 523-545.

⁶⁸ MRC Minutes III, (2 June 1929): 110.

⁶⁹ MRC Minutes III, (11 April 1930): 68.

⁷⁰ J. Austoker and L. Bryder (eds.), (1989): 71-2, 74, 79, 81.

⁷¹ MRC Minutes III, (25 January 1927): 17; (27 January 1928): 18.

⁷² F. Dickens, "Edward Charles Dodds", Biographical Memoirs of Fellows of the Royal Society 21 (1975): 227 – 267.

⁷³ MRC Minutes III, (11 April 1930): 73, 74.

⁷⁴ MRC Minutes III, (24 October 1930): 150.

helminths;⁷⁵ L. W. Harrison at St Thomas' on the absorbability of bismuth compounds;⁷⁶ R. D. Lawrence and R. A. McCance at King's College Hospital for work on foodstuffs.⁷⁷

Even with this increase in clinicians funded by the MRC, the problem in assessing new therapies for treatment was that few individual doctors saw sufficient cases and fewer still were scientifically trained or research minded. Few of the above operated large clinical centres.

The benefits of synthetic drugs were not apparent to all doctors and approaches such as diet, exercise, and massage, were seen as alternatives. A contemporary editorial spelt out that: "only in exceptional circumstances should they (drugs) be considered as curative".⁷⁸ During the war there had been no alternative but to use the British synthetic drugs when there were no natural replacements for German drugs such as Salvarsan, Veronal, and Aspirin, despite the occasional reluctance of British doctors to accept the quality of the British versions.⁷⁹

The MRC did invoke the use of statistics to a degree, but mostly for their public health, epidemiology and vaccination studies. Major Greenwood collaborated with Dr. Leonard Hill on a ventilation study. This interaction profited in the later interactions with Hill's third son Austin Bradford Hill, who became an MRC statistician. In 1920 John Brownlee was the leading statistician at the MRC and together with Greenwood and Prof. E. C. Collis established the Industrial Health Statistics Department at the Industrial Fatigue Research Board.⁸⁰ This committee extended a grant to Austin Bradford Hill in January 1923 to collect information for the nutrition committee on the disease mortality

⁷⁵ P. C. C. Garnham, "Robert Thompson Leiper" Biographical Memoirs of Fellows of the Royal Society (1970) 16: 385-404.

⁷⁶ MRC Minutes III (22 March 1929): 54

⁷⁷ MRC Minutes III (24 May 1929): 90; R. A. McCance "Obituary", British Medical Journal (27 March 1993): 851.

⁷⁸ "Reform in Medical Education" British Medical Journal (1 January 1921): 20.

⁷⁹ J. E. R. McDonagh, "The Manufacture of Salvarsan Products in England and France" British Medical Journal (17 April 1915): 697.

⁸⁰ MRC Minutes II, (27 May 1921): 76.

related to migration from rural to industrial areas.⁸¹ A statistics department was established in May 1922 with Udney Yule added and in February 1925 the Industrial Health Statistics Committee was renamed as the Statistics Committee. However it was not until the final pre-war meeting in 1939 that Bradford Hill attended Therapeutic Trials Committee meetings.

This section has discussed how the MRC took a central role in establishing clinical research centres and in collaborating with other institutes such as the DSIR, the Lister Institute, British Empire Campaign, and the Colonial Office.⁸² This and the wartime work of the MRC provide the background to why pharmaceutical companies were so keen to collaborate with the MRC.

6.3 The ABCM Approach to the MRC for a Clinical Testing Scheme in 1922

The extension of the Key Industry Act in 1921 to include pharmaceuticals and other fine chemicals offered only partial protection for uncompetitive British pharmaceutical firms. While they welcomed new restrictions on the importation of drugs from abroad that had not been biologically tested, only clinical trials in patients could offer conclusions about the clinical efficacy and safety of their own new powerful, and yet potentially toxic drugs, but these were not mandatory. The Food and Drugs Act of 1899 and Dangerous Drugs Act of 1920 only required the strength and content of new drugs to be specified. There was no legislative requirement to prove efficacy. In theory nothing prevented a company from placing new products on the market. However, without supporting data from leading pharmacologists and clinicians a new drug would be unlikely to be a commercial success. Joshua Burn, the former Burroughs Wellcome researcher who was responsible for biological standardisation at the National Institute of Medical Research and then at the Pharmaceutical Society, later summarised the difficulties of performing trials:

“Clinical research work is difficult because the experimental animal is the patient, who is not at the disposal of the experimenter, and whose welfare

⁸¹ MRC Minutes II, (12 January 1923): 6.

⁸² J. Beinart, “The Inner World of Imperial Sickness: the MRC and Research in Tropical Medicine” in Joan Austoker and Linda Bryder (1989): 109-135.

must remain a more important consideration than the outcome of the research. Nor can the patients usually be collected in large groups like mice".⁸³

In the absence of clinical testing, manufacturing companies instead followed medical publications and when a new concept or method of treatment was described they rushed to produce a drug with the relevant characteristics. Examples include the multitude of antiseptics marketed after Lister's discovery, including also bismuth salts, calomel, mercuric sulphate, salol, beta-naphthol and naphthalene tetrachloride, and the plethora of phosphates, hypophosphates, and glycerophosphates, when they were shown to decrease demineralisation of bones. Further examples followed the discovery of vitamins. Clinical trials were not always needed in such cases as the company could refer to the scientific 'proof' already established. The firms were just providing their version of a proven active ingredient and they differentiated their drugs on purity and strength. The problem with this approach was that the new therapy was not exclusive and could be prepared by many firms. For novel drugs, pharmaceutical firms needed at least a favourable clinical 'opinion' published in a medical journal, even if it took only a few patients to achieve this aim. British firms that had difficulty in arranging clinical tests felt that if their products were given a seal of approval from the MRC, this would give them an advantage over German firms.

The few British firms that invested in synthetic chemistry had major difficulties arranging for clinical trials of their new drugs as most British doctors were not accustomed to dealing directly with pharmaceutical manufacturers and remained suspicious of British synthetic drugs. Previously clinical trials had not been performed because companies were simply manufacturing extracts required by physicians to treat patients according to time-honoured traditions. As semi-synthetic or synthetic drugs had never previously been given to humans, firms had the additional hurdle of first convincing the sceptical medical profession of their potential value, whereas previously they had simply produced alkaloidal extracts or inorganic medicines of known efficacy that doctors requested and had prescribed for decades. Physicians were also aware of the contemporary legal position; "while it is the duty of a physician or surgeon to keep up

⁸³ J. H. Burn, *The Background to Therapeutics* (Oxford: Oxford Medical Publications, 1948): preface.

with the advancement made by his profession it is also his duty not to attempt to forge ahead of it by trying experiments on his regular patients”.⁸⁴

In 1922 the MRC had just acquired the rights to insulin and were about to establish clinical trials. The Association of British Chemical Manufacturers (ABCM) that had become the collective voice of the pharmaceutical industry following its campaigns for collaboration, for the training of chemists and as a result of its chemical mission to Germany in 1919, approached the MRC about facilities for testing new medicines at the end of 1922. They were represented by four leading industry men; Francis Carr, who had developed the chemical departments at Burroughs Wellcome and Boots; Charles Hill, the Managing Director, who had recently recruited Carr to British Drug Houses; George Pearson, General Manager of Burroughs Wellcome, and Frederick Gamble, pharmacist and senior manager at Allen & Hanbury’s.⁸⁵ They represented the major scientifically based British companies which had expanded during the war, but which most felt the impact of a squeeze on profits in 1921-22. The ABCM argued, as they had since their inception in 1916, that the British industry “ought to be independent of foreign supplies”.⁸⁶

The first meeting with the MRC took place on 15 February 1923 following a memorandum from Woolcock,⁸⁷ secretary of the ABCM, which summarised the problems, which Pearson and his staff had experienced at Burroughs Wellcome:

“There are two main difficulties in securing the medical cooperation required under the present conditions: the scarcity of medical research

⁸⁴ Quoted from a 1918 legal encyclopedia by K. Lawrence Altman, Who Goes First? the Story of Self-Experimentation in Medicine (New York: Random House, 1987): 12.

⁸⁵ G. E. Pearson to W. J. Ulney Woolcock, (18 December 1922) and W. J. U. Woolcock to M.R.C., (19 February 1923), MRC File 1523.

⁸⁶ “British Fine Chemicals” British Medical Journal (29 April 1922): 666.

⁸⁷ W. J. Ulney Woolcock CBE, was previously active in the Society of the Chemical Industry. Woolcock had studied at University College, and the School of Pharmacy in London. Between 1913 –18 he was Registrar and Secretary of the Pharmaceutical Society. He was General Manager of the ABCM from 1918 to 1928. Later he took management roles with Mond and ICI; “W. J. U. Woolcock” Chemistry & Industry (27 December 1947): 807.

workers, [and] the professional position of medical men who may become associated with manufacturing firms”.

“When a manufacturer had evolved by research, a substance which was believed to be of therapeutical value it had to be first tried by a pharmacologist to make sure that it would be safe for clinical trials. Such pharmacologists were scarce in England and few, if any, had assistants in training. The pharmacologists were also engaged in their own lines of research from which they did not wish to be diverted. As a result of this it is only by a lucky chance that the manufacturers can get a new product tried pharmacologically in this country and continuous cooperation in a long research such as that which in the course of something like 15 years work in Germany led to 'Bayer 205' is simply out of the question in England”.⁸⁸

Bayer 205 or tryparsamide (Germanin) was a new German drug for treating sleeping sickness.⁸⁹ It was significant not only for its medical impact, which would be limited to the colonies, but as a further example of the superiority of German synthetic chemistry and pharmacology in combating a previously untreatable disease. Pharmacology had developed as an important science, first in France and Germany and was then exported to America by doctors trained in Germany. Pharmacologists in Germany worked closely with pharmaceutical or dye manufacturers, who provided the chemicals to gain a better understanding of drug action. The science was not as developed in Britain, partly because of the earlier Antivivisection laws, but also because of the limited availability of novel compounds, limited fellowships allowing physicians to perform research and few clinical researchers with access to patient beds, as described previously.⁹⁰

The Woolcock/ Pearson note from the ABCM continued:

“Assuming the manufacturer is fortunate enough to overcome the pharmacological difficulty he is then faced with the more serious matter of getting clinical reports on his new product. Here again the number of men competent to do such work is extremely small and it is not too much to say that the average clinical report obtainable in this country is worthless. What the manufacturer really wants is a trustworthy report showing what advantage and disadvantages the new drug has when compared with

⁸⁸ W. J. U. Woolcock to W. M. Fletcher (19 February 1923) based on a note from G. E. Pearson to W. J. U. Woolcock, (18 December 1922). “Chemical Manufacturers and the MRC 1922-1949” (13 February 1923), MRC File 1523.

⁸⁹ From Germanin to Acylureidopenicillin; Research that Made History. (Leverkusen: Bayer 1980): 13 –19; 50 Years of Bayer Remedies 1888-1938 (Leverkusen: Bayer, 1938).

⁹⁰ MRC Minutes II, (17 July 1925): 122, and (30 April 1926): 63.

existing remedies and calling attention to any unexpected features in the nature of its action. It is safe to say that such reports are only obtainable in exceptional circumstances in England today. What usually happens is that a medical man undertakes to furnish a clinical report and after long delay says that owing to pressure of other duties he has been unable to undertake the work or to finish a report, which merely states that the drug is or is not satisfactory. This difficulty can only be overcome in the long run by the provision of more pharmacologists and expert clinical observers and this can only be done by the medical colleges in this country giving more attention to these subjects and encouraging students to specialise in them at a fairly early stage in their careers. But in addition to this some arrangement is required whereby manufacturers can obtain as a matter of course, pharmacological and clinical reports on new drugs, just as they can already obtain reports from chemists, lawyers and other professional men on chemical, legal and other questions. Perhaps this could be done by the MRC forming a panel of pharmacologists, clinicians and other medical experts whom manufacturers could consult either direct or through the Council. It is possible that the Council could itself arrange for some of this work to be done in its own laboratories but it would no doubt be necessary to supplement such facilities very considerably in order to cope adequately with the work and the formulation of a panel of men whom the council consider suitable for such work would, it is thought be of great assistance, not only as regards the immediate difficulty but also in the way of stimulating interest in these subjects and encouraging students to specialise in these directions.

2) Professional role of medical men with manufacturers

It is clear from the foregoing that if this country is to take its proper place in chemo-therapeutical research and in the fine chemical manufactures, which should result from it, there will have to be a much closer association of medical men (using that term in the broad sense to include pharmacologists, physiologists, etc.) with manufacturers than has hitherto been the case in England and the question has been raised whether men who thus become associated with industrial firms for such purposes will lose caste in the eyes of their professional brethren and may even run the risk of being looked at askance by the authorities of the medical colleges. It is not easy to state this difficulty precisely and possibly the nearest approach to accuracy may be to say that there seems to be a feeling among certain medical men that professional association with a firm is regarded by the leaders of the medical profession as "not quite the right thing". This is a rather intangible matter and admittedly difficult to deal with but it will be realised that in a country like England where the 'correct thing' in conduct is a factor of no small importance, such a feeling, if it exists, may be a serious obstacle to progress. On this matter it is hoped that the M.R.C. may be able to afford manufacturers some guidance and possibly to issue some statement on the general questions dealt with in this memorandum in which would be incorporated, should they see fit, to do so, some expression of opinion, indicating that they will be glad to see close cooperation between medical

experts and manufacturers for the common object of securing progress in therapeutics. In this connection it may perhaps be mentioned that there are already in existence in the country institutions either endowed or supported by national funds which have on their staffs eminent scientific and medical men and which undertake purely commercial investigations and work in close association with industrial firms. The prestige of such institutions seems to be in no way influenced by such association, nor is the standing of their staffs affected and in view of this there seems to be no reason why the direct association of medical men with industrial firms should act in any way to their detriment".⁹¹

The stigma of liaisons with the pharmaceutical industry regarding advertising and selling of drugs remained in Britain following the campaigns against the patent medicine producers. Doctors relied on London-based conferences and on editorials written by the medical elite for their information on new drugs. Only rarely were dogmatic claims substantiated with extensive clinical data. Individual case reports predominated in British medical journals. To what extent this reflected editorial policy, the physicians' precept that therapy had to be tailored to the individual, or the difficulties of arranging tests of new drugs is difficult to assess. Trade names of drugs were frowned upon and the role of the manufacturing company was rarely acknowledged.

Clinical trials had been performed in the past with vaccines and antitoxins, but local health boards organised these in accordance with Government policy.⁹² All of the available vaccines were the results of academic research rather than commercial enterprise. Firms such as Evans Lescher & Webb collaborated with the Liverpool School of Hygiene and Tropical Medicine, while Allen & Hanbury's collaborated with the Lister Institute to produce vaccines.⁹³ The firms then acted in a manufacturing capacity and offered sales and distribution services for vaccines. Now that some pharmaceutical firms

⁹¹ G. E. Pearson to W. J. U. Woolcock, A.B.C.M., (18 December 1922), MRC File 1523.

⁹² A. I. Stolly, W. H. Birk, "Studies on Immunisation Versus Respiratory Disease. VII. Report on the Prophylactic Vaccination of 1536 Persons Against Acute Respiratory Diseases 1919-1920" *Journal of Immunology* 6 (1921): 103-15.

⁹³ Geoffrey Tweedale, *At the Sign of the Plough: 275 Years of Allen & Hanbury's and the British Pharmaceutical Industry 1715 - 1990* (London: Murray, 1990): 120; Walter Sneader, (1985): 230-1, 233, 235, 244, 265, 280, 332.

were developing their own drugs they sought wider interactions with medical researchers and having limited direct success they had turned to the MRC.

6.4 Insulin: an MRC Preoccupation and a Production Challenge

Although the first contact between representatives of the MRC and the ABCM regarding clinical trials took place at the end of 1922, no immediate progress was made. The reason seems to be that the MRC became pre-occupied with their work on biological standards and especially on the British development of insulin, following the approach from Toronto University with an offer of the British rights to insulin and this overshadowed the immediate plans to arrange studies of the British firms products.⁹⁴ The MRC agreed to test the extract, known as insulin as long as no restrictions were placed upon them.⁹⁵

Insulin was a purified hormone, initially extracted from pancreatic glands of cattle, which appeared to control blood glucose levels, so offering hope for the life-threatening condition of diabetics. The Toronto team had already collaborated with Eli Lilly of Indianapolis in the USA for production of insulin,⁹⁶ which had already been shown to be remarkably active, held far more interest for the MRC than the untried 'new' synthetic drugs available from British firms. By the same token, if they could obtain it, insulin offered the British firms the chance of much larger profits than any of their other lines as it was not initially available in Germany. The insulin story has been told in detail by Bliss and by Sinding, so I will focus only on some key issues which affected the British firms and the testing of their own drugs.⁹⁷ Both Quirke and Cox-Maksimov took insulin as one of their thesis case studies. Both referred to the 'seminal' study by Liebenau, though this was based upon a limited appraisal of the MRC source records, referring to insulin as a

⁹⁴ M.R.C. Minutes II, (17 November 1922): 375; (8 December 1922): 389.

⁹⁵ The first discussions about insulin were on 24 March 1922, MRC Council Minutes II, (21 July 1922): 318.

⁹⁶ Michael Bliss, *The Discovery of Insulin* (Edinburgh: Faber & Faber, 1983).

⁹⁷ C. Sinding, "The Making of Insulin" *Bull. Hist. Med.* 76 (2002): 231-70.

“pituitary (rather than a pancreatic) hormone”.⁹⁸ In September 1922 Henry Dale and his chemist Harold Ward Dudley⁹⁹ visited U.S. manufacturers at Ann Arbor (Parke Davis) and Indianapolis (Eli Lilly) to discuss the standardisation of insulin.¹⁰⁰ As with other extracts it could be of variable strength and given its role in controlling blood glucose, the dose administered had to be accurate. Dale and Dudley met American clinicians involved in early clinical trials of insulin, but also discussed American studies of influenza, bacterial chemistry, and vitamins and they visited the U.S. hygienic laboratories in Washington to discuss standards of Salvarsan, pituitary extracts and antitoxins.¹⁰¹

The MRC secured British patents on insulin.¹⁰² However, this change of their policy regarding patents was highly controversial and troubled them for many years.¹⁰³ Protests appeared from Sir William Bayliss of University College, London.¹⁰⁴ The

⁹⁸ J. Liebenau, “The MRC and the Pharmaceutical Industry” in Joan Austoker and Linda Bryder (eds.), Historical Perspectives on the Role of the M.R.C. (Oxford: Oxford University Press, 1989): 163-180 on p. 169.

⁹⁹ H. H. Dale, “Harold Ward Dudley” Obituary Notices of Fellows of the Royal Society 1 (1935): 595 - 606.

¹⁰⁰ H. H. Dale, H. W. Dudley, “Report to the Medical Research Council of our Visit to Canada and the United States” (30 October 1922): 318, MRC File 1092/15.

¹⁰¹ H. H. Dale, H. W. Dudley, “Report to the Medical Research Council of our Visit to Canada and the United States” (30 October 1922): 318, MRC File 1092/15; MRC Minutes II, (8 December 1922): 389; MRC 1092/25; M. Bliss, (1983): 166; “The New Treatment of Diabetes by Insulin” Lancet (18 November 1922): 1086; J. Austoker and L. Bryder, “The National Institute for Medical Research and Related Activities of the MRC” in Joan Austoker and Linda Bryder (eds.), (1989): 44-45.

¹⁰² MRC Minutes II, (21 July 1922): 318; A method of concentration of insulin, granted to Dudley and the Council; MRC Minutes II, (25 March 1923): 26.

¹⁰³ The MRC debated patents extensively and draft guidelines on patents were drawn up in 1928; MRC Minutes II, (1927): 24, 56, 84, 208; (1928): 4, 131, 161; A. Landsborough Thompson, Volume 2 (1975): 236.

¹⁰⁴ Bayliss was the co-discoverer of ‘Secretin’, and along with E. H. Starling the first to use the term hormone; W. Bayliss, “Insulin, Diabetes and Rewards in Diseases” Nature (10 February 1923): 188-191.

educationalist, Professor H. E. Armstrong also sent a strongly worded letter of complaint to *The Times* about the patenting of medical discoveries.¹⁰⁵

Fletcher argued that patenting was in line with the MRC policy of ensuring the quality of new medicines and “that proper steps towards standardisation and towards the help and guidance of the profession in the therapeutic use of the substance (are given), preventing improper exploitation by commercial interests”.¹⁰⁶ Insulin was also protected by tariffs and Francis Carr later fought against removal of the tariff on Danish insulin and the possibility of low-priced imports.¹⁰⁷ Insulin tariffs were discussed up until 1933, when a parliamentary tribunal was established under the Safeguarding of Industries Act.

Insulin was clearly an important advance, but it involved a complex extraction process and without pharmaceutical industry support, supplies would have been limited. Holding the patents would enable the MRC:

“to exercise a moral control over manufacturers and would induce the latter to submit to a system of supervision, as regards this product, which the law does not enable the Council at present to enforce (and) would regularise and define the council's authority. Therefore manufacturers would submit to control as per Salvarsan”.¹⁰⁸

“It had always been the policy of the Council not to countenance patenting with a view to pecuniary profit” and yet they had “in the past accepted assignment of patent rights with a view to securing control in the public interest and in special circumstances promoted patenting purely as a defensive measure against improper exploitation of a medical discovery – they had declined patents in the case of Streptococcal antitoxin and scarlet fever”.¹⁰⁹

¹⁰⁵ H. E. Armstrong to *The Times* (21 November 1922); reply by H. H. Dale, *Nature* (24 February 1923): 253-4; W. M. Fletcher to W. Bayliss (14 February 1923); W. Bayliss to Walter M. Fletcher (15 February 1923); MRC File 1092; J. Liebenau in J. Austoker and L. Bryder (eds.), (1989): 171-2.

¹⁰⁶ MRC File 1092, (30 August 1922).

¹⁰⁷ J. Liebenau, in J. Austoker and L. Bryder (eds.), (1989): 176; BDH statement (January 1934), MRC 1092.

¹⁰⁸ Report of Trip to America, H. W. Dudley, (30 October 1922), M.R.C. File 1092.

¹⁰⁹ MRC Minutes III, (29 April 1927): 56.

The MRC were however criticised in some quarters for their policy, for example, Bayliss wrote: “there is a strong feeling here against patenting the products of value in the area of disease”.¹¹⁰

The MRC later argued that had they not taken up the patent rights in Britain, manufacturing by our firms could not have been achieved here: “if we had let manufacturers begin 2 months ago they would probably have made little progress and would now be scrapping their plant for changed methods”.¹¹¹ They recognised that in order to produce insulin, firms required: “elaborate equipment, biological laboratories (licensed by the Home Office) and highly skilled personnel” and that: “a process which succeeds on an experimental scale in the laboratory, presents new and much more serious difficulties on a manufacturing scale”.¹¹²

Early trials of insulin in the USA had given results “of brilliant promise” creating a “huge demand” before the active principle and its manufacture were identified. The MRC came under pressure to release insulin rather than to perform further tests, but they defended the tests that were to promote:

“whatever enterprise or organisation is best fitted for securing the earliest production of the insulin extract under proper conditions of safety and control. In this way the necessary scientific trials of the treatment can be most readily obtained”.¹¹³ The MRC secured supplies of pancreas glands and this kept the price of insulin low.¹¹⁴

Three alternative strategies were considered:

a) Patenting then licensing out to various firms with specification of quality, safety and price and testing at the NIMR.

¹¹⁰ Sir William Bayliss “Insulin. Diabetes and Rewards for Discoveries” Nature (10 February 1923): 188-91.

¹¹¹ H. H. Dale and H. W. Dudley, (8 January 1923), MRC File 1092.

¹¹² W. M. Fletcher to C. J. Bond, (11 January 1923), MRC File 1092.

¹¹³ “The Treatment of Diabetes by Insulin” Lancet (18 November 1922): 1081-2.

¹¹⁴ W. Bayliss to W. M. Fletcher, MRC 1092: 23; Sir William Bayliss, “Insulin. Diabetes and Rewards for Discoveries” Nature (10 February 1923): 188-91; H. H. Dale, “Insulin” Nature (24 February 1923): 253-254.

b) Production of initial supplies at the NIMR or other non-commercial centres.

c) Studies at selected firms each with local manufacture.¹¹⁵

The MRC Secretary wrote to Burroughs Wellcome, BDH (acting together with A&H), Boots, Evans Sons Lescher & Webb, and Duncan Flockhardt regarding insulin supplies.¹¹⁶ Their preferred choice was Burroughs Wellcome for “The vast experience of these people in making such preparations as adrenalin, iodothyroglobulin, pituitrin, etc. - it is more likely that they will hit upon improvements”.¹¹⁷ They realised there would be the jealousy of other manufacturers “but the position of such a firm as Burroughs Wellcome is so outstanding from the scientific aspect that this may be dismissed.” Regarding Wellcome, Bond felt that: “every pound of his is worth two of everybody else's owing to the unique facilities at his disposal”.¹¹⁸ If they had gone entirely towards a regional policy with only one firm in London to choose it would have to be Burroughs Wellcome, giving them the opportunity to be ahead of the rest of the British firms.¹¹⁹

Dale, as Head of the Physiology Section of the NIMR and his chemist, Harold Ward Dudley advised the MRC to go ahead with small-scale production at several centres, but the MRC laboratories first addressed some of the problems of production. They achieved an 8-fold increase of yield, decreased alcohol requirements by 80%, decreased the production time and found a means of heat sterilisation.¹²⁰ They felt this justified delaying commercial production, but once production issues were resolved they were able

¹¹⁵ H. W. Dudley, (30 October 1932), MRC File 1092: 15.

¹¹⁶ MRC Council Minutes II, (12 January 1923).

¹¹⁷ N. Paton (Glasgow) to W. M. Fletcher, (23 November 1922), MRC File 1092: 15.

¹¹⁸ C. J. Bond to W. M. Fletcher (12 January 1923), MRC File 1092: 15.

¹¹⁹ J. Liebenau, in J. Austoker and L. Bryder (eds.), (1989): 173-4.

¹²⁰ Insulin Minutes, (8 January 1923), MRC File 1092.

to grant licences.¹²¹ Meanwhile the MRC took out further patents on Dudley's improved method of production.¹²²

An Insulin Committee was set up and established trials at MRC sponsored laboratories that had applied for a license to perform trials in November 1922.¹²³ Five of these centres were in London (St. Bartholomew's, (Fraser) Guy's (Dr Poulton), St. Thomas's, University College Hospital, and The London) and others were in Sheffield (Mellanby and Leathes), and two in Edinburgh (Meakins, and Murray Lyon) and these began in December. Later J. A. Nix in Bristol and Prof. Noel Paton in Glasgow joined in.¹²⁴ Trials were arranged on the condition that there was no extra cost to the MRC though they later allowed the purchase of equipment and hiring of laboratory assistants.¹²⁵ Paton recommended that Burroughs Wellcome should be involved and they made enquiries about gaining a license at the start of December 1922.¹²⁶ After initial discussions with ten firms, three London firms established commercial production of insulin early in May 1923. Fletcher sat on a committee with the Ministry of Health to discuss the best means of distribution.¹²⁷

¹²¹ W. M. Fletcher to W. M. F. Paton, (23 November 1922), MRC File 1092.

¹²² "A Method of Concentration of Insulin", granted to Dudley and the Council; MRC Minutes, (25 March 1923): 26; Overseas Patents, MRC Minutes, (15 June 1923): 79; (20 July 1923): 85; US Patents, (14 January 1924): 27 and (14 March 1924): 35.

¹²³ A committee was established to monitor insulin clinical trials which began in December 1922; Members were William Leischmann up to 23 January 1923 (replaced by Sir F. Andrewes), The Baron Mildmay of Flete, T. R. Elliott, Lord Goschen who went to Madras 12 December 1923, and H. H. Dale. (Production was by Drs. Babkin (London), T. A. Hughes (UCH), Poulton (Guys), Dr Graham and Prof. Fraser (St. Bart's); C. H. Kellaway, T. A. Hughes, "Observation on the Effect of Insulin on Normal Metabolism" British Medical Journal (28 April 1923): 737.

¹²⁴ MRC Minutes II, (17 November 1922): 376; (12 January 1923): 3.

¹²⁵ MRC Minutes II, (17 November 1922): 376; (8 December 1922): 389.

¹²⁶ J. Liebenau, in J. Austoker and L. Bryder (eds.), (1989): 172-3.

¹²⁷ MRC Council Minutes II, (23 March 1923): 26, 53.

Allen & Hanbury's and British Drug Houses worked together and Burroughs Wellcome worked alone.¹²⁸ There were also subsequently three firms involved from other parts of the country, namely Boots, Evans Sons, Lescher & Webb, and Duncan Flockhardt.¹²⁹ Every batch of insulin had to undergo independent tests, upon payment of a fee and could not be sold until certified. However the NIMR were unable to cope with all of the testing, so from July 1924 for a trial period of around 2 months, British manufacturers performed their own tests on the insulin that they produced, with control batches being sent to the NIMR. A small amount of US insulin was being imported but the US tests were trusted. For a preliminary period all sales had to be directed through the Council. A maximum net selling price was fixed, and only the name insulin could be used. No misleading or exaggerated claims of efficacy were allowed and the Council furnished statements on the mode of administration and precautions. Activity had to be stated in plain figures, in standard units, with a batch number and reference to tests and a nominal royalty was to be payable to the MRC.¹³⁰ By setting down these rigorous controls the MRC became the arbiters of drug safety and efficacy of insulin.

Although insulin was not synthetic, its production on a manufacturing scale was complex. The pancreas had to be isolated from cattle within hours of death, and alcohol had to be added to prevent destruction by enzymes. Extracts had to be refrigerated in acid conditions to prevent breakdown and insulin was then purified, and precipitated under exact conditions. One ton of pancreas produced only one gram of insulin.¹³¹

¹²⁸ H. H. Dale to W. M. Fletcher, (4 May 1923): 53, MRC File 1092.

¹²⁹ MRC Minutes II, (12 January 1923): 43. On the 23 February 1923, the MRC announced that insulin was being produced 'standardised' and on 23 April it was further stated that B.D.H. (in association with A & H) and Burroughs Wellcome had satisfied all the requirements and tests of the Council for authenticity and standard value, therapeutic activity and sterility: D. C. Huston and E.C. Cripps, Through a City Archway: The Story of Allen and Hanbury's 1713-1953 (London: Murray, 1954). A similar agreement was reached with Boots.

¹³⁰ W. M. Fletcher letter "Manufacture of insulin", MRC Minute Book II, (17 July 1924): 109; J. Liebenau, in J. Austoker and L. Bryder (eds.), (1989): 170

¹³¹ F. H. Carr, H. W. Dudley, "Scientific and Industrial Problems of Hormones" British Medical Journal (24 July 1926): 167.

In setting the terms of manufacture, the strategy of the MRC for the future development of novel drugs was evident. Firms wanting a licence had to have the manufacturing plant, equipment and staff for biological tests and sterility experiments, and some firms had applications turned down. This gave real incentives to firms to improve their facilities. Carr of BDH arranged for the erection of a large scale production plant at Graham Street, in London so that in combination with Allen & Hanbury's 'Insulin AB' was first sold in March 1923 and up to 50,000 doses per week were produced by July 1923. It was a highly profitable business.¹³² Between April and October 1923 their A.B. brand sold 2,525 thousand units compared to Burroughs Wellcome's 490 thousand units. By the end of 1923, the AB brand held 95% of the market and established BDH as a major force in the British pharmaceutical industry.¹³³ As a result, prices dropped dramatically.¹³⁴ Britain was self-sufficient and stopped importing insulin from America in the summer of 1923. Perhaps because of their uncertainty of the benefits of insulin, or in order to perform work independent of other companies, Burroughs Wellcome arranged their own trials of insulin. For once this was not a difficult task considering the demand for the new treatment, but they had clearly lost the initiative, which had been taken up by BDH. Dale was furious to find that O'Brien of the WPRL had arranged independent trials at St. Bartholomew's Hospital of the early batches of insulin, behind the back of the MRC.¹³⁵ He was even more concerned about imitation products from small companies, poorly standardised, but given similar names to insulin to create a demand.¹³⁶

¹³² The close relationship between BDH and Allen & Hanbury's was unusual at the time, but it made the most of Carr's experience, the manufacturing capacity of BDH and the analytical facilities and packing and distribution network of A & H. Geoffrey Tweedale, (1990): 129-130; H. H. Dale to W. M. Fletcher, (21 March 1923, 3 April 1923) MRC File 1092; Allen and Hanbury's profited from previous experience with parathyroid hormone; MRC Minutes II, (23 March 1923): 53.

¹³³ Geoffrey Tweedale, (1990): 129 –130; "Insulin Trials" British Medical Journal (22 December 1923): 110.

¹³⁴ J. Liebenau, in J. Austoker and L. Bryder (eds.), (1989): 175.

¹³⁵ H. H. Dale to W. M. Fletcher, (1 January 1923), M.R.C. Files 1092.

¹³⁶ Such products included Armour's Insulase, Philadelphia's Insulans, Harrower's Pan-Secretin. Pancreatokinase, British Medical Journal (16 December 1922): 1194.

Burroughs Wellcome and other firms were eventually allowed to sell their oral brand of insulin as sterile tablets, without any specific testing, after Dale reviewed their plans for manufacture. Yet, the MRC refused to grant a license to the Danish company, Leo, at the end of 1923.¹³⁷ The MRC also excluded the original Eli Lilly preparation, despite the fact that at one time they could supply the world needs, and the firm spent £2,500 to £3,000 per week on testing and utilised over 100,000 animals in the first month to meet the strict U.S. quality requirements. Eli Lilly could have completely overrun the British market. The MRC argued that sufficient insulin was already in production, made by British firms. Liebenau made this same point that the MRC was “protecting the industry”.¹³⁸ This point is notable for these were the first times that the MRC overtly turned away non-British producers except for quality defects.¹³⁹ At the end of 1923 Britain was far ahead of Germany in the production of hormones and vitamins. It was well into 1924-5 before large- scale production of insulin was achieved in Germany or France, and then the MRC also inhibited the importation of insulin from Bayer.¹⁴⁰

The MRC remained preoccupied with insulin trials for the two years and results were published in their annual reports.¹⁴¹ The arrangement over insulin worked well because the pharmaceutical company profits were balanced by achieving economical synthesis in the national interest. The firms involved extended their manufacturing plant considerably and gained valuable experience of the problems of large-scale production. In parallel the MRC extended their role of overseeing the purity of biological standards and arranged clinical trials of an important new substance. It should be noted once more that it

¹³⁷ MRC Council Minutes II, (17 July 1924): 109.

¹³⁸ J. Liebenau, in J. Austoker and L. Bryder (eds.), (1989): 171.

¹³⁹ MRC Council Minutes II, (17 July 1924): 109; M. Fletcher, (1957): 330-1.

¹⁴⁰ Michael Bliss, (1983): 165; J. Liebenau, in J. Austoker and L. Bryder (eds.), (1989): 175.

¹⁴¹ The MRC statistical committee prepared a report on “the effect of insulin on the mortality of diabetes”. However of the 1161 private patients, 61% were lost sight of, half in the first year of treatment, and about a quarter of patients had been seen only once: “Insulin” *British Medical Journal* (24 February 1923): 341; “Insulin for Sale” (21 April 1923): 690-1; “Insulin Available in this Country-Conditions of Sale and Precautions to be Observed” (21 April 1923): 695; “Some Clinical Results on the Use of Insulin – a Report of the MRC (28 April 1923): 737-40; “Estimation of Sugar in Blood” (5 May 1923): 777.

was at the end of 1922, in the early stages of collaboration on insulin, that manufacturers asked for support from the MRC in arranging clinical trials of their own products but the system put in place was specific for insulin.

6.5 Francis Carr and his Growing Influence.

Liebenau credited the MRC with taking on “a conservative research project to standardise production and lower costs, which by 1924 succeeded in cutting prices by almost 75 %”.¹⁴² It will be recalled however that the MRC initially considered limiting manufacture to certain firms and their clear favourite was Burroughs Wellcome. However, the balance of power in the British pharmaceutical industry was shifting significantly towards British Drug Houses.

As we have seen, Francis Carr was already a well- known figure in the British pharmaceutical manufacturing industry. He had collaborated with Dunstan at the Pharmaceutical Society before taking over as Works manager at Burroughs Wellcome in 1898. Having established a manufacturing capacity for semi-synthetic drugs and alkaloids, he manufactured Salvarsan in 1914 and was ‘headhunted’ to join Boots to establish their manufacturing capacity during the War. Immediately after the War he was enticed for a large salary to join British Drug Houses. In each case he was able to attract a significant number of his colleagues to move with him. In 1919 he was part of the ABCM mission to visit German factories and in 1921 he co-authored a textbook that outlined for British chemists the methods of synthesising organic drugs. He was also an active member of the Society of Public Analysts, and a member of the Council of the Society of the Chemical Industry from 1920-23. He had previously contributed to significantly improving the manufacturing yield of thyroxin, but it was his achievements in making Britain self-sufficient in insulin that brought him worldwide fame: “ F. H. Carr, who has played a distinguished part in the development of the British fine chemical industry, closely associated with early production of insulin in this country”,¹⁴³ and “he has exhibited, as in the notable case of insulin, a very practical capacity for mastering the engineering and

¹⁴² J. Liebenau in J. Austoker and L. Bryder (eds.), (1989): 171.

¹⁴³ The Financial News (17 June 1926), Chemical Industry Congress, London.

other technical difficulties of large scale production”.¹⁴⁴ Carr used his chemical engineering skills to increase yields of insulin by 20 fold. The price of insulin fell from 25 shillings to 2 shillings 8d per 10 doses over 12 months.¹⁴⁵ It fell further: “The scientific industry of this country had reason to be proud of the fact that within 18 months of its introduction, production had increased so greatly that a balance was available for export and the original price decreased to 1/11d.”¹⁴⁶

Although insulin could be assayed, its mechanism of lowering blood sugar was unknown. Carr did not support Ehrlich's theory of the direct action of drugs arguing “although the chemical constituents of a therapeutic agent determines its action, the body mechanism also participates in the resultant chemical change”.¹⁴⁷ This implied to him that the only way to properly test drugs was in the human body, hence his strong urge for a defined system of clinical tests. Carr believed that doctors in the U.K. were concerned about pecuniary interests with pharmaceutical firms, and although Fraser of the MRC disputed this, Carr argued for trials to be arranged through a central independent body. He suggested that after such official tests, individual medical men would be less afraid of performing their own personal trials and of publishing the results. Carr described how individual medical men generally made tests in Germany, where the manufacturers quoted findings in advertisements. Only the previous year an editorial in the *British Medical Journal* referred to medical research on new remedies in Britain where “those careful of their reputations must step warily”.¹⁴⁸

¹⁴⁴ The Times (16 June 1926), B. Carr archives IV cuttings, Imperial College.

¹⁴⁵ Daily Telegraph (12 July 1927). F. H. Carr's personal archives at the Imperial Institute include cuttings from the Natal Mercury (30 June 1927) and Daily News Colombo (5 July 1927). The prices of insulin were kept closely in line throughout this time “The Price and Unit Value of Insulin- Announcement by the MRC” British Medical Journal (22 December 1923): 1232. Burroughs Wellcome prices for 100 units (10 doses) were initially 25/-, then 17/8, 12/6 and were reduced to 6/9 from 25 February 1924 and an extra trade discount of 20% BDH and A. & H. reduced prices on the same days.

¹⁴⁷ “Address to the Society of the Chemical Industry” British & Colonial Pharmacist (August 1927): 268.

¹⁴⁸ Robert George Hogarth (Surgeon, Nottingham) “The Medical Practice and the Public: BMA Presidential Address” British Medical Journal (24 July 1926): 145-50.

Carr gave several keynote lectures on the state of the British pharmaceutical industry in the mid- 1920's including the Streatfield Memorial Lecture at the end of 1925.¹⁴⁹ By 1926 British Drug Houses were probably the leading fine chemical company in Britain (ahead of Burroughs Wellcome and Boots.) Much of their progress came from the success in manufacturing insulin, which Carr recounted in February 1926.¹⁵⁰ He also played a prominent role in the manufacture of vitamins.¹⁵¹ By 1926 Carr had been elected President of the Society for the Chemical Industry. He acknowledged the reliance upon physiologists for the testing of drugs but emphasised that it was also necessary to know the limits of stability of the agents to temperature, acid or alkali, and the amounts of impurities.¹⁵²

In his Presidential address in Edinburgh in 1927, on “*Chemistry in the Progress of Medicine*”, Carr re-emphasised that: “in this country for one reason and another there are almost insuperable difficulties in the way of getting likely substances adequately tested”, nor was there any organisation by which the clinical testing of such substances can be carried out in our hospitals and elsewhere. Similarly he spoke as Pearson had four years earlier of the problem that: “medical men hesitate for professional reasons to be associated with manufacturing concerns in making known to their colleagues the properties of new substances which they have tested”.¹⁵³

“In most of our laboratories devoted to pharmacology there is but a small band of workers, and they are generally fully occupied with academic research of a nature considered to be more acceptable to those whose opinions count most. So the routine testing of substances likely to have valuable therapeutic properties receives scant attention. Nor is there any organisation by which the clinical testing of such substances can be carried on in our hospitals and

¹⁴⁹ “Pharmaceutical Society Meeting- The Application of Scientific Method to the Solution of Industrial Problems” Chemist & Druggist (12 December 1925): 835-8.

¹⁵⁰ F. H. Carr, “Insulin and its Manufacture” to Royal Society of Arts, (23 February 1926) in B/CARR F. H., Carr Archive, Imperial College.

¹⁵¹ F. H. Carr, “Vitamins in their Relationship to Medical Supplies” Chemist & Druggist (1926) 897-99.

¹⁵² F. H. Carr, “The Position and Prospects of the Organic Chemical Industry in this Country” Chemist & Druggist 105.1 (24 July 1926): 170.

¹⁵³ F. H. Carr, “Chemistry in the Progress of Medicine” Chemist & Druggist 106.3 (9 July 1927): 233

elsewhere. In particular medical men hesitate for professional reasons to be associated with manufacturing concerns in making known to their colleagues the properties of new substances which they have tested".¹⁵⁴

Carr concluded that there had to be closer co-operation between manufacturers, and research departments as some form of research association to decrease overlaps between firms and allow constructive criticism.¹⁵⁵

Alfred Renshaw of the Laboratory of Applied Physiology in Manchester made a plea for multidisciplinary collaboration between biochemists, medics and organic chemists and he quoted the conclusions of the American Society of Chemistry:

"Medical men must realise that the task of building up necessarily complex substances, which alone seem to have therapeutic value is a matter for careful thought and patient experiment, the chemists must realise the intense difficulties of obtaining and correlating medical and clinical data, and above all the commercial organisation, which endorses such a product, must be prepared to wait, not months, but years for the fruitful results, which must of necessity arise from such a combination of resources".¹⁵⁶

In particular there was a need to bridge the gap between what it was possible to prepare in the research laboratory and in a production plant. He felt that Britain had to become strong in every part of the chain from observation, through experiments, development, pilot plant scale-up, clinical testing and marketing.¹⁵⁷

When Burroughs Wellcome were approached by the DSIR to collaborate in 1926, Thomas Henry wrote:

"It is almost impossible to carry on work of this description without pharmacologists and clinical researchers. In this country it is always difficult to obtain trained pharmacologists and research institutes generally have to

¹⁵⁴ *Ibid.*

¹⁵⁵ *Ibid.* Carr's address to the Society of the Chemical Industry was widely reported: British & Colonial Pharmacist (August 1927): 268; Manchester Guardian (14 July 1927)

¹⁵⁶ A. Renshaw, "Chemical Research in Britain" British Medical Journal (6 November 1926): 857.

¹⁵⁷ F. H. Carr, "Manufacture of Organic Medicinal Chemicals", lecture to S.C.I., Chemist & Druggist 105.1 (24 July 1926): 170; The lecture was widely reported, The Financial News, (17 June 1926); The Times (16 June 1926); British and Colonial Pharmacist (August 1926): Cuttings of these reports and notes in preparation for the lecture are in F. H. Carr Archives, 2130 B/CARR IV Press Cuttings: 8,

train their own. It is equally difficult to get clinical trials of new drugs made. These difficulties do not seem to occur in France, Germany and the U.S. and this gives these countries a considerable advantage. The department might, acting in correspondence with the MRC, usefully see if anything can be done to increase facilities for pharmacological and clinical research of new drugs in the country".¹⁵⁸

Carr gave a further keynote speech to the Royal Society of Arts on 23 February 1927 with Henry Dale in the chair.¹⁵⁹ Returning to his 1927 lecture on the "*Chemistry in the Progress of Medicine*", Carr described the progress made in synthesising adrenaline, histamine and thyroxine,¹⁶⁰ giving his interpretation of chemotherapy along the lines of Ehrlich. He referred to the changes undergone in the body by trypanocidal agents, Bayer 205 and Fournau 309, both colourless and though active in vivo, had little in vitro activity, as with bismuth and he cited the depot effects of long-lasting forms of bismuth and arsenicals, and the effect of sunlight on ergosterol. He felt that:

"progress lies in the direction of biochemistry and more effective working contact between individuals in chemistry, bacteriology, physiology and clinical medicine to avoid overlapping. Chemical experiment must proceed in the very closest association with animal experimentation and with clinical trials. There are many conditions, which can only be studied in man himself and the importance of properly organised clinical trials and the proper inter-relation of all these elements of progress cannot be too strongly emphasised".¹⁶¹

He saw this as the rationale for testing drugs in man. Carr re-emphasised the need for both pure and applied research in collaboration, for the majority of anti-infective compounds developed had been for protozoal infections for which animal experimental models existed, such as in the development by Barger of the quinoline derivative, plasmoquine,

¹⁵⁸ T. Henry to A.W. Crossley, (9 July 1925), WF: STC S/G/49.

¹⁵⁹ F. H. Carr, "How Insulin is Isolated" from "Insulin and its Manufacture" *Chemist & Druggist* 106.2 (26 February 1927): 263.

¹⁶⁰ "Chemistry in the Progress of Medicine" presented at the SCI in Edinburgh, *Chemist & Druggist* 106.3 (9 July 1927): 233; *Daily Telegraph* (12 July 1927).

¹⁶¹ F. H. Carr, "Chemistry in the Progress of Medicine", *Chemist & Druggist* 106.3 (9 July 1927): 233; "Address to the Society of the Chemical Industry" *British & Colonial Pharmacist*, (August 1927): 268.

(Pamaquin).¹⁶² He felt the preparation of synthetic insulin, for example was the way forward.

In addition to his work in improving production methods, Carr developed tests for the potency of the firms' products, such as ether.¹⁶³ He also examined the potency of vitamins along with other industry representatives, describing the difficulties of performing assays that involved comparing rats fed on standard and deficient diets of a 6-week period, concluding that a synthetic version could save all of the effort on diet testing. One of the problems noted with vitamin A was a loss of potency on storage.¹⁶⁴ Norman Evers of May & Baker complimented Carr on his modification of the only practicable test available to date.¹⁶⁵ He showed the superiority of his firms' products over and above the requirements of the pharmacopoeia. Carr was awarded a D.Sc. from Manchester University in 1929 in recognition of his contributions to the development of medicines. In his speech of acceptance he stated "Once the world had proclaimed victorious analysis: the cry is now victorious synthesis".¹⁶⁶

6.6 MRC Extended Role in Clinical Trials: Individual MRC Subcommittees

¹⁶² F. H. Carr, "Chemistry in the Progress of Medicine" Chemist & Druggist 106.3 (9 July 1927): 233 as reported in the Daily News, Colombo, Ceylon: Carr archives. B. CARR at Imperial College.

¹⁶³ F. H. Carr, "Ether clonus" British Medical Journal (8 October 1927): 664.

¹⁶⁴ F. H. Carr, "Vitamins in Relation to Industry" British Medical Journal (18 December 1926): 1194; F. H. Carr, "Vitamins in their Relationship to Medical Supplies" Chemist & Druggist 105.2 (18 December 1926): 897-99. Carr suggested that instead of time consuming growth tests using animals, vitamin A could be assayed using colour tests.

¹⁶⁵ F. H. Carr, E. A. Price, "Colour Reactions Attributed to Vitamin A" Biochemical Journal 20 (1926) 497-501.

¹⁶⁶ Manchester Guardian: Chemistry and Industry (26 July 1929): 725-8; The Times (12 July 1929): 929.

The MRC continued to add further sub-committees as new opportunities arose.¹⁶⁷ Some were established under the auspices of other academic bodies but under MRC guidance, such as that appointed by the Obstetric Section of the Royal Society of Medicine to evaluate pituitary extracts.¹⁶⁸ In addition to supporting work on cancer, previously described, the MRC also supported research by the Colonial Office.¹⁶⁹ MRC subcommittees involved several current and former Burroughs Wellcome staff including Henry Dale, Andrew Balfour, Edward Mellanby, R. A. O'Brien and C. M. Wenyon.

Once clinical trials were underway with insulin, the MRC began to link some of their other research programs into the clinical testing of drugs. Prof. George Dreyer, Director of the Standards laboratory at the Dunn School of Pathology in Oxford, joined the MRC Council in June 1923. The Committee discussed testing his new diaplyte vaccine for tuberculosis and established a sub-committee with Walter Fletcher, Capt. Stewart Douglas, Director of the Department of Bacteriology at the NIMR, and C. J. Bond¹⁷⁰ and Arthur MacNalty to draw up a scheme for trials.¹⁷¹ MacNalty suggested that Dreyer's work was likely to revolutionise not only tuberculosis, but also other bacterial diseases.

¹⁶⁷ "Committee on Rheumatism" MRC Council Minutes II, (10 December 1920): 191; "Committee on the Physiology of Respiration and the Cardiovascular System" (18 March 1921): 30; "Committee on Anti-meningococcus and Anti-pneumococcus Sera", "Committee on Anti-dysenteric Sera" and "Committee on Anti-diphtheria and Anti-tetanic Sera" (20 January 1922): 190; Committee on the Clinical Uses of Oxygen (24 March 1922): 273; Committee on Haemoglobin (8 December 1922): 396; Committee on Anaesthetics (29 January 1926): 8; Vaccination Committee (29 January 1926): 10; tuberculin and bacteriological committees; L. Bryder "Tuberculosis and the MRC" in J. Austoker and L. Bryder (eds.), (1989): 9-10.

¹⁶⁸ Use of pituitary extract- Committee appointed by the Obstetric Section of the Royal Society of Medicine, MRC Council Minutes II, (27 May 1921): 78.

¹⁶⁹ MRC Council Minutes II, (22 July 1921): 112.

¹⁷⁰ Sir Patrick Laidlaw, "Stewart Rankin Douglas" Obituary Notices of Fellows of the Royal Society 2 (1936): 175 – 182.

¹⁷¹ MRC Council Minutes II, (15 June 1923): 73; (20 July 1923): 88; (12 December 1923): 152; (22 February 1924): 27; L. Bryder "Tuberculosis and the MRC" in J. Austoker and L. Bryder (eds.), (1989): 8-10; A. S. MacNalty, British Journal of Tuberculosis 22 (1928): 16-18.

Although the treatment turned out to be no more effective than available therapies, Dreyer was appointed Director of the Standards Laboratory in Oxford in February 1924.¹⁷²

Undeterred by their disappointment with Dreyer's vaccine, the MRC agreed to do further clinical trial work in tuberculosis with Sanochrysin or sodium auro-thiosulphate. This therapy discovered by Holger Moellgaard, Professor of Animal Physiology in Copenhagen in 1923, had a gold content of 37% together with a serum.¹⁷³ The MRC were asked by him to arrange clinical trials with a view to confirming results in Denmark. Fletcher planned a trial along the following lines in December 1924. He recounted that (Moellgaard):

“is providing supplies of the gold compound and of the serum to be used in conjunction with it for the purposes of this work and none will be available for general use by the profession in this country until these confirmatory trials have been successfully performed. The treatment has not been found suitable for cases of surgical tuberculosis and it is proposed to limit the present studies to cases of pulmonary tuberculosis, to which some cases of tuberculous meningitis may be added; in each of the clinics diagnosis has been confirmed by proof of the presence of bacilli”.¹⁷⁴

The Council subcommittee suggested recruiting “not more than ten cases” in each centre, restricting cases to pulmonary tuberculosis proven by the presence of bacillus.¹⁷⁵

Prof. H. Arthur Ellis at the London Hospital was prepared to take up to 10 patients into a study, along with the Prof. of Medicine in Edinburgh (Sir Robert Philip), the Chief Medical Officer at King Edward VII Medical Association of Wales in Cardiff (Prof. S. Lyle Cummins) and “Directors of the University Medical clinics in London”: thus, T. R.

¹⁷² MRC Minutes II, (22 February 1924): 21.

¹⁷³ MRC Minutes II, (24 October 1924): 132; W. M. Fletcher to H. MacLean, (St. Thomas' Hospital), (1 December 1924) “Sanochrysin” (Sodium aurothiosulphate), MRC File 1380/3; L. Bryder, “Tuberculosis and the MRC” in J. Austoker and L. Bryder (eds.), (1989): 1-21; MRC Special Report Series 96, (London: HMSO, 1925); M. Fletcher, (1957): 337; B. Smith, “Gullible's Travails: Tuberculosis and Quackery 1890-1930” *J. Contemporary History* 20: 733-56.

¹⁷⁴ W. M. Fletcher to Arthur Ellis, (1 December 1924), MRC File 1380/3.

¹⁷⁵ The organising committee were, George Dreyer, Cuthbert Wallace, Henry Dale, Captain Douglas, and Arthur MacNalty: MRC File 1380/3; W. M. Fletcher, MRC Minutes II, (24 October 1924): 132; W. M. Fletcher to A. Ellis, (1 December 1924), MRC File 1380/43.

Elliott at UCH, G. Marshall at Guy's, Dr L. S. T. Burrell at Brompton Hospital.¹⁷⁶ Sanochrysin was sent to Dr Geoffrey Evans at St. Bartholomew's who involved F. R. Fraser and C. F. Harris; to Prof. Frederick Langmead at St. Mary's; to Prof. Hugh MacLean,¹⁷⁷ a chemical pathologist at St. Thomas' Hospital; Dr F. R. E. Heaf at Warwick King Edward VII Hospital, and Dr A. Trimble who coordinated work in Northern Ireland. Fletcher later clarified to Langmead that there was no need for all 10 patients to be treated in parallel, and that he could treat two or three and increase as experience indicated. Evans reported that it was "highly toxic".¹⁷⁸ Ellis reported that he had treated 7 cases and 3 had "violent reactions".¹⁷⁹ MacLean recounted: "It seems to me that the Council have hardly appreciated the difficulties connected with this investigation. Certainly when I promised to carry out the tests I did not appreciate them myself".¹⁸⁰

Researchers had difficulty distinguishing any effects of therapy from the variable background cause of the disease.¹⁸¹ Dr. Sechar, presumably representing the Danish group, reviewed the cases selected at his centre and all were excluded as being of the wrong type of patient: "a certain kind of patient is required, and it seems quite impossible that any Unit of other Institution should be able to get a large number of this type at once".¹⁸² The therapy was dangerous in advanced cases, which were common in Institutions. If on the other hand only early cases with little tissue damage are treated, the results looked good, but then so did other therapies. MacLean finally gave an anecdotal

¹⁷⁶ W. M. Fletcher to H. A. Ellis, (1 December 1924), MRC 1380/3.

¹⁷⁷ MacLeod had been sent to France by the MRC in 1915 to investigate acute trench nephritis. J. Austoker and L. Bryder (eds.), (1989): 66, 212.

¹⁷⁸ MRC File 1380/3, (17 March 1925).

¹⁷⁹ G. Evans to W. M. Fletcher (17 March 1925); H. A. Ellis to W. M. Fletcher (9 February 1925), MRC 1380/3. Ellis had previously applied to the MRC for a grant to perform work on the chemotherapy of tuberculosis.

¹⁸⁰ H. MacLean to W. M. Fletcher, (8 February 1925), "Sanochrysin" MRC File 1380/3.

¹⁸¹ L. Bryder, "Tuberculosis and the MRC" in J. Austoker and L. Bryder (eds.), (1989): 12; MRC Files 1380/3 on sanocrysin.

¹⁸² H. MacLean to W. M. Fletcher, (8 February 1925), "Sanochrysin" MRC File 1380/3.

hopeless case which was said to be too far advanced for treatment with sanochrysin and was not allowed into the study:

“The so-called hopeless case is now apparently well and already (within 5 weeks) shows practically no symptoms. Had we treated him by the Gold method we would naturally have ascribed the extraordinary improvement to the gold injections. The result would have been entirely misleading”.¹⁸³

Further adverse reports came from other London hospitals.¹⁸⁴ The complex nature of assessing the new drug is given in the reports of one of the investigators who only managed to treat 2 cases.¹⁸⁵ Ultimately, it was concluded that Sanochrysin was of little benefit.¹⁸⁶

In 1925 the MRC reported studies in which they had compared quinine and quinidine finding the latter “far surpasses others”.¹⁸⁷ However, up to 1925 the majority of new products from industry were variants of already available drugs and the MRC had little interest in them, preferring to concentrate on important physiological questions, hormonal extracts, tropical medicine and standardisation of biological drugs.¹⁸⁸

¹⁸³ H. MacLean to W. M. Fletcher, (8 February 1925) for quotes, and final report (27 March 1925), MRC Sanocrysin File 1380/3.

¹⁸⁴ Reports from Prof. Fred Langmead at St. Mary’s and H. J. MacLean at St. Thomas’ were in Prof. Elliott’s report, MRC 1380/3; MRC Minutes II, (27 March 1923); H. J. MacLean to W. M. Fletcher, (8 February 1925), MRC File 1380/3.

¹⁸⁵ H. J. MacLean to W. M. Fletcher, (8 February 1925), “Sanochrysin” MRC File 1380/3.

¹⁸⁶ Studies on Sanocrysin were inconclusive until one study from Michigan studied matched pairs randomly allocated from 1926: J. Burns Anderson Jnr, B. T. McMahon, M. Pinner, “A Clinical Trial of Sanocrysin in Pulmonary Tuberculosis” American Review of Tuberculosis 24 (1931): 401-435; Prof. H. R. Dean, “Science and Medicine” British Medical Journal (10 October 1931): 668; “Second Report of the Gold Treatment of TB,” MRC British Medical Journal (24 July 1926): 158-60.

¹⁸⁷ “Quinine and Quinidine” British Medical Journal (12 September 1925): 488; “Committee on Cinchona derivatives and Malaria: Clinical Comparisons of Quinine and Quinidine” MRC Special Report Series 96 (London: HMSO, 1925): 110; T. J. Lipkin of Liverpool investigated quinine, MRC Minutes II, (15 October 1920): 154.

¹⁸⁸ In 1922 the first such M.R.C. report was published; J. H. Burn and H. H. Dale, “Report on Biological Standards (I) Pituitary Extracts” MRC Special Report Series 69

6.7 Lobbying for Clinical Trials: The ABCM and The Chemotherapy Committee.

Bayer 205 (Germanin) was discovered during the First World War and underwent clinical trials in 1920 for treating sleeping sickness in Africa, and gave promise of new therapeutic agents against bacterial and parasitic diseases and so an increasing amount of MRC funding was put into research on chemotherapy.¹⁸⁹ Henry Dale, (chairman) C. H. Browning¹⁹⁰ and Andrew Balfour, from the MRC collaborated with George Barger (ex-Burroughs Wellcome), Prof. Gilbert Thomas Morgan¹⁹¹ and Prof. Robert Robinson¹⁹² from the DSIR. At the Council meeting of 22 October 1926, a Committee was established jointly with the DSIR to report before March 1927 on the scope of work required in Chemotherapy.¹⁹³ In November 1926 the ABCM General manager, W. J. U. Woolcock formally approached the Council about clinical trials again when he wrote,

“Do you remember how three years ago a small deputation from the Association (visited you)...with regard to chemical firms obtaining assistance from you in getting in touch with certain scientific workers. It arose out of our firms making new chemical products and requiring expert assistance in having

(London: HMSO, 1922); “Standardisation of Pituitary Extract” British Medical Journal (2 December 1922): 1087-88.

¹⁸⁹ From Germanin to Acylureidopenicillin: Research that made History (Leverkusen: Bayer, 1980)

¹⁹⁰ C. L. Oakley, “Carl Hamilton Browning” Biog. Memoirs of Fellows of the Royal Society 19 (1973): 173 – 215.

¹⁹¹ Morgan had trained under Meldola at the Finsbury Technical School, and the Institute of Chemistry. He started as an assistant at Read Holliday dye firm then performed research at the Royal Colleges of Science in London and Dublin He gained his professorship there and became Professor at the Finsbury Technical College then Birmingham University. He directed the Chemical Research laboratory at Teddington. James Irvine, “Gilbert Thomas Morgan” Obituary Notices of Fellows of the Royal Society 3 (1941) 355- 362.

¹⁹² Lord Todd and J. W. Carnwath “Robert Robinson” Biographical Memoirs of Fellows of the Royal Society 22 (1976) 415 – 527; T. I. Williams, Robert Robinson, Chemist Extraordinary (Oxford: Clarendon Press, 1990).

¹⁹³ MRC Council Minutes II, (2 October 1926): 151.

them tested clinically. My recollection is that the question of insulin became very prominent just at that time and nothing further was done”.¹⁹⁴

Fletcher replied that:

“The MRC have for long been anxious to see better provision made for coordinated research in chemotherapy and they have had this under discussion with the Department of Scientific and Industrial Research”.¹⁹⁵

Handwritten comments in the margin of this file by Landsborough Thompson of the MRC confirmed the principal reasons of why the collaboration on trials of novel drugs had faltered; “(lack of) clinical workers, shortage of pharmacologists, medical ethics, and use of animals”.¹⁹⁶ This tied in with ongoing controversies relating to doctors putting their names to drug advertisements and to articles in the lay press.¹⁹⁷ The Council responded in line with the new focus on chemotherapy as a result of the proposed collaboration with the DSIR, which aimed to provide the MRC with a source of new synthetic compounds of possible therapeutic value.¹⁹⁸

6.8 Collaboration with the DSIR- Establishment of the Chemotherapy Committee.

As a result of the report of the Joint Committee of the MRC and DSIR, the Chemotherapy Committee became operational in July 1927, including Prof. John Berend Cohen,¹⁹⁹ Warrington Yorke of Liverpool,²⁰⁰ Prof. Thomas Elliott, and Sir Hugh Kerr

¹⁹⁴ W. J. U. Woolcock to W. M. Fletcher, (17 November 1926), “Therapeutic Trial Committee” MRC File 1523/15; K. H. Beyer, Discovery, Development and Delivery of Drugs (New York: S.P. Medical & Scientific, 1978): 153.

¹⁹⁵ W. M. Fletcher to W. J. U. Woolcock, “Therapeutic Trial Committee”, (19 November 1926), MRC File 1523/15.

¹⁹⁶ A. L. Thompson handwritten notes on W. J. U. Woolcock to W. M. Fletcher, “Therapeutic Trial Committee”, (17 November 1926), MRC File, 1523/15.

¹⁹⁷ Andrew A. G. Morrice, “The Medical Pundits: Doctors and Indirect Advertising in the Lay Press 1922-1927”, Medical History 38 (1994): 255-80.

¹⁹⁸ M.R.C. Council Minutes III, (15 July 1927): 155.

¹⁹⁹ H. S. Raper, “Julius Berend Cohen” Obituary Notices of Fellows of the Royal Society 1 (1935): 503 – 513.

Anderson.²⁰¹ Prof. R. T. Leiper,²⁰² who the MRC had supported to study bilharzias in Egypt during the War, was added in November 1927, to advise on antihelminthics.²⁰³ Christopher H. Andrewes became secretary of the Chemotherapy Committee in January 1928.²⁰⁴ The MRC provided £2,800 to the Department of Scientific and Industrial Research to perform research in synthetic chemotherapy so that promising compounds were to be put forward to clinical trials at the teaching hospitals on an informal basis.²⁰⁵

The Chemotherapy Committee also aimed to assist with the biological and clinical testing of synthetic compounds, prepared at the NIMR by Harold King and his colleagues. They noted the “desirability of providing facilities for clinical trials of new remedies under stated conditions agreed between the joint committee and representatives of ABCM.” Its guidelines for handling applications for test new drugs were: that details of the applicant would not be provided to those doing the testing, and that the Council had the right to refuse the testing of any remedies without having to state a reason. The applicant had to give an undertaking that no alternative trial arrangements would be made until the Committee trials were complete, and the nature and composition of the compounds had to be disclosed in confidence together with details of any relevant publications, experiments carried out in the manufacturers own laboratories and the patents obtained or applied for. The arrangements for testing were entirely a matter between the Committee and the experts undertaking the research. The Committee decided that they would not publish

²⁰⁰ C. M. Wenyon “Warrington Yorke.” Biographical Memoirs of Fellows of the Royal Society 4 (1944): 523-545.

²⁰¹ Sir Charles Scott Sherrington, “Hugh K. Anderson” Obituary Notices of Fellows of the Royal Society Proceedings B 104(1929): xx-xxv.

²⁰² P. C. C. Garnham, “Robert Thompson Leiper” Biographical Memoirs of Fellows of the Royal Society 16 (1970): 385 – 404.

²⁰³ MRC Minutes II, (22 October 1926): 151; MRC Minutes III, (15 July 1927): 127; (14 October 1927): 155; MRC Minutes III, (11 November 1927): 181.

²⁰⁴ MRC Council Minutes III, (27 January 1928): 7. Christopher (later Sir) was the son of Sir Frederick Andrewes F.R.S. He became a great authority on viral research, working together with Patrick Laidlaw on dog distemper at the NIMR: J. Austoker, L. Bryder, in J. Austoker and L. Bryder (eds.), (1989): 41 - 43.

²⁰⁵ The D.S.I.R. laboratory work was to be performed by Prof. R. Robinson, Prof. G. Barger, and Dr. G. J. Morgan. M.R.C. Minutes II, (1927): 127, 155, 187, 227.

information if it made no scientific contribution and might cause damage to the interests of the applicant. All expenditure had to be met by the applicant, but if the experts proposed tests that required significant expenditure on equipment, salaries or travelling expenses, details of proposals would be sent to the applicant for consideration.

The Chemotherapy Committee initially arranged tests of antihelmintics, antimalarials, and trypanocidals, which fitted in well with the research interests of the MRC and their Tropical Institutes. In June 1927 a joint Colonial Medical Research Committee was set up, combining membership of the MRC with the Colonial Office. The chair was Right Hon. William G. A. Ormsby-Gore and his deputy was Sir George Maxwell, together with Dr. John William Watson Stephens, who was originally based at the Tropical Medicine Institute and performed research on malaria and blackwater fever,²⁰⁶ Sir Leonard Rogers²⁰⁷, Dr. Andrew Balfour, Dr. Charles Todd²⁰⁸, Dr. Phillip E. Manson-Bahr²⁰⁹, Dr. Charles M. Wenyon²¹⁰ of Burroughs Wellcome, and MRC Secretary, Walter M. Fletcher.²¹¹

The ABCM also interacted directly with the Colonial Research Committee as they sometimes received remedies from overseas, which they forwarded to the MRC for consideration: one example was a new remedy, “superior to all others against malaria fever and syphilis” from a Dr. Louis Johnston of Bucharest. It was also said to be “efficient against all forms of tuberculosis”. It required only a few injections and was

²⁰⁶ Sir Rickard Christophers, “John William Watson Stephens” Obituary Notices of Fellows of the Royal Society 5 (1947) 525 - 540.

²⁰⁷ Sir John Boyd, “Leonard Rogers” Biographical Memoirs of Fellows of the Royal Society 9 (1963) 261- 285.

²⁰⁸ C. H. Andrewes, “Charles Todd” Biographical Notices of Fellows of the Royal Society 4 (1958) 281- 290.

²⁰⁹ “Sir Phillip Manson-Bahr, Obituary” British Medical Journal (26 November 1966): 1332; “Obituary” The Lancet (26 November 1966): 1198-9; P. E. Manson-Bahr, S. Willmott, “Dermatology and the Royal Society of Tropical Medicine and Hygiene” Int. J. Dermatology 20 (July-August 1981): 429-30.

²¹⁰ C. A. Hoare, “Charles Morley Wenyon” Obituary Notices of Fellows of the Royal Society 6 (1949) 627-42; M. Worboys, “The Comparative History of Sleeping Sickness in East and Central Africa” Hist. Sci. 32 (1994): 89-102; M. Worboys, “The Manson-Ross Controversy: Tropical Medicine and Imperialism” Soc. Hist. Med. Bull. 21 (1977): 37-9.

²¹¹ MRC Council Minutes III, (29 April 1927): 58, (24 June 1927): 101.

“absolutely not poisonous”. However, the Chemotherapy Committee discounted it as an obvious quack remedy and pointed out that the claims about syphilis would be illegal in this country. The MRC arranged the biological testing of any suitable compounds in its own laboratories.²¹²

Meanwhile, pharmaceutical firms and especially Burroughs Wellcome played an increasing role in tropical research, as described in the chapter on their Scientific and Technical Committee. May & Baker clearly received support in their developments from the London School of Hygiene and Tropical Medicine and they contributed £150 towards expenditure on chemotherapy investigations.²¹³

6.9 Further MRC Trials: Synthalin, Pneumococcal Serum and Liver Therapy

In 1927 the MRC had an offer from Schering to test Synthalin, a synthetic oral guanidine compound which had undergone trials and been introduced in Germany for diabetes the previous year. The recommendation for testing came from the Insulin Committee, but only on the condition that its chemical formula was provided.²¹⁴ The rationale for this compound was that it had previously been shown that removal of the parathyroid gland led to a sudden drop of blood sugar and that this was due to abnormal levels of guanidine in the blood. Guanidine itself was too toxic to be given to diabetics, but an alkaloid characterised by Barger and White in 1923 was shown to be a guanidine derivative, and a series of chemically substituted guanidines made in Germany were shown to be safer.²¹⁵ It was evaluated in a variety of centres including the Manchester Royal Infirmary, the Salford Royal and Ancoats in Manchester but “the results were patchy and the methods employed to obtain them often less than rigorous”.²¹⁶ Despite the

²¹² MRC Council Minutes III, (15 July 1927): 127, 155; (11 November 1927): 190.

²¹³ MRC Council Minutes III, (26 April 1929): 69.

²¹⁴ MRC Council Minutes III, (18 March 1927): 26.

²¹⁵ Walter Sneader, (1985): 217, 256.

²¹⁶ Helen Kathryn Valier, (University of Manchester: PhD thesis, 2002) The Politics of Scientific Medicine in Manchester 1900 – 1960: 168.

introduction of a second version known as Synthalin B, there were continued problems of liver toxicity.²¹⁷

As with insulin, the initial concept for liver therapy for treating pernicious anaemia came not from industry, but from the work George Minot and William Murphy at Harvard in 1926. Two years later the chemist and biologist, Edwin Cohn of Harvard identified “an extract of liver containing in small bulk, the unknown factor which produces the ameliorating effect”.²¹⁸ Harvard University shared results with the MRC and invited them to set up trials. A pernicious anaemia committee including Elliott, Dale, and Fraser was appointed to arrange trials of this new liver treatment.²¹⁹ Francis Fraser of the MRC and St. Bart’s Hospital prepared the first British liver extracts, which the MRC passed on to several firms. By 1928 the Boots Pure Drug Company, British Drug Houses, and Burroughs Wellcome had provided the MRC with sufficient material by a modification of the American methods to establish trials at 8 centres.²²⁰

John Frederick Wilkinson had established the Manchester University Department of Clinical Investigation in 1925 at the Royal Infirmary and was a central figure in the MRC trials of pernicious anaemia. However, according to Valier who examined his career in detail, the MRC’s testing of liver extracts was abandoned after a few months with Wilkinson identified as the culprit, seemingly because of his direct collaboration with industry (Boots).²²¹ The MRC had collaborated with the Association of Clinical

²¹⁷ The compounds continued to be sold and used until the 1940’s when better oral antidiabetics became available. Synthalin interested the MRC further after it was discovered to have anti-trypanosomal action and both Harold King at the NIMR and later Arthur Ewins at May & Baker made further analogues for testing by Warrington Yorke in Liverpool. Walter Sneader, (1985): 217, 256; “Synthalin”, *Lancet* (3 March 1938): 482.

²¹⁸ “Liver Extract in the Treatment of Pernicious Anemia: a Report by the Medical Research Council” *British Medical Journal* (3 March 1928): 380.

²¹⁹ MRC Council Minutes III, (15 July 1927): 156.

²²⁰ The 8 centres included many of the researchers supported by the MRC (T. R. Elliott, UCH; E. C. Dodds, The Middlesex; Arthur Ellis, The London; Stanley Davidson, who had been supported by MRC grants in both Edinburgh and then later as Professor of Medicine at Aberdeen and Edward Mellanby (Sheffield) but also Thomas Houston (Belfast), W. E Hume, Newcastle on Tyne; and John Cowan, of Glasgow; Helen Kathryn Valier, (University of Manchester: PhD thesis, 2002): 173, 195-96.

²²¹ Helen Kathryn Valier, (University of Manchester: PhD thesis, 2002): 164-198.

Pathologists (ACP) in identifying suitable centres to perform biochemical tests.²²² Valier argued that the sub-division of trials run through the ACP and testing of samples by Wilkinson, was to blame for the failure of the pernicious anaemia study. In a swipe at Wilkinson, Prof. Raper at Manchester was told by Edward Mellanby that in order receive continued funding they should “sever its unhealthy links with commercial interests”.²²³ The MRC increasingly recognised the difficulty of performing studies of clinical effects at the bedside where they had no means of assaying the therapy. The MRC strongholds were centres of research and laboratories performing biological assays rather than the wards.

Although the MRC abandoned the study it was successfully concluded independently. The results of the clinical trials were published in the *Lancet* and *British Medical Journal* in March 1928, allowing the firms to describe the preparations as “made by a process tested and found efficient by the MRC”, exactly the kind of endorsement they needed.²²⁴

The MRC promoted liver extracts not only for the therapeutic effects, but also the methods used to evaluate them, namely experiments in animals followed by evaluation in man and monitoring of blood counts, which is why Wilkinson in Manchester became central as he had developed an extensive biochemical and clinical medicine service. Valier argues that the MRC regarded the treatment as “yet another opportunity to further shape and refine relationships with industry”.²²⁵ To me, this is less clear as all they were doing was using British firms to manufacture the extracts, unless what is meant is that they then hoped that pharmaceutical firms would go on and identify, prepare and standardise the active ingredient.

The pharmaceutical firms, particularly Boots, were reluctant to give up their own private contacts with doctors such as Wilkinson. In effect the battle lines were drawn, for

²²² Helen Kathryn Valier, (University of Manchester: PhD thesis, 2002): 175.

²²³ C. C. Booth, “Clinical Research” in J. Austoker and L. Bryder (eds.), (1989): 318.

²²⁴ MRC Council Minutes III, (2 March 1928): 23; The work was completed in 1928 and published in “Liver Extract in the Treatment of Pernicious Anemia” *British Medical Journal* (10 March 1928): 398-399 and “Liver Extract for the Treatment of Pernicious Anemia” (MRC) *The Lancet* (10 March 1928): 514.

²²⁵ Helen Kathryn Valier, (University of Manchester: PhD thesis, 2002): 171.

Fletcher insisted that all contact with clinicians should be through themselves to control the direct access that firms wanted to doctors, to save the doctors from the embarrassment of dealing with any one firm, but also not to limit their own direct contact with clinicians. This was not what the manufacturers had in mind: “The manufacturers are anxious.... that arrangements for routine testing should not deprive them of the co-operation of clinicians in experimental work aimed at the improvement of the preparations”.²²⁶

Fletcher, recognising the need for firms to have their products tested, felt that the London firms were more deserving of their help, whereas the northern firms (such as Boots who extensively supported the Manchester unit) seemed to have their own arrangements.²²⁷ From 1929 Allen & Hanbury’s produced Eugastrol, a form of desiccated Hog stomach for treating pernicious anaemia. Between 1930 -1931 there were also several published reports of success in the treatment of pernicious anaemia by liver extracts, as well as Hog’s stomach.²²⁸

In October 1929 the Chemotherapy Committee agreed to promote clinical trials of a concentrated pneumococcal serum that had again been first described in America, at the Royal Infirmary, Edinburgh, at UCH and with Dr. R. Cruickshank in Glasgow, with supplies from Burroughs Wellcome though several further batches were obtained from America.²²⁹ Cox-Maksimov took this trial as her main example of a trial by the

²²⁶ Helen Kathryn Valier, (University of Manchester: PhD thesis, 2002): 181 quoted from Clinical testing of commercial preparations for the treatment of pernicious anaemia. (Agenda for the second conference (18 January 1934), PRO, FD1/2257).

²²⁷ Helen Kathryn Valier, (University of Manchester: PhD thesis, 2002): 183-4.

²²⁸ J. F. Wilkinson, “Pernicious Anemia. Preliminary Report on the Results Obtained with Certain Preparations of the Stomach” British Medical Journal (8 February 1930): 334-5; J. F. Wilkinson, “Treatment of Pernicious Anaemia with Hog’s Stomach, Report of 108 cases” British Medical Journal (17 January 1931): 85-91; C. S. D. Don, C. E. Jenkins. “Hogs Stomach in Pernicious Anemia” (24 January 1931): 158-9; C. S. D. Don, C. E. Jenkins, “Ovarian Hormone” British Medical Journal (30 May 1931): 940: “The Value of the Liver in Treatment of Anemia” British Medical Journal (4 April 1931): 584-5 in which Wilkinson reported 140 cases including 108 treated for 6 months or more and no single case failed to respond.

²²⁹ MRC Minutes III, (25 October 1929): 167; MRC Minutes III, (16 May 1930): 94.

Therapeutic Trials Committee, despite the fact that it was started before the Committee was established in 1931.²³⁰

There were other approaches to the MRC for clinical studies, including one accepted from Lever Brothers to have their concentrated vitamin A preparation tested.²³¹ This was passed on to the MRC's Accessory Food Factors Committee, but in 1929 there was still a paucity of clinical researchers:

“There can never be a successful and maintained recruitment of young men of ability for clinical research until there is at least a few stable positions in sight, the occupation of which in middle age will provide reasonable and adequate power of educating a family”.²³²

6.10 The Third Campaign of the ABCM for Clinical Trials, 1927-31.

The ABCM members remained active towards the end of the decade in their campaign to have their drugs tested. The most important pharmaceutical members of the ABCM during the period 1927-31 were Charles A. Hill and Francis H. Carr (of BDH), David Lloyd Howard of Howard's, who became vice-president in 1931, and W. J. U. Woolcock of the Pharmaceutical Society.²³³

The ABCM produced an alphabetical list of over 3,000 chemicals and advised on the producers of drugs not in the directory. In 1931 they set up a task force “in order to put British chemical standardisation on a proper basis”. In recognition of their efforts the ABCM were allocated 5 members on the provisional council, with E. F. Armstrong as Chairman. By 1931 the ABCM noted they “can produce irrefutable data to prove that the

²³⁰ D. Cox-Maksimov, The Making of the Clinical Trial in Britain, 1910 – 1945. Expertise, the State and the Public, (Cambridge: PhD thesis, September 1997).

²³¹ MRC Minutes III, (11 April 1930): 51.

²³² “MRC Report 1929-30” British Medical Journal (7 March 1931): 412 and (14 March 1931): 466.

²³³ ABCM, British Chemicals: Their Manufacturers and Uses (London: ABCM, 1927 & 1929 & 1931) in Science Museum Archive.

Key Industry duty has been instrumental in promoting the development of this important key industry”.²³⁴

The final impetus to establish a system for the clinical testing of British drugs came not just from medical or scientific needs, but as a result of the deteriorating economic climate, which led the Government and hence the MRC to support development of a strong British chemical industry. The economic climate of 1930-1 bore several similarities to 1920-1 but in addition to Germany, America had emerged as an important economic rival with greater optimism, standardisation, investment and plant capacity in the field of chemical engineering. The Depression and the collapse of international trade following the Wall Street crash of 1929 continued with rising unemployment in Britain and an increased strain upon the Health Insurance Fund.²³⁵

It was against this economic background that the ABCM tried for a third time to establish a formal process of clinical testing by the MRC. In 1930, George Pearson of Wellcome gave specific examples of studies where it had been difficult to recruit patients: “Our position is that it appears impossible to get an adequate clinical test carried out followed by a report in a medical journal.” Wellcome's highly purified liver extract had been sent to the WPRL for clinical testing but they had received only one report back. Bulbocarpaine sales were increasing despite the fact that again they had tried to have it tested by the WPRL without success.²³⁶ Diginutin clinical trials were arranged by Head Office and partly by the WPRL and although “results were favourable there was no publication”.²³⁷ Pearson also commented that:

“the British medical practitioner appeared to be reluctant to publish clinical reports even when ample clinical results were available. However, unless the data was published it could not be quoted, except anonymously, which was clearly of less value. Avenyl and Neostam were trialed by the WPRL (overseas) and Neo-Infundin (posterior pituitary lobe extract) was under trial

²³⁴ ABCM (London: ABCM, 1927, 1929, 1931).

²³⁵ A. J. P. Taylor, *English History 1914-45* (Oxford: Clarendon Press, 1988): 287-297.

²³⁶ Bulbocarpaine was an isoquinoline alkaloid used to treat excessive movements and spasms, T. A. Henry, (1939): 174-75, 304, 311.

²³⁷ G. E. Pearson to ABCM, (24 November 1930), File of the TTC, MRC File 1523/15.

but attempts to have Kurchi bark and the alkaloidal conessine or Harmine tested for Parkinsonism, rigor or paralysis and malaria, led to their failure”.²³⁸

J. Davidson Pratt who had led the ABCM since 1928 forwarded the letter from Pearson to the MRC. He wrote: -

“The ABCM is, as you know, very interested in the problem of clinical testing of new medicinal products and first raised the question with you in 1926 (sic) the Association submitted various proposals on this subject and these were discussed at your request with the newly formed Chemotherapy Committee when the main features of a suitable scheme were agreed. The scheme, has not, however achieved all that was intended and the development of new medicinal products is being seriously handicapped by the inadequacy of the facilities which are available in this country for proper clinical tests. The Association feels that the time is ripe for a further effort to develop a suitable system and would be glad if the members who are vitally interested in the subject could have an opportunity of frank discussion of the whole problem with your committee in the hope that by cooperative action it may be possible to devise a scheme of clinical testing which will eliminate the obstacles, which are at present retarding the development of new medicinal products to the national detriment”.²³⁹

A further approach to the MRC was recorded and the recognition of the continued problems on both sides stimulated further discussions.²⁴⁰ Pratt followed up with a further letter and a formal meeting between the representatives of the ABCM and the MRC took place on 16 February 1931.²⁴¹ The MRC members were Elliott, Fraser, Dale, Fletcher, and Landsborough Thompson. The company representatives were Francis Carr

²³⁸ G. E. Pearson to MRC forwarded by J. Davidson Pratt of the ABCM to W. M. Fletcher of the MRC, “Therapeutic Trials Committee” (24 November 1930), MRC File 1523/15; Avenyl, Neostam, and Neo-infundin are discussed further in the chapters on the STC and TTC. Kurchi bark (sic) was the bark of an Indian plant *Halarrhena antidysenterica*. Conessine was one of several alkaloids isolated from it, used for treating amoebic dysentery and both conessine and Harmine had laboratory activity against tuberculosis. Harmine was active as an antihelminthic and it inhibited smooth muscle contraction, hence its potential for Parkinsonism. T. A. Henry, (1939): 457-60, 617-22.

²³⁹ J. Davidson Pratt to Walter Morley Fletcher, (28 November 1930), MRC File 1092, TTC 1523/15.

²⁴⁰ The meeting was recorded in the MRC Minutes III, (16 January 1931): 4.

²⁴¹ J. D. Pratt to W. M. Fletcher, (26 January 1931), MRC File 1092.

(BDH), Fred. W. Gamble (Allen & Hanbury's),²⁴² Leonard Anderson (Boots)²⁴³, Dr H. A. Mitchell (Evans Sons Lescher & Webb)²⁴⁴, Mr C. Chapman (Graesser-Monsanto)²⁴⁵, George E. Pearson and T. A. Henry (Burroughs Wellcome)²⁴⁶, and Mr R. W. E. Stickings of May & Baker.²⁴⁷

Walter Fletcher recalled that the Council had been in general agreement about arranging studies for the ABCM in 1927, but "it had not been necessary, in the absence of

²⁴² Frederick William Gamble, encountered briefly in chapter 2 when he joined A&H as a pharmacist. Since then he had been involved in committees of the London Chemists Association and the first Pharmaceutical Codex (1903 - 1907) and in revisions of it in 1911 and 1923, the year in which he chaired the British Pharmaceutical Congress. He was a Board member of Allen & Hanbury's from 1913 and had a genius for friendly relations with the medical consultants. Between 1925-28 Gamble was on the Council of the Society of the Chemical Industry and in 1930 was elected first chairman of the Wholesale Drug Trade Association (the forerunner of the ABPI); Mr. G. E. Pearson sales manager of Burroughs Wellcome; Mr. R. W. E. Stickings, Works manager of May & Baker, J. Slinn, A History of May & Baker 1834 - 1984 (Cambridge: Hobsons Ltd., 1984): 122, 125, 128, 142, 150, 156; Mr. J. Davidson Pratt, general manager since 1928 and secretary of the ABCM; "Therapeutic Trials Committee" MRC File 1092.

²⁴³ Mr. Leonard Anderson of Boots worked in the saccharin department during the war and took control of the alkaloid department post-war, W. H. Sims "notes" (8 November 1963): 2.

²⁴⁴ I was unable to find any details about Dr. H. A. Mitchell of Evans Sons, Lescher & Webb and he does not feature any further.

²⁴⁵ Graesser- Monsanto chemical produced phenol, salicylic acid including 'aspirin' preparations, vanillin and saccharin. As for Mitchell, I could find no details about Chapman and Graesser Monsanto remained aligned to chemicals, never getting involved in clinical trials.

²⁴⁶ Dr. T. A. Henry, Burroughs Wellcome, director of the WCRL, and in 1931 Chairman of the Library Committee of the Society of the Chemical Industry, a post, which he held until 1935. He was Vice President of the Society of the Chemical Industry from 1929-32. T. S. Moore and J. C. Phillips, The Chemical Society 1841 - 1941. A Historical Review (London: The Chemical Society, 1947): 143; Robert Bentley, A Textbook of Organic Materia Medica (London: Longmans, Green & Co., 1887). – Presented to Thomas Anderson Henry, Jacob Bell Scholar 1893-4.

²⁴⁷ Stickings was the works manager at May & Baker. He served the company for 36 years before he died suddenly in December 1955, when he was deputy managing director and Director of Production. J. Slinn, (1984): 122, 125, 128, 142, 150, 156.

requests from manufacturers for clinical trials of new drugs".²⁴⁸ This comment probably reflects the fact that companies considered that the Chemotherapy Committee was inappropriate. J. Davidson Pratt emphasised "that some provision for efficient clinical trials of new remedies in this country was urgently needed".²⁴⁹ Referring to the ABCM:

"It desires full collaboration with the medical profession in such matters and has for some time been working in close touch with the Chemotherapy Committee of the MRC and with the Colonial Research Committee in the production of new substances required for extensive clinical trials. It is hoped practitioners will support British industry".²⁵⁰

In order to begin the necessary arrangements for trials, Prof. Thomas Elliott enquired of the ABCM what the largest number of likely requests would be in the course of a year. He pointed out that "clinical testing of a new remedy must at least take a period of weeks or months, particularly as it might be necessary for a given drug to be tested by several different clinicians".²⁵¹

The renewed calls for a system of testing British drugs came as a 'Buy British' campaign was led by the Government, Empire Marketing Board and the Prince of Wales:

"On November 16 the Empire Marketing Board is launching a campaign. Every retailer is asked to assist to further British trade and employment. The Campaign has the active support of the Association of British Chambers of Commerce, the Confederation of British Industries and several other bodies. Foreign products should find no place in British materia medica".²⁵²

The medical profession, who suggested that doctors should also 'Prescribe British' readily took up the bait.²⁵³ A physician describing himself simply as 'Countryman' wrote:

²⁴⁸ Report of Joint Meeting between the MRC and ABCM, (16 February 1931), MRC File 1092 of the Therapeutic Trials Committee.

²⁴⁹ Report of Joint Meeting between the MRC and ABCM, (16 February 1931), MRC File 1092 of the Therapeutic Trials Committee.

²⁵⁰ "British Chemicals and Drugs" British Medical Journal (31 January 1931): 193.

²⁵¹ T. R. Elliott at meeting with ABCM, (16 February 1931), MRC File 1092 of TTC.

²⁵² "Buy British" Chemist & Druggist (24 October 1931): 509.

²⁵³ "Prescribe British" by Countryman British Medical Journal (12 December 1931): 1120; Dr. W. Bertram Watson of Harrogate, "British Drugs" British Medical Journal (3 October 1931): 638.

“As a profession we have been asked to accept cuts in our fees, and to many of us the income tax has become a still more dreadful worry. At present the campaign of 'Buy British' should find as whole-hearted support among the profession as it is apparently doing among the general public”.²⁵⁴

6.11 Formation of the Therapeutic Trials Committee in 1931.

The Chemotherapy Committee failed to meet the needs of the ABCM members and focused too much on tropical medicine with studies overseas. The British pharmaceutical firms still had no means by which to get clinicians in Britain to test their new drugs. It was always assumed that an organised system of testing existed in Germany, though this probably was not the case and German companies had to arrange their own studies. However, as they had no difficulty in getting trials performed by German doctors, this gave them a competitive advantage. Carr was later able to provide evidence that Bayer's scientific director Dr. Mertens in 1923-5 headed a group organising their clinical trials in Germany and another for sales propaganda. The former included five physicians split between general and tropical medicine. Trials were carried out first by 1-4 external clinicians, and if promising, the program was broadened over 3-4 years, though less than 5% of the products stayed the course to be issued. Application was then made to the Government but permission was usually granted.²⁵⁵ German doctors did however raise concerns about the safety of new drugs after a widely reported tragedy occurred in Lübeck in 1930, when many children died and were injured after administration of contaminated Bacillus Calmette-Guerin (BCG) vaccine to newborn babies.²⁵⁶

²⁵⁴ “Buy British” British Medical Journal (19 December 1931): 1160. Dodd complained about the high prices for catgut, rubber gloves, instruments, plaster of Paris and bandages.

²⁵⁵ “British Objectives Subcommittee” Pharmaceutical Journal (2 March 1946): 137; 50 Years of Bayer Remedies 1888-1938. (Leverkusen: Bayer, 1938);

²⁵⁶ “The Lübeck Tragedy – BCG” British Medical Journal (21 February 1931): 334; M. C. G. Israels, A. D. MacDonald, “The Pharmacology of Peracaine” British Medical Journal (28 November 1931): 986-988, “The BCG Tragedy at Lübeck” British Medical Journal (28 November 1931): 1016; S. R. Rosenthal (ed.), BCG Vaccine: Tuberculosis-Cancer (Littleton, Mass: PSG Publishing, second edition 1980): 35-8; L. Bryder in J. Austoker and L. Bryder (eds.), (1989): 10-11.

There were similar concerns in the British medical literature in 1930-1 when Bayer's anaesthetic, Avertin, was associated with toxic jaundice.²⁵⁷ One of the main reasons for the delay in establishing clinical testing of new drugs in Britain was the relative paucity of novel chemicals; estimated to be six per year as still most of the new synthetic drugs were still from Germany.²⁵⁸ Sir William Willcox, physician to St. Mary's and Home Office pathologist wrote:

“It showed how necessary it was that, before they were placed on the market, these drugs should be submitted to careful toxicological and therapeutic tests on the human subject as well as on animals” “The chemical manufacturing industries (were)...daily launching imperfectly tried complex organic drugs on the market” and the system of testing drugs was “unsatisfactory, exposing the people of this country to great danger from the taking of new drugs advertised as possessing wonderful curative properties”.²⁵⁹

As a result of the growing concerns, modifications were made to the Therapeutic Substances Act, requiring withdrawal of all of a batch from sale if it failed to meet standards, and the Act came into force on 25 July 1931.²⁶⁰

6.12 Conclusions.

The clear conclusion of this chapter is that after the Pharmaceutical industry willingly submitted to having their Salvarsan preparations assayed during the war, representatives of the companies approached the MRC several times in the period 1922-

²⁵⁷ Sir William Willcox, "Control of Drugs: A Warning", British Medical Journal, (4 April 1931): 597; "The Choice of an Anaesthetic" (14 February 1931): 265-6; "Avertin Anaesthesia" (21 February 1931): 330; "Avertin in Anaesthesia" British Medical Journal (20 June 1931): 1095; F. B. Parsons, "Avertin" British Medical Journal, (4 October 1930): 554-7; F. B. Parsons, "Avertin anaesthesia" British Medical Journal (1 November 1930): 756; Francis E. Shipway, "Avertin Anaesthesia" British Medical Journal (8 November 1930): 799; Basil Hughes (Bradford), "Avertin Anaesthesia" British Medical Journal (22 November 1930): 887. Over 100,000 narcotic doses were placed at the disposal of clinics before marketing.

²⁵⁸ "Preparations and Appliances – Nembutal" British Medical Journal (28 February 1931): 359; "Neo-infundin" (7 March 1931): 406.

²⁵⁹ "Control of Drugs: A Warning", Sir William Willcox, British Medical Journal (4 April 1931): 597 (in lecture to Roy. Coll. Phys 19th – 26th March).

²⁶⁰ "Therapeutic Substances Act" H. H. Dale Archives 93 HD Box 21.2.129.

1931, with the aim of securing a system of clinical testing of their novel drugs, including synthetics. After the first approach at the end of 1922, the MRC and the companies became pre-occupied with insulin production. Quite apart from the apparent clinical efficacy already seen in North America with insulin, the MRC held the patents for the UK and they could control the distribution. A second approach was made in 1926 around the time when the MRC was embarking on the discussions with the DSIR, which were to result in the Therapeutic Substances Act of 1925. A Chemotherapy Committee was established, reflecting the new focus of the MRC and DSIR following the discovery of Bayer 205 in Germany. There remained a series of other committees, for anaesthetics and so on. One of the reasons for the failure to establish the TTC earlier may have been simply that it was estimated by the ABCM that there would only be half a dozen new products each year. Studies of antisera and antitoxins were quite different and were relatively easy to organise through the Board of Trade.

This chapter also saw the continued ascendancy of Francis Carr. He finished the War with honours and was given a prestigious job at British Drug Houses and went on to fame for his success with thyroxin and insulin production. By 1926-27 he was the influential President of the Society for the Chemical Industry and campaigned for better training of chemists and a system of clinical trials. The Chemotherapy Committee of 1927 did not meet the Manufacturers needs and the ABCM campaigned once more for a clinical trial system in 1930. They were successful this time, in part due to the timing of their approach in the midst of harsh economic conditions and against a background of increasing government involvement. The following chapter evaluates how the British companies used the new Therapeutic Trials Committee and attempts also to assess whether the availability of a clinical testing system influenced their strategy of drug development.

CHAPTER SEVEN: Burroughs Wellcome Strategy in the Interwar Period

7.1 Introduction.

After the end of hostilities, firms like Burroughs Wellcome that had committed to producing synthetic and other German drugs, had to make difficult choices about directions of their future research. Having lost several key members of staff during the war, Burroughs Wellcome suffered further significant staff losses immediately post war. For the firm that already produced antitoxins, vaccines, synthetic drugs and alkaloidal extracts, there were soon to be further strategic choices as organ extracts and vitamins came into prominence. Would they return to importing drugs, rather than discovering their own and would a Burroughs Wellcome Tabloid brand of each new medicine be prepared or would they specialise?

In this section I evaluate some of the factors, which may have shaped their policy. Those that I have identified include the changing market post-war, the fiscal and regulatory environment, the size and scope of their own manufacturing and testing facilities, and the availability of researchers to perform clinical trials on their new drugs. In order to address these issues, Burroughs Wellcome moved towards a more formal method of defining company strategy, in the form of their Scientific and Technical Committee, established in 1925: this chapter is based around the minutes of this committee.

7.2 Staff Changes and Facilities.

In the past two chapters I have highlighted some of the problems faced by Burroughs Wellcome due to the loss of experienced staff, particularly chemists such as Carr, Ewins, Barger, and Power. On 22 February 1919, Pyman, head of the WCRL, became Professor at the College of Technology in Manchester and a Fellow of the Royal Society in 1920.¹ Dr. Thomas Anderson Henry, who took over as Director of the WCRL, had studied the chemistry of alkaloids at the Pharmaceutical Society from 1893 and at Imperial College from 1896.²

¹ H. King, "Frank Lee Pyman" Obituary Notices of Fellows of the Royal Society 4 (1944): 681-697.

² Dr. Thomas Anderson Henry (1873 - 1958) served on the British Pharmacopoeia Commission, and the committees of the Biochemical Society and Chemical Society, L. G.

As described in the last chapter, in March 1919 Harold King, another experienced chemist left Burroughs Wellcome to join Dale at the National Institute for Medical Research.³ Robert R. Baxter who had synthesised pilocarpine, Kharsivan, Salol and various alkaloids during the war, resigned in December 1919, moving to Manchester to take up a commercial position. A further experienced chemist, Marmaduke Barrowcliff, who had co-authored a book on synthetic chemicals with Francis Carr, took up a role in Malaya with a rubber firm.⁴

Alfred Louis Bacharach, a Cambridge graduate food chemist, who had worked at the WCRL and Analytical department since 1915, departed in January 1920.⁵ Bacharach was introduced in the last chapter when he joined Nathan's, a forerunner of Glaxo, because he disliked his tedious daily journey from Hampstead to the new site at Dartford.⁶ Robert G. Fargher, who had prepared arsenicals including Kharsivan (Salvarsan), resigned in September 1920 to take up a post as head of the Chemistry Section of the Shirley Institute in Didsbury, Manchester. Herbert W. B. Clewer, who produced synthetic chemicals including neosalvarsan, salicylic acid, and pyrimidine, moved to the firm of Messrs. Mason & Sons in Rotherham at the end of the War, and Frank P. Walton, went to Imperial College in 1923. It was not easy to find suitable chemists to replace losses as: "it must be remembered that the Foundation cannot obtain straight from the universities men suitable for this work and it is only after a year or two's training in our laboratory that they become really useful".⁷

Matthews, History of Pharmacy in Britain (Edinburgh & London: E. & S. Livingstone, 1962): 255- 256; T. A. Henry, F. L. Pyman in E. F. Armstrong (ed.), Chemistry in the Twentieth Century; an Account of the Achievement and the Present State of Knowledge in Chemical Science (London: Ernest Benn, 1924); T. A. Henry, The Plant Alkaloids (London: J. & A. Churchill, 3rd edition 1939).

³ WF: YL Box 46, Works History; Sir Charles Harrington, "Harold King" (1887-1956) Biographical Memoirs of Fellows of the Royal Society 3 (1956): 159.

⁴ M. Barrowcliff, The Vitamins (Kuala Lumpur: St. Johns Press, 1923); WF: YL Box 46 Works History.

⁵ WF: YL Box 46, Works History.

⁶ R. P. T. Davenport- Hines, J. Slinn, Glaxo: A History to 1962 (Cambridge: Cambridge University Press, 1962): 47, 71-72; WF: Box 25, Work Records.

⁷ "Facilities for Chemical Work", (23 December 1926), STC WF: S/G/49.

There were also further changes at the WPRL, which had already lost Dale, Laidlaw, Burn, Ewins and Barger. A. F. Watson succeeded Percival Hartley as Head of Biochemistry in 1921, as Hartley departed for the NIMR.⁸ In order to replace some of the staff lost at the end of the War, researchers such as John W. Trevan and R. A. O'Brien were recruited. Trevan was a brilliant medical student at St Bartholomew's, then a demonstrator, obtaining a B.Sc. in physiology before a brief spell in the Army. He was appointed as Head of Pharmacology to the WPRL at Langley Court in 1920.⁹ R. A. O'Brien, a bacteriologist joined from the Lister Institute, as did G. S. Walpole, and their main focus was on vaccines.¹⁰ O'Brien was responsible for the daily running of the laboratory, reporting to Charles Wenyon, who had been a consultant pathologist during the war. Wenyon was an expert protozoologist and he was secretary of the Royal Society of Tropical Medicine for 25 years. All new senior staff had to be approved by Andrew Balfour, who as we saw in chapter 3 was appointed as head of the WBSR in 1913, until he too departed in 1923 to join the London School of Hygiene and Tropical Medicine.¹¹

In 1920 Burroughs Wellcome moved the WPRL from Brockwell Hall, Herne Hill to a 108-acre site at Langley Court, Beckenham costing £30,000.¹² New facilities were established at Temple Hill, including a chemical section, water tower, boiler house, and

⁸ Sir Henry Dale, "Sir Percival Hartley" Biographical Memoirs of Fellows of the Royal Society (1957) 3: 81-110; H. J. Parish, "The Wellcome Research Labs and Immunology" WF: 85/20: 2 Chapter 3.

⁹ J. H. Gaddum, "John William Trevan 1887 – 1956" Biographical Memoirs of Fellows of the Royal Society 3 (1957): 272 – 288. Trevan became Director in 1941 and Research Director in 1952; A. S. Milton, "Burn Oxford for a Start" Brit. J. Pharmacology 119 (1996): 1293-9.

¹⁰ W. S. Feldberg, "H. H. Dale (1875 – 1968)" Biographical Memoirs of Fellows of the Royal Society 16 (1970): 79-174. Walpole left Burroughs Wellcome to set up his own manufacturing business. O'Brien, Australian by birth went on to become Director of the WPRL after Dale departed in 1914; H. Chick, "The Lister Institute of Preventative Medicine" Endeavour (July 1949): 106-111; R. A. O'Brien, "Pharmacological Activities of the Foundation", WF: S/G/49.

¹¹ H. J. Parish, WF: 85/20: 2, chapter 5.

¹² "Opposition to Proposed Laboratory" Chemist & Druggist 94.3 (14 May 1921): 35; "WPRL" Chemist & Druggist 94.3 (11 June 1921): 61.

materia medica farm; a new exploratory laboratory was opened in May 1923 and chemical manufacturing was moved to Temple Hill in July 1925.¹³

By 1926 the WCRL buildings also needed enhancement:

“With regard to the WCRL the present premises are inadequate and uneconomical for modern chemical works and more could be done with the present staff if they were housed in larger premises and with modernised equipment”.¹⁴

The manufacture of ephedrine, pseudoephedrine, thyroxine and adrenalin had to be stopped because of lack of equipment, and there was no “reserve for emergencies or sudden demands”.¹⁵ The experimental laboratories were refurbished at the end of 1926, and the WCRL was altered to allow for more chemists to be recruited.¹⁶ By 1931 an observer noted:

“The firm at Dartford... [had] a new chemical laboratory of remarkable beauty and interest. The works at Dartford under the management of Jowett, is a remarkable works to visit and scientific control of the manufacture and packing appears to be as complete as human ingenuity can devise”.¹⁷

During this period Henry Wellcome increasingly left the running of the business to George Pearson, who was renowned for his ‘parsimony’, exemplified by constant complaints over salaries and that he “starved essential accounts and equipment”. The staff was encouraged to improvise and not spend”.¹⁸ Pearson’s defence was that he never really knew when Wellcome would demand thousands of pounds to pay for his anthropological collections acquired overseas.¹⁹

7.3 The Scientific and Technical Committee.

¹³ G. E. Pearson, A Chronology of the History of B.W & Co. 1878- 1936 WF: 88/34: 41d: 13 – 14.

¹⁴ Memo: “Facilities for Chemical Work”, (23 December 1926), WF: STC S/G/49.

¹⁵ *Ibid.*

¹⁶ STC Meeting, (17 December 1926), WF: STC S/G/49.

¹⁷ Burroughs Wellcome Insulin Ledgers (1930-1): 44- 45, WF: 89/24.

¹⁸ H. J. Parish, WF: 85/20:2 Chapter 5.

In the period immediately following the war, Burroughs Wellcome shaped their future according to the demands of changing markets and regulatory constraints rather than by setting down a specific policy. At the end of the War, production of some German drugs such as phenacetin ceased (in January 1921), as German patents were re-instated. Drugs that had been needed for the war were required in smaller quantities but export markets that had been compromised by the war were re-opened.

After trade deteriorated in 1921, Burroughs Wellcome struggled to decide whether they should return to their roots, or to follow the synthetic approach taken during the War. However, they were not fully prepared to invest in the long-term research as performed in Germany, and so they were left with the pickings from copying drugs out of patent, chemically modifying those that remained patent-protected, and producing semi-synthetic versions of natural extracts. The only 'new' products marketed immediately post-war by Burroughs Wellcome were Menthofax (September 1920) and Moogrol (July 1921), and these analeptics (stimulants) were only copies of drugs already available on the market.²⁰ There was, of course, insulin arising as an external opportunity and this dominated efforts in the period 1923-25, and as described previously.

Burroughs Wellcome learned a great deal through Trevan's explanations of why some batches tested by Burroughs Wellcome failed tests at the NIMR due to inherent biological variation within the animals used for testing.²¹

Burroughs Wellcome returned in part to their pre-war strategy of characterising drugs extracted from plants, but despite the loss of many experienced chemists, they still prepared some active principles and semi-synthetic analogues at the WCRL, before exploring their pharmacology and standardising them at the WPRL. Requests for Tabloids came from all over the globe, but particularly from Africa and India.²² Glenny at the

¹⁹ H. J. Parish, WF: 85/20: 2 chapters 5, 6; Minutes of the Wellcome Trustees (23 April 1935).

²⁰ A. W. Haggis, "Typescript History of the Works", WF: 85/20:2.

²¹ A. S. Milton, "Burn Oxford for a Start" *Brit. J. Pharmacology* 119 (1996): 1293-9 on p. 1294.

²² R. A. O'Brien to G. E. Pearson, (16 January 1925), WF: S/G/49. Research Reports, Scientific and Technical Committee Notes of Minute(s) and Correspondence, (January

WPRL continued to prepare and standardise diphtheria antitoxin and evaluated optimised dosing regimens and assays of immunity. Clinical trials of antisera and antitoxins were arranged via the senior medical officer of the Ministry of Health at schools, naval ships and training schools for nurses, but Burroughs Wellcome had limited success with new vaccines, though a scarlet fever vaccine was developed and Staphylococcal toxins were evaluated.²³

The establishment of the Scientific and Technical Committee (STC) in January 1925 aimed to further improve the communication between the various Burroughs Wellcome laboratories and to provide a formal means of reporting to George Pearson, the General Manager.²⁴ The STC met monthly to define the Research strategy and included Wenyon of the WBSR, Trevan (WPRL), Henry (WCRL), O'Brien, (WPRL), Jowett (Works), Taylor and Smith (Analytical). Although not overtly stated, the establishment of the Committee may have been related to the imminent Therapeutic Substances Act which was passed in 1925, coming into operation in 1927, which indicated greater government control of both synthetic and biological substances, as described in a previous chapter. O'Brien, Glenny, Okell and Parrish were consulted regarding the drafting of the Therapeutic Substances guidelines, but the Burroughs Wellcome input was only regarding controls for vaccines.²⁵

As a strategic committee the STC addressed issues ranging from research accommodation and facilities for research, to interactions and collaborations with external doctors and organisations such as the DSIR, ABCM and Colonial Office; it also reviewed ongoing projects, making sure that everything was in place to evaluate and introduce new drugs. At its inception, the STC reviewed progress over the past few years. Burroughs Wellcome had been slow in showing their interest in insulin and lost ground to Allen &

1925 to December 1934); STC Meeting, (20 January 1925); Letter from Bombay, (23 February 1926), WF: STC S/G/49.

²³ H. J. Parrish, "Clinical Research on Diphtheria (I) (1922-40)", *The Wellcome Research Labs and Immunology*, chapters 3-4, 6, WF: 85/20/2.

²⁴ The first meeting of the STC was on 13 February 1925, WF: STC S/G/49.

²⁵ H. J. Parrish, "The Wellcome Research Labs and Immunology", chapter 8, WF: 85/20/2.

Hanbury's and British Drug Houses and their first commercial production of insulin was not achieved until September 1924.²⁶

When supplies of pancreas became restricted, Dale at the NIMR had suggested that in future if there was an insufficient supply of any hormonal preparations, manufacturers should co-ordinate their efforts so that each firm concentrated on a different hormone. Whereas Francis Carr of British Drug Houses approved of this suggestion and indeed may have been behind it, Burroughs Wellcome was concerned that they would be allocated "the leavings after BDH have had their pick".²⁷

If such a policy were to win favour it would run counter to Burroughs Wellcome's policy of preparing standard 'Tabloid' preparations of all substances that were in demand. Ideas for new drugs came from the medical literature and attendance at meetings, scientific requests from physicians for a particular supply, or feedback on unmet clinical needs. If a drug showed promise Burroughs Wellcome would always ensure that they had a version available.²⁸

Occasionally, physicians approached the firm with specific requests, such as one who asked for a drug for anaemia, and they provided ferric cacodylate; another wanted "a really reliable drug to act as a sedative in epilepsy".²⁹ These requests had to be managed efficiently, so that efforts were not wasted preparing small batches. The opposite situation also occurred when Burroughs Wellcome found they made too much of a drug such as

²⁶ Insulin manufacture started in May 1923 and moved from the Experimental lab to the WCRL in September 1923, the first sterile batch of Tabloid insulin hydrochloride being ready in September 1924: Hogg, "Typescript History of the Works", WF: 85/20: 2

²⁷ H. A. D. Jowett to G. E. Pearson, "The Relation of the Foundation to Research Workers and Clinicians: Memorandum re; Scientific Societies etc." (12 October 1926): 4. WF: BA/S/6/49.

²⁸ Such was the case when G. Voegtlin reported the benefits of reduced glutathione for inhibiting the poisoning by organic arsenicals, STC Meeting, (25 January 1925), WF: STC S/G/49. Journal of Pharmaceutical and Experimental Therapeutics (1925): 297; The synthesis had just been reported by Stewart and Tunnicliff, Biochemical Journal XIX (1925): 207; R. A. O'Brien to G. E. Pearson, (28 May 1925), WF: STC S/G/49; However the only source from Germany was poor quality, (21 October 1925), WF: STC S/G/49.

²⁹ H. A. D. Jowett to G. E. Pearson, (15 January 1925): A request also came for concentrated vitamin A, STC Meeting, (20 January 1925), WF: STC S/G/49.

hordenine (anhaline) - an alkaloid isolated from barley malt germs, and characterised by Barger in 1909 – and so “needed to find an outlet”.³⁰ The physiologists at the WPRL were tasked with finding alternative uses. This substance had psychic and motor excitation effects similar to ephedrine but at high doses it could cause death by inhibiting respiration.³¹

The post-war decade saw an increased interest in hormonal preparations. Organ extracts, or ‘organotherapies’ were variable in strength and in order for Burroughs Wellcome to investigate and prepare new hormonals, O'Brien suggested to Pearson that physiologists and organo-chemists should work in adjacent laboratories. “With regard to the WCRL the present premises are inadequate and uneconomical for modern chemical works and more could be done with the present staff if they were housed in larger premises with modernized equipment”.³²

In 1925 the STC were approached by the DSIR with an offer to collaborate. In 1920 a large government laboratory had been established by the DSIR at Teddington with the aim of preparing some of the chemical intermediates, required in small quantities by drug firms, and where it was not cost-effective for the firms to prepare these. The idea was that the DSIR could prepare these in bulk and make them available to British firms, to save them relying on overseas suppliers. A pharmacology building was added in 1923, adjoining the National Physical Laboratory and the chemist G. T. Morgan was appointed Director of the DSIR in 1925.³³ Morgan began his training at Finsbury Technical College, like Francis Carr. He had also been a research assistant to the chemist William A. Tilden at the Royal College of Mines in London. Representatives of the Chemical Society contacted

³⁰ H. A. D. Jowett to G. E. Pearson, (15 January 1925), WF: STC S/G/49.

³¹ T. A. Henry, (1939): 561.

³² “Facilities for Chemical Work”, (23 December 1926), STC WF: S/G/45.

³³ Gilbert Thomas Morgan (1870-1940) was an assistant at the dye firm of Read Holliday then Demonstrator at the Royal College of Science, first in Dublin in 1912, then Professor of Applied Chemistry at Finsbury Technical College from 1916, and Prof of chemistry at Birmingham University 1919-25. In 1926 he became the Director of the Chemical Research laboratory of the DSIR at Teddington where he remained until 1939; James Irvine, “Gilbert Thomas Morgan” Obituary Notices of Fellows of the Royal Society 3, (1941): 354-62; M. R. Fox, Dyemakers of Great Britain 1856-1976 (Manchester: I.C.I. plc, 1987): 91.

Burroughs Wellcome (and other firms) early in June 1925 with an offer from the DSIR to collaborate more closely in developing new chemotherapeutic drugs. Following the description of Bayer 205 there was a renewed interest in chemotherapy and the government was prepared to invest further research money into a search for new chemotherapeutic agents.

Dr. Henry replied to the DSIR that the research performed by Burroughs Wellcome was “quite satisfactory,” and “I am emphatically of the opinion that no success could attend any co-operative effort to encourage and stimulate scientific research and the best way is to allow each firm to make their own arrangement”. He emphasised O'Brien’s earlier consideration that what was required was “close collaboration between chemists and physiologists” as could already be achieved at Burroughs Wellcome.³⁴ The firm remained reluctant to share their expertise with others.

However, Burroughs Wellcome were quick to suggest that if any products arose from the DSIR, which were likely to be of industrial interest, then the experimental department would be keen to take up the work. Henry commented further that the DSIR plan for collaborative research:

“ does not strike me as feasible, partly because of the complications involved by the medical side of the question and partly because of the circumstances, objects and outlook of the component parts of the individual are too varied in character to permit it”.³⁵

The DSIR made a formal approach to the MRC to collaborate to develop new chemotherapeutic agents, but these chemistry ventures eventually foundered, especially as they could only offer non-exclusive licenses and because they relied on external laboratories. As money became short, joint collaborations were eventually abandoned.³⁶

³⁴ T. A. Henry to A. W. Crossley, (9 July 1925), WF: STC S/G/49 (reply to letter of 23 June 1925).

³⁵ T. A. Henry to A. W. Crossley, (9 July 1925), WF: STC S/G/49.

³⁶ I. Varcoe, “Scientists, Governments and Organised Research in Great Britain 1914-6. The Early History of the D.S.I.R 1914-16” *Minerva* 8 (1970): 192-216; R. McLeod, E. K. Andrews, “The Origins of the D.S.I.R. Reflections on Men and Ideas, 1915-6” *Public Administration* 48 (1970): 23-48; E. Hutchinson, “Scientists as an Inferior Class: The Early Years of the D.S.I.R.” *Minerva* 8 (1970): 396-411; J. D. Bernal, *Science in History* (London: C. A. Watts & Co., 1965); C. E. K. Mees, *The Path of Science* (Chichester:

Since the departure of Carr and his colleagues, Burroughs Wellcome had adopted a protective approach, limiting staff from presenting data and attending external meetings for fear of even more being poached. The insularity, which had been the hallmark of Burroughs Wellcome, already apparent in their dealings with the MRC, began to be questioned by STC members in mid 1926.

The event which seems to have triggered this reappraisal seems to have been the inaugural presidential address: “The Position and Prospects of the Organic Chemical Industry in this Country” by Francis Carr to the Society of the Chemical Industry at its Manchester meeting in July 1926. He called for greater emphasis on synthetic drugs rather than the biologicals and the standard preparations upon which Burroughs Wellcome had chosen to concentrate.³⁷ Jowett referred to Francis Carr's new position as President of the SCI in a letter to Pearson: “Mr. C's (sic) new position will improve his opportunities of getting in touch with universities and kindred institutions”. Jowett was concerned about the increasing tendency to patent discoveries, primarily of synthetic drugs, and he suggested that a special agenda should be addressed at the next meeting of the STC: “To consider the best means of getting into touch with workers in universities and kindred institutions so that the company may have their proper share of the commercial exploitation of any discoveries”.³⁸ Jowett referred to a previous report to Pearson in which he first raised these concerns.³⁹

John Wiley, 1946); J. Jewkes, D. Sawers, R. Stillerman, The Sources of Invention (London: MacMillan, 1955); A. C. Seward (ed.), Science and the Nation (Cambridge: Cambridge University Press, 1971); A. Marwick, The Deluge, British Society and the First World War (Boston: Little Brown, 1965) especially chapter 7.

³⁷ Lecture notes of S.C.I. meeting, (July 1926). B.CARR. publications, F. H. Carr, Archives; F. H. Carr, “The Commercial Production of Hormones” Chemist & Druggist 105.1 (24 July 1926): 181.

³⁸ H. A. D. Jowett to G. E. Pearson, “Co-operation”, STC Meeting, (24 July 1926), WF: STC S/G/49.

³⁹ The letter outlined the formation of the STC, when it first met on 16 January 1925 to discuss the pharmacological activities of the Foundation. R. O'Brien to G. Pearson, (16 January 1925), WF: STC S/G/49.

The debate about the firms' relationship with academics and clinicians was evidently difficult to arrange, due to Pearson going away.⁴⁰ Fortunately this led to both O'Brien and Jowett setting out position papers to Pearson on external relations.⁴¹ Jowett described how prior to and at the outbreak of the War, it was only natural for the Government to consult Burroughs Wellcome on matters of policy relating to drugs, as the firm was held in high regard for its research work. He recalled how this reputation was further enhanced by the work on Salvarsan. However, it appears that Burroughs Wellcome, after the loss of Carr and the post-war exodus became very cautious about allowing their trained staff to establish links with outside professional bodies.⁴²

From 1926 the STC allowed increasing contact with external investigators and began to allow the release of free samples of new drugs for testing. When this policy was reviewed some years later the STC noted that: "in sending preparations for trial outside the Wellcome Research Institute there is a certain risk of premature disclosure of results, a risk which must, however, under the present circumstances be taken".⁴³ It was, however, a matter of policy to have clinical tests performed on all new biological products.⁴⁴

Jowett could only speak for the policy regarding the works staff, but that was the department, which Carr had left in 1914. The policy thereafter was: "That it was inadvisable for members of the staff to take up work either in local or technical affairs as it would absorb their energies, which would more profitably be conserved in the interest of the firm".⁴⁵

Jowett had experienced refusals and discouragement regarding attendance at external meetings, though he felt that after 30 years at the firm his motives for attending

⁴⁰ R. A. O'Brien to G. E. Pearson, (28 October 1926), WF: STC S/G/49.

⁴¹ H. A. D. Jowett to G. E. Pearson, (12 October 1926): 4, WF: STC S/G/49; Minutes of Research Conference, 1. Raw Material to Researchers, (29 October 1926).

⁴² H. A. D. Jowett to G. E. Pearson, "The Relation of the Foundation to Research Workers and Clinicians; Memorandum re Scientific Societies etc", (12 October 1926), WF: BA/S/6/49.

⁴³ STC Meeting, (28 February 1930), WF: STC S/G/49.

⁴⁴ STC Meeting, (24 October 1930), WF: STC S/G/49.

⁴⁵ Memo H. A. D. Jowett to G. E. Pearson, (12 October 1926), WF: STC S/G/49.

could not be questioned. He stated that: "I have only the interests of the firm at heart and do not in any way seek personal advancement or 'kudos' outside the firm".⁴⁶ There were exceptions to the rules, for Jowett was associated with the Dartford Association and the Local employment committee, attended some scientific conferences and performed editorial work, but he rarely got involved in pharmaceutical, chemical and analytical societies in the same way as Carr, Gamble and Hill.

However, Jowett clearly implied that Carr, who had previously reported to him, had now gained an upper hand because of the restrictive policies at Burroughs Wellcome. During the war, Lord Moulton, Prof. Jocelyn Field Thorpe, of Leeds University, (author of "*Dictionary of Applied Chemistry*" and "*The Synthetic Dyestuffs industry and Intermediates*")⁴⁷ and other Government officials, consulted Jowett - until Carr came onto the scene. Both Carr and Jowett were asked to serve on committees such as the Poisonous Gases Committee, but whereas Boot fully supported Carr, Jowett had to decline the offers.

Jowett referred to two other important factors that had been in Carr's favour: One was the influence Boot had with Lloyd George and Dr. Addison (Minister of Health), and the other was Carr's friendship with Col. E. F. Harrison of the RAMC and with Dr. Henry Dale at the NIMR.⁴⁸ Jowett continued to explain that Carr's manufacture of both saccharin and gas granules, brought 'kudos' to Boots and he was personally rewarded with the C.B.E. while Boot received the O.B.E. and M.B.E. - but the only Burroughs Wellcome member similarly recognised was O'Brien. Carr was also chosen to take part in the ABCM mission to Germany in 1919 along with General Hartley and Herbert Levinstein.⁴⁹

As a consequence of their lack of involvement in external activities, Jowett felt that Burroughs Wellcome no longer occupied a privileged position in Britain. These were

⁴⁶ H. A. D. Jowett to G. E. Pearson, (12 October 1926), WF: STC S/G/49.

⁴⁷ "Jocelyn Field Thorpe, Obituary" *J. Chem. Soc.* (1941): 444.

⁴⁸ Carr was an intimate personal friend of Edward Frank Harrison and he delivered the Harrison lecture in 1919, *Pharmaceutical Journal* 124 (1930): 45.

⁴⁹ Association of British Chemical Manufacturers, (ABCM) *Report of the British Chemical Mission on the Chemical Factories in the Occupied Area of Germany.* (London: H.M.S.O., 1919).

“years of consolidation”.⁵⁰ Burroughs Wellcome had been initially cautious in their assessment of insulin whereas Jowett stated: “British Drug Houses staked everything on it”. Jowett realised that: “Carr and BDH are now always associated with insulin, and Burroughs Wellcome and myself are without recognition”.⁵¹ He regretted that “in regard to their present position in the pharmaceutical and chemical world, BDH are looked upon as the most progressive of the fine chemical manufacturers (including medicinal chemicals).” Also “from very many hints given to me, from personal acquaintances most favourably inclined to the firm, I should say that BDH lead, with Boot's running Burroughs Wellcome & Co. a close second”.⁵² Burroughs Wellcome had lost ground to BDH on borocaine, hexylresorcinol and thyroxin, as well as insulin. In order to avoid lagging behind in the future, Burroughs Wellcome had to think not only of exploiting their own discoveries, but also those made externally, and in order to achieve this closer contact was required with external establishments and with clinicians.

It will be recalled also that 1926 saw major upheavals in the industry with the establishment of IG Farben and Imperial Chemical Industries. When British Drug Houses was established as a public limited company in February 1926, they employed 30 trained chemists and around 40 pharmacists with a payroll of over 1,200 and an authorised capital of £642,000. The firm produced 1 million pills per day, three-quarters of a ton of ointments and over 1,000 gallons of 3,500 chemicals monthly.

Burroughs Wellcome had not capitalised on its early links with government and its unique position as the first holder of a Home Office license to perform biological standardisation tests. Increasingly, the staff of the MRC and the Pharmaceutical Society took a central role and yet they had all gained their experience at Burroughs Wellcome: Dale, Laidlaw, Hartley and Burn.⁵³ Jowett's concern was that:

⁵⁰ “Henry Solomon Wellcome” in D. J. Jeremy et al, Dictionary of Business Biography V (London: Butterworths, 1986).

⁵¹ H. A. D. Jowett to G. E. Pearson, “Memorandum re. Scientific Societies” (12 October 1926), WF: BA/S/6/49.

⁵² *Ibid.*

⁵³ J. H. Burn, Methods of Biological Standardisation (Oxford: Oxford University Press, 1937).

“Government departments and Institutions are now taking part which is likely to extend in the control of drugs both as regards conditions of manufacture and standards of purity etc. and BDH are more in touch with these departments than Burroughs Wellcome & Co.”⁵⁴

Indeed, it was not only Carr, as F.W. Gamble of Allen & Hanbury’s was the first chairman of the Wholesale Drug Trade Association and was also well connected.⁵⁵

Post-war Burroughs Wellcome lacked scientific direction with Henry Wellcome increasingly preoccupied with collecting artifacts in Africa and Pearson, the General manager was renowned for penny- pinching, and in the laboratories they missed the drive of Power and Pyman.

The STC therefore proposed a return to the policy introduced by Silas Burroughs in the final decade of the nineteenth century, to grant *gratis* materials to researchers.⁵⁶ The director of the Institute and works manager were therefore encouraged to stimulate contacts with medical and allied researchers by attendance at meetings, acceptance of honorary duties with scientific societies, and by provision of materials at their discretion. It was hoped that such a policy would encourage publication of data, giving acknowledgement to the Wellcome Research Institute, or to Burroughs Wellcome as opposed to the individual. Expenses to support these new activities were placed in a special account.⁵⁷ In succeeding years they distributed samples *gratis* of 78 bottles of 25 Tabloids and 22 bottles of 100 Tabloids. “Whilst liberal distribution along the lines adopted by certain competitors is not to be recommended we might give samples a little more freely in those cases where we are satisfied that a substantial demand for the substance really exists”.⁵⁸

⁵⁴ H. A. D. Jowett to G. E. Pearson, “Memorandum re. Scientific Societies”, (12 October 1926): 3. WF: BA/S/6/49.

⁵⁵ Geoffrey Tweedale, At the Sign of the Plough: 275 Years of Allen & Hanbury’s and the British Pharmaceutical Industry 1715 - 1990 (London: Murray, 1990): 99, 102, 157,174; D. Chapman-Huston, and E. C. Cripps, Through a City Archway, the Story of Allen & Hanbury’s 1715-1954 (London: John Murray, 1954): 212.

⁵⁶ STC Meeting, (29 October 1926). WF: STC S/G/49.

⁵⁷ STC Meeting, (29 October 1926), WF: STC S/G/49.

⁵⁸ STC Meeting, (24 May 1937; WF: STC S/G/49, Minutes of Research Conference, 1. Raw Material to Researchers.

In terms of new drugs, O'Brien noted that there were two alternative approaches: "the line that has been particularly developed in Germany may be followed Synthetic chemotherapy or they could continue their primarily physiological approach, it may seem wise to develop one or other or both".⁵⁹ In offering these alternatives he reminded Pearson that in Germany:

"Hundreds of chemists and physiological assistants are employed working under the central direction of the pharmacologist. A vast organisation is necessary, the cast is large and results cannot be expected without years of work. Hundreds of compounds were synthesised before Salvarsan was discovered. I recently saw records at Frankfurt showing that M(eister), Lucius, Brüning had synthesised and tested over 2,000 separate substances up to 1924. I was told that the pharmacologist essentially responsible for the discovery of Bayer 205 had worked for 15 years directing a band of several hundred physiologists and chemists before this one success was achieved".⁶⁰

[Thus] "There is a natural temptation to investigate compounds made by other chemical firms and to try by substitution to improve on them. Probably it will be impossible to avoid this". He recommended synthetics but "not as the main course".⁶¹ In fact Burroughs Wellcome did not make the switch to synthetics at the expense of biology and immunology, and found they attracted a different kind of researcher to join the firm; having the 'alkaloid' expert Thomas A. Henry at the helm of the WPRL probably influenced this.

Jowett was given the important task to formalise the procedure of considering any new product for research. He established guidelines for the supply of raw vegetable, animal and mineral materials, the policy for purchasing intermediates or manufactured articles and whether sources were limited or there were several sources. He wanted to know if there were any patents and who held them, what were the possible outlets, disease scope and geographical distribution and what would be the cost of the final product.⁶² It was important that these guidelines were adhered to when requests came in to prepare small quantities of an unlisted remedy so that the firm did not waste time pursuing

⁵⁹ R. A. O'Brien to G. E. Pearson. Pharmacological Activities of the Foundation, (16 January 1925), WF: STC S/G/49.

⁶⁰ *Ibid.*

⁶¹ R. A. O'Brien to G. E. Pearson, re. Synthetic Chemistry, STC Meeting, (16 January 1925), WF: STC S/G/49.

⁶² STC Meeting, (19 May 1925), WF: STC S/G/49.

unprofitable lines.⁶³ Jowett suggested that the STC should be extended to include members of the works, the general manager, publicity department, and representatives of the sales department.⁶⁴ He wrote that:

“Before any new substance is sent out for clinical trial it should be prepared in the Experimental department of the Works with the same approach to manufacturing conditions. We should be prepared for a small demand, if this should come along suddenly as a result of a clinical trial”.⁶⁵

While following these principles for standard therapies researchers at the WPRL continued trying to identify novel active principles from sources as diverse as Wandorobo arrow poison.⁶⁶

7.4 Burroughs Wellcome and Vitamins: Indecision and Decisions.

During the nineteenth century much work was done in France and Germany to identify the essential nutritional elements: a balanced diet of fat, protein, carbohydrate and certain minerals was required. In publications between 1901 and 1912, Gowland Hopkins showed that additional microscopic amounts of accessory food factors were required and Edward Mellanby collaborated with him to show the benefits of certain foods in rickets. Casimir Funk, a Polish investigator at the Lister Institute isolated the crystalline substance protective of neuritis (beriberi) and believing it to be an amine, coined the term *vitamine*. It was only after his colleague Jack Drummond recognised that these accessory factors were not amines that the term was changed to *vitamin* in 1920 and Drummond proposed naming the vitamins alphabetically. By 1924 Drummond was at UCH and he developed a steam distillation method to prepare vitamin A from cod liver oil, and the following year he and Rosenheim developed an assay of the vitamin, giving a purple colour with arsenic hydrochloride.⁶⁷

⁶³ STC Meeting, (3 April 1925), WF: STC S/G/49.

⁶⁴ H. A. D. Jowett to G. E. Pearson, (15 February 1925), WF: STC S/G/49.

⁶⁵ STC Meeting, (19 May 1925), WF: STC S/G/49.

⁶⁶ STC Meeting, (29 October 1926), WF: STC S/G/49.

⁶⁷ Walter Sneader, Drug Discovery: the Foundation of Modern Medicines (London: John Wiley, 1985): 227-247.

Early in 1925 Burroughs Wellcome began extracting vitamins, though they decided not to do any specific work on preparing the antiscorbutic (vitamin C) and antineuritic (vitamin A) principles and did not seem to have a clear strategy, often following the lead of other firms or external investigators. They assessed Drummond's process of preparing concentrated vitamin A from irradiated cholesterol, but were not successful.⁶⁸ Lees analysed extracts, while Trevan arranged trials, keeping samples to observe how much deteriorated on storage.⁶⁹ Burroughs Wellcome responded positively to a request for a vitamin A concentrate to be administered with sodium morrhuate for treating tuberculosis, after researchers in Japan and America had shown benefits of the combination, and several other firms were interested in sodium and ethyl morrhuate. Burroughs Wellcome then heard second hand that one of the clinicians testing ethyl morrhuate in tuberculosis had added Glaxo's Vitamin A to produce good results, and was considering a publication in the *British Medical Journal*, so they prepared a supply in case a demand ensued.⁷⁰

When vitamin A was prepared they were left with the rest of the cod liver oil starting material and sought ways of utilising this.⁷¹ Burroughs Wellcome noted that Glaxo added vitamins to their milk products.⁷² They analysed supplies of Ostelin, produced by Glaxo for vitamin A and D content, so they could challenge the claims made by Glaxo and gain a competitive advantage.⁷³ However, the Burroughs Wellcome extracts also did not contain appreciable Vitamin A.⁷⁴ After 1925 when McCollum showed that vitamin D deficiency was the cause of rickets, Harriett Chick at the Lister Institute showed that

⁶⁸ Sir Jack Drummond, Professor of Biochemistry at University College hospital was an expert in this field and became Scientific advisor to the Ministry of Food during the Second War: F. G. Young, "Jack Cecil Drummond" *Obituary Notices of Fellows of the Royal Society* 9 (1954): 99 – 129; J. C. Drummond, A. F. Watson, "The History of Foodstuffs for Vitamins" *Chemist & Druggist* 95.2 (12 November 1921).

⁶⁹ STC Meetings, (13 February 1925 and 3 April 1925), WF: STC S/G/49.

⁷⁰ T. A. Henry, STC Meeting, (8 May 1925), WF: STC S/G/49.

⁷¹ STC Meeting, (20 January 1925), WF: STC S/G/49.

⁷² R. P. T. Davenport-Hines, and Judy Slinn, *Glaxo: A History to 1962* (Cambridge: Cambridge University Press, 1992): 68-97.

⁷³ STC Meeting, (21 October 1925), WF: STC S/G/49.

⁷⁴ STC Meetings, (2 February 1926), WF: STC S/G/49.

children were cured by exposure to ultraviolet light and doctors in New York found that irradiation of foods increased vitamin D a thousand fold, but before they published their findings, Harry Steenbock of Wisconsin University took out patents on the irradiation process, while Burroughs Wellcome continued to use the steam distillation process on imported Scandinavian fish oils.⁷⁵ Burroughs Wellcome eventually also decided to prepare and market two concentrated preparations, Radio-malt and Oscodal and monthly 'propaganda' was sent to the representatives.⁷⁶ Herring and dugong oils were tested as alternative sources and found to be better than the cod oils used for Glaxo's Ostelin.⁷⁷ However, it was not long before Burroughs Wellcome decided to stop work on concentrates and turned their attention to their assays. They faced a dilemma in making concentrated vitamin preparations: "Burroughs Wellcome could not with the knowledge at their disposal, take part in the extravagant claim for concentrated preparations now being made in various quarters".⁷⁸ British Drug Houses and Glaxo had greater success than Burroughs Wellcome with the production of Vitamin D as they took up licenses to the Steenbock patents.⁷⁹ British Drug Houses were competing in this area as well and their vitamin A preparation was issued as 'avoleum' and their material was said to be free of vitamin D as it had been tested by Carr's new colorimetric test, so that the preparation will facilitate clinical examination of the therapeutic properties of vitamin A. Once again Burroughs Wellcome were two steps behind, but in 1927 the pre-irradiation substance was characterised in Germany as an already known product, ergosterol.

Having decided that it was difficult to make concentrated vitamin preparations, Burroughs Wellcome soon doubted that they had made the correct decision; they were certain that if they did not market concentrates, others less scrupulous would do so, despite their versions containing little in the way of vitamins. Jowett notified O'Brien of the BDH interest in a concentrated preparation combining both vitamins A and D noting that: "there will probably be a real demand". They had also noted Rosenheim's letter in *Nature* and

⁷⁵ C. M. Wenyon to G. E. Pearson, (17 February 1926), WF: STC S/G/49.

⁷⁶ STC Meeting, (25 February 1926), WF: STC S/G/49.

⁷⁷ STC Meeting, (29 October 1926), WF: STC S/G/49.

⁷⁸ STC Meeting, (25 February 1926), WF: STC S/G/49.

⁷⁹ R. P. T. Davenport-Hines and J. Slinn, (1992): 69-78, 240.

attempted his extraction of oil from cow liver.⁸⁰ By early 1928, the decisions had been reversed again. The STC decided to go ahead with the concentration of vitamins A, B and C. Trevan had been consulting widely with clinicians in Oxford and with Sir Charles Martin at the Lister Institute, and supplies of vitamins B and C were tested in a new analytical laboratory, organised by Jowett at Dartford.⁸¹ In addition the Experimental department began to investigate the use of marmite or yeast as a source of vitamin B.⁸²

Cod liver oil was advertised as containing not only vitamins, but also 95-98% fat, providing nourishment, and as the fat was mostly unsaturated, it was better absorbed. Malt extract was said to protect against oxidation during extraction and the product was 97.7% digestible. Representatives were told to make no references to the geographic origin of the preparations, but to emphasise the transparency, lack of odour and taste. Vitamin A concentrate and vitamin D, made artificially by irradiation were added to a range of Burroughs Wellcome products and the vitamin content was guaranteed.

In order to ensure the demand was not seasonal, the strategy was to emphasise the need in spring to counter the low sun levels, in summer to counter over exertion (vitamin B fortifies), in autumn to build up levels and in winter to provide the equivalent of sunshine.⁸³

Jowett prepared a memo outlining the scientific rationale behind the work on vitamins, which was to be the basis of a sales campaign.⁸⁴ Vitamin B was prepared from rice polishings and vitamin C from orange juice. The old Kepler malt and oil product had its vitamin A content increased ten-fold as assayed by the Drummond-Rosenheim colour test and its vitamin D increased by irradiation of ergosterol. Boots, and BDH also presented irradiated vitamin preparations Radiostol, Radiostoleum and Radio-malt at the British Industries Fair in 1930.⁸⁵

⁸⁰ STC Meeting, (11 October 1927), WF: STC S/G/49.

⁸¹ STC Meeting, (8 February 1928), WF: STC S/G/49.

⁸² G. E. Pearson to C. M. Wenyon, (5 November 1926, 20 February 1928), WF: STC S/G/49.

⁸³ STC Meeting, (31 May 1928), WF: STC S/G/49.

⁸⁴ STC Meeting, (6 June 1928), WF: STC S/G/49.

⁸⁵ "The British Industries Fair" Pharmaceutical Journal 124 (22 February 1930): 201.

Despite the external support for the products, there remained a feeling within Burroughs Wellcome that vitamin concentrates were not necessarily beneficial. Vitamin C did not keep and there was “no reason to anticipate a large clinical demand”.⁸⁶ Nevertheless the concept of giving vitamins for deficiency diseases was well established.⁸⁷ The problem was that the preparations had limited and variable vitamin content. Peters had provided a methodology to prepare vitamin B, but Burroughs Wellcome found this to be inactive.⁸⁸ In order to evaluate the need for a preparation, travelers were asked to find the demand from institutes of Tropical Medicine in India, Assam and Malay.⁸⁹ Vitamin B1 was prepared at the Tuckahoe site until a Bayer process patent was described for the synthesis. In 1929 other fish livers were found to be better than previous versions and Parke Davis & Co. made a preparation from halibut liver.

Work on vitamins continued throughout the interwar period until Vitamin E of a satisfactory concentration was made at Dartford in 1939 and passed to the Works. The initial aim was “To issue with non-committal advertising literature as the clinical value of vitamin E concentrate has not been finally established”.⁹⁰ Subsequently Hoffmann la Roche put on the market a synthetic product, ‘Ephynal’ leaving Burroughs Wellcome with the dilemma of whether to market the concentrate or arrange issue of a synthetic version. The view of the STC was that the synthetic substance possessed so many advantages over the natural concentrate but they learned from Roche that the manufacture was still experimental in Basel so they decided to await a surplus clinical supply.

7.5 Clinical Trials Arranged by Burroughs Wellcome.

⁸⁶ STC Meeting, (6 June 1928), WF: STC S/G/49.

⁸⁷ F. G. Hopkins, Lancet (1 March 1919): 363.

⁸⁸ STC Meeting, (5 October 1928), WF: STC S/G/49.

⁸⁹ STC Meeting, (8 February 1929), WF: STC S/G/49.

⁹⁰ STC Meeting, (24 March 1939), WF: STC S/G/49.

Working with the MRC on insulin had not helped firms to establish a clinical trial process for their new drugs, and the issue seems to have resurfaced as soon as the insulin development reached its conclusion. Many of the Burroughs Wellcome approaches produced novel chemicals not previously given to patients, so a key problem was how to get them tested in clinical trials. They arranged their own clinical trials whenever possible, such as with the arsenical, Stovarsol. Dr. Lees, at the WPRL, performed studies of a combination of bismuth and an arsenical in preparation for clinical trials.⁹¹ However, when the WPRL staff tried to arrange clinical tests of promising new agents with external physicians, they met with many difficulties.

They set up trials of 'Iodicin' with Dr. Cohen of Liverpool University (the future Lord Cohen of Birkenhead)⁹²: "but it is too much to expect that he will spend much time upon it. We collect in the course of time, and by painfully slow degrees clinical evidence of the value of Iodicin".⁹³ And yet when a representative was asked about alternative means of administering Iodicin and whether it was found subsequently in the urine, a further study was arranged with Cohen, as there seemed to be no alternative trialists.⁹⁴ The best chance of having clinical trials done was as a result of an ongoing collaboration in basic research. Dr. E. Charles Dodds had already participated in trials of insulin. In 1925 he described new methods of studying the effects of Burroughs Wellcome's hormonal extracts directly on uterine cells. At 25, he was the youngest Professor in London, at the Middlesex Hospital and we will see further collaborations with him in chapter 8.⁹⁵

⁹¹ STC Meetings, (21 October 1925 and 29 October 1926), WF: STC S/G/49.

⁹² G. Ansell, "Obituary, Lord Cohen of Birkenhead" Clin. Radiology (July 1978) 29(4): 370; N. Poynter, "Lord Cohen of Birkenhead (1900-1977)" Med. Hist. 22 (1) (January 1978): 90-1; J. American Medical Assoc. 238 (10 October 1977): 1672; British Medical Journal (20 August 1977): 525; Lancet (20 August 1977): 413-4; "The Liverpool of Hygiene and its Physicians" Med Hist. (16 October 1972): 310-20.

⁹³ 'CY' (a representative) to Burroughs Wellcome, (15 July 1925), discussed at STC meeting on 23 February 1926, WF: STC S/G/49.

⁹⁴ STC Meeting, (23 February 1926), WF: STC S/G/49.

⁹⁵ R. O'Brien to G. Pearson, (24 June 1925), WF: STC S/G/49; F. Dickens, "Edward Charles Dodds" Biographical Memoirs of Fellows of the Royal Society 21 (1975): 227 – 267.

By November 1926 the same products, produced by U.S. firms appeared. Trevan analysed the Swiss (CIBA) and American versions of ovarian extracts at the WPRL. Because the former was inactive, Burroughs Wellcome planned to contact the MRC to complain that the original patentee could not make it.⁹⁶ Trevan found from Dodds that the active principle, Oestrone, which he had isolated, had first been described in Germany in 1915. He also discovered that other London firms had already begun working on this problem. O'Brien told Pearson that he intended to visit several medical conferences in London with the aim of discussing ovarian and parathyroid hormone preparations and the new methods of testing them. When Trevan and Jowett next met with Dodds, he requested hundredweight quantities of the hormonal preparation, which he then tested for Burroughs Wellcome in patients. However in this case, Burroughs Wellcome was slow in developing the preparation when they had an offer of clinical trials.

Burroughs Wellcome managed to get analgesics and antiseptics tested by Dr. E. A. McMahan at the Royal Infirmary in Edinburgh.⁹⁷ Yet when Trevan arranged a study of benzoyl ephedrine as a local anaesthetic at Guy's Hospital, he failed to receive a single report.⁹⁸ Some small studies gave results that did not support the intended use of novel medicines. Henry arranged a study of ascaridole in children in Darlington but it was unsuccessful despite the parent chenopodium oil (oil of American wormseed)⁹⁹ being used successfully in Germany and the United States, and appearing to work well in animal experiments performed by Dr. Laidlaw at Mill Hill. Further studies in dogs were planned by O'Brien at Beckenham to resolve this and the data was eventually published.¹⁰⁰ When plans for the Therapeutic Trials Committee were finally announced, members of the STC met and discussed which of their products would be forwarded and the outcome of these deliberations will be discussed in the next chapter. It was recommended that the

⁹⁶ R. O'Brien to H. A. D. Jowett, (26 May 1925), WF: STC S/G/49.

⁹⁷ STC Meeting, (28 October 1926), WF: STC S/G/49.

⁹⁸ STC Meeting, (5 November 1926), WF: STC S/G/49.

⁹⁹ Chenopodium oil as listed in the B. P. of 1948 was an oil distillate, which had to contain at least 65% w/v of ascaridole, British Pharmacopoeia (London: Constable, 1948): 372-3.

¹⁰⁰ Chemistry and Industry (29 October 1926): 803.

Chemotherapy Committee (sic) be asked to undertake a clinical comparison of the various pure digitalis glycosides available at Dartford, and Trevan wanted to investigate the use of ascaridole as a general antihelmintic in children. They were to be also offered supplies of harmine for post-encephalitis. The STC suggested that in future further substances might be sent for trial such as ouabain and concentrated oily or ester solutions of avenyl or neo-avenyl, both anti-syphilitics. Full reports of ergotoxine ethane sulphonate, digoxin and digitalinum verum were sent to the ABCM for the TTC.¹⁰¹ Thus the proposed establishment of the TTC offered the chance for Burroughs Wellcome to re-evaluate their policies of collaborating with external agencies. In doing so they were clear that this was only appropriate in order to secure clinical trials, which had been their major failing since 1921.

7.6 Tropical Diseases- a Case Study from Laboratory to Clinic.

The MRC and Burroughs Wellcome had a common interest in the support of Tropical Medicine. Henry Wellcome had established The Wellcome Tropical Laboratories in Sudan in 1902, while the MRC supported research in tropical medicine at Liverpool and at the London School of Tropical Medicine.¹⁰² These links were cemented further when Sir Andrew Balfour left Burroughs Wellcome in 1923 to become Director of the London School of Hygiene and Tropical Medicine when it was formally established the following year.¹⁰³ In 1924 the much-traveled Charles Morley Wenyon succeeded Balfour as Director in Chief of the WBSR and continued to receive visitors from all over the world as he maintained an independent research philosophy without the encroachment of business interests. Wenyon served on various committees including the Royal Society and the Tropical Research Committee of the MRC and the Colonial Medicine Research Committee

¹⁰¹ STC Meeting, (27 March 1931), WF: STC S/G/49.

¹⁰² E. B. Worthington, Science in Africa: a Review of Scientific Research Relating to Tropical and Southern Africa (London: Oxford University Press, 1938): 463-9; M. Worboys, "Science and British Colonial Imperialism, 1895- 1940" (University of Sussex, D. Phil thesis, 1979); D. Fisher, "Rockefeller Philanthropy and the British Empire and the Creation of the LSHTM" History of Education 7 (1978): 129-143.

¹⁰³ "A. Balfour, Obituary" British Medical Journal (7 February 1931): 245-6; H. Parrish, "The Wellcome Research Labs and Immunology", WF: 85:20/2; "London School of Hygiene and Tropical Medicine: a Child of my Parents" Med. Hist. 35 (91) 385-408.

that was set up in 1926 between the MRC and Colonial Office, immediately following the Imperial Conference.¹⁰⁴

One of the concerns of the Colonial Office was the re-emergence of Germany as a force in pharmaceuticals, and a special concern was the progress made by Germany in developing drugs for tropical infectious diseases. Bayer 205 or tryparsamide was a specific therapy for treating trypanosomal infections. Just as Britain had relied on Germany for antiseptics, anaesthetics, painkillers and Salvarsan in the 1914, a potential concern was the reliance now on Germany for antimalarials should such a political situation arise again.

When the STC was established in 1925 there were already some ‘Tropical Medicines’ on clinical trial, mostly overseas. Henry pointed out to the DSIR that Burroughs Wellcome was already collaborating with the schools of Tropical Medicine in England and India, with the medical department of Bristol University, and with other medicinal institutes in Britain, China, Brazil and Formosa.¹⁰⁵ The work on antimalarial drugs is a good example of the commitment of Burroughs Wellcome to produce novel chemicals, to evaluate them extensively in animal tests and to test them in clinical trials, being prepared to modify the products if results were not as desired. For two years stibamine glucoside, (Stibosan) an organic antimonial underwent clinical trials with very successful results in kala-azar, a common form of leishmaniasis, a disease which affects millions of children, which previously had a mortality of 70%. Before it was given to patients, the drug was tested for 6 months in hamsters infected with kala-azar. Nevertheless some batches still failed further toxicity tests in mice.¹⁰⁶ The results of treating kala-azar with Stibosan were compared against those of Neostam (stibamine glucoside).¹⁰⁷ Burroughs Wellcome remained cautious while they still regarded the drug

¹⁰⁴ C. A. Hoare, “Charles Morley Wenyon” Obituary Notices of Fellows of the Royal Society 6 (1949): 627-42.

¹⁰⁵ T. A. Henry to A. W. Crossley, (7 July 1925), WF: STC S/G/49.

¹⁰⁶ STC Meetings, (13 February 1925, 21 October 1925; 25 February 1926; 23 March 1928) WF: STC S/G/49.

¹⁰⁷ Industrial Journal of Medical Research 14 (1926): 263; (21 October 1925, and 5 November 1926), WF: STC S/G/49.

as under trial.¹⁰⁸ Before its release it was tested in thousands of mice and batches were only released if they passed tests on at least 120 mice. Wenyon established further trials of stibamine glucoside for treating worm infestations and lymphogranulomatous disease and for sleeping sickness in Cairo and Natal, several centres in India and in the Belgian Congo but the tolerated dose no better than the old tartar emetic.¹⁰⁹ Another antimonial referred to as Sb 150/136 was sent to the same clinic in Natal and to two further centres in South Africa to treat bilharzias.¹¹⁰ Neil Hamilton Fairley¹¹¹ tested it in schistosomiasis,¹¹² and Wenyon discussed the results of animal tests with a further stibonate derivative.¹¹³ Dr. G. Carmichael Low of University College Hospital, London published a favourable account of stibamine and as a result Burroughs Wellcome began advertising and made “strenuous efforts to get a product of low toxicity”.¹¹⁴

Neostam was difficult to manufacture, but Jowett made enough to supply Dr. Edward Hindle of the kala-azar committee.¹¹⁵ By 1928 there were sufficient stocks to advertise the product.¹¹⁶ Still, there were occasional unexpected failures of a batch in toxicity tests.¹¹⁷ Eventually the problems became too much and it was decided not to renew the patent of Neostam. Though there remained a demand from India and China,

¹⁰⁸ Leonard. G. Goodwin, “Pentostam (sodium stibogluconate); a 50-Year Personal Reminiscence” Trans. Soc. Trop. Med. Hyg. 89.3 (May-June 1995): 339-41. Goodwin joined the Wellcome laboratories in 1939 and became Director of the Tropical Laboratory from 1958-63.

¹⁰⁹ Tartar emetic or antimony potassium tartrate had been used since 1906. It was very effective when given intravenously but could also be highly toxic. STC Meetings, (2 February 1926), (28 October 1926), (24 May 1934) and (7 October 19), WF: STC S/G/49.

¹¹⁰ STC Meeting, (25 May 1934), WF: STC S/G/49.

¹¹¹ Sir John Boyd, “Neil Hamilton Fairley” Biographical Memoirs of Fellows of the Royal Society 12 (1966): 123-145.

¹¹² STC Meeting, (21 October 1925 and 29 October 1926) WF: STC S/G/49.

¹¹³ STC Meetings, (12 July 1935 and 13 March 1936), WF: STC S/G/49.

¹¹⁴ STC Meeting, (25 February 1926), WF: STC S/G/49.

¹¹⁵ STC Meeting, (31 May 1927), WF: STC S/G/49.

¹¹⁶ STC Meeting, (20 February 1928), WF: STC S/G/49.

¹¹⁷ STC Meeting, (23 March 1928), WF: STC S/G/49.

sales were small despite some favourable clinical reports. In its place the firm began to test Brahmachari's urea stibamine¹¹⁸ and von Heyden's neostibosan from India, neither of which were available in Europe.¹¹⁹

Despite its problems, Trevan was still testing Neostam in 1936 when he evaluated its stability in solution.¹²⁰ It was then tested in a new form, for light and temperature stability and samples were sent to China for evaluation.¹²¹ Neostam formulated with glucose was less toxic, but then Burroughs Wellcome became aware of a new German preparation, Bayer 561 that threatened to compete.¹²² Much of the renewed interest in tropical medicine came from the German demonstration of the activity of Bayer 205 in trypanosomal infections; Wenyon arranged for tryparsamide or Bayer 205 to be tested within Burroughs Wellcome.¹²³ Morgan at the DSIR evaluated aryl-thioarsinites and allied arsenocompounds for trypanosomiasis at the Chemical Research Laboratories and a series of arsonic acids were evaluated in collaboration with Warrington-Yorke in Liverpool and with Prof. Robert Robinson. In 1937 Trevan re-examined some arylguanidines for trypanocidal activity, having previously evaluated them in 1926-7. Smith met with representatives of the ABCM to arrange for a trial.¹²⁴

Because drugs based upon antimony were effective, a Dr Muir also evaluated two new drugs based on mercury for leprosy in Calcutta, India.¹²⁵ Having completed one leprosy study, Muir asked Burroughs Wellcome for a supply of 'Dr. Blair Bell's lead

¹¹⁸ U. N. Brahmachari "Chemotherapy of Antimonial Compounds in Kala-azar Infection part IV Further Observations on the Therapeutic Values of Urea Stibamine" (1922), Indian J Med Res. (January 1989) 89: 393-404; STC Meeting, (2 February 1926) WF: STC S/G/49.

¹¹⁹ STC Meeting, (8 May 1929), WF: STC S/G/49.

¹²⁰ STC Meeting, (29 May 1936), WF: STC S/G/49.

¹²¹ STC Meeting, (22 January 1937), WF: STC S/G/49.

¹²² STC Meeting, (19 November 1937), WF: STC S/G/49.

¹²³ C. M. Wenyon to G. E. Pearson, (17 February 1926), WF: STC S/G/49; Dr. Dressel and Bayer 205, Laboratory Notes etc. 1914-1923, Wellcome Institute, GC/62; British Medical Journal (16 July 1923): 87; Tryparsamide was available from the Rockefeller Institute for licensing, WF: STC S/G/49, (23 February 1926).

¹²⁴ STC Meeting, (13 May 1938), WF: STC S/G/49.

¹²⁵ STC Meeting, (2 February 1926), WF: STC S/G/49.

preparation' or colloidal lead "with the understanding that the risk of taking it was to be his own responsibility", and the STC suggested that he be offered some of the gold compound, sanochrysin for trial, and later copper derivatives including copper glycine, sodium copper citrate, potassium copper cyanide, neo-avenyl and¹²⁶ the rare metal, Tellurium.¹²⁷ Having found a willing trialist Burroughs Wellcome were clearly keen to use Muir to the full. The new benzoylated cocaine anaesthetic derivatives and organic mercurials were tested in syphilis, tuberculosis and leprosy.¹²⁸ At the STC meeting on 12 July 1935 Henry raised the question of testing methylene blue and also vitamin products for leprosy.

Drugs provided for use in tropical climates were tested for stability at a higher temperature, as when Trevan sent ephedrine to India and Baghdad.¹²⁹ Trevan also tested the effects of keeping neo-avenyl over a long period. The WCRL also evaluated materials sent back from the Tropics such as *Alstonia congensis* bark received from the Government of Uganda through the Imperial Institute for malaria. There were so many possibilities that Burroughs Wellcome did not have enough facilities to perform chemistry work on the antimalarials they wished to test.¹³⁰ However, through their endeavours in tropical medicine, Burroughs Wellcome circumvented many of the problems of having drugs tested clinically in Britain.

The firm showed particular interest in antimalarials following the success that Bayer had with Atebrin (mepacrine) discovered in 1930. Previously there had been limited success with antimalarials, the only synthetics to show promise being methylene blue and arsphenamine, neither of which were as active as natural quinine. William Roehl of Bayer developed techniques for testing potential drugs in canaries and in insane patients. Promising leads were chemically modified until after testing several hundred compounds, plasmoquine was tested clinically and marketed, when it was shown that it acted in a different way to quinine and improved the efficacy of the latter when given in

¹²⁶ STC Meeting, (5 November 1926), WF: STC S/G/49.

¹²⁷ STC Meeting, (18 February 1938), WF: STC S/G/49.

¹²⁸ STC Meeting, (20 January 1925), WF: STC S/G/49.

¹²⁹ STC Meeting, (29 October 1926), WF: STC S/G/49.

¹³⁰ STC Meeting, (5 November 1926), WF: STC S/G/49.

combination.¹³¹ Dr. Green of Malaya suggested that Burroughs Wellcome should prepare a Tabloid form of Bayer's (IG Farben) promising Atebrin.¹³²

The MRC and DSIR began research on antimalarials in 1929 and Barger in Edinburgh and Robert Robinson at UCH elucidated the structure of Plasmoquine before IG Farben published it. Robinson had already synthesized harmine in 1927. Nothing came directly from the early antimalarial work in 1929 despite the synthesis of 120 compounds, and indeed it was Bayer who discovered further antimalarials, the most active of which was mepacrine or Atebrin, on which publications appeared from 1931. The Secretary of the Chemotherapy Committee told Thomas Henry that the MRC proposed concentrating the testing of antimalarials in Cambridge with Dr. Keilin, the David Quick Professor of Biology at the Molteno Institute in Cambridge.¹³³ Wenyon discussed clinical tests with Col. James, who had first tested harmine and harmaline and found them useless; he then evaluated hydroquinine.¹³⁴

From 1931 new medicines suitable for testing within Britain were discussed with the TTC, although only tropical medicines, beyond 1931 have been described in this section. The most important chemotherapeutics developed in Britain were the sulphonamides – these are discussed in the next chapter.

Over the next several years Burroughs Wellcome collaborated with several external scientists to try to develop antimalarials and other tropical medicines to avoid further reliance on Germany. However in May 1934 they resolved not to do any further work on already patented compounds such as Atebrin and Plasmoquin.¹³⁵ At the NIMR, Harold King performed tests to establish chemically why quinine and other cinchona alkaloids were

¹³¹ W. Sneader, (1985): 268-75.

¹³² STC Meeting, (14 Feb 1934), WF: STC S/G/49.

¹³³ Mark W. Weatherall, Gentlemen, Scientists, and Doctors: Medicine at Cambridge 1800-1940 (Cambridge: Boydell Press, 2000).

¹³⁴ STC Meeting, (28 March 1930), WF: STC S/G/49.

¹³⁵ STC Meeting, (19 May 1934), WF: STC S/G/49.

antimalarial.¹³⁶ Ethylapoquinine and apoquinine and chinchona alkaloids were examined at the WCRL and WPRL and in clinical trials.¹³⁷

Iodo-Bismutide of quinine was considered for Australia where demand for bismuth metal preparations was decreasing. This new product could be given long term without stomatitis and the Wassermann test was negative earlier.¹³⁸ Henry asked Trevan for references on the action of dihydroquinine, dihydroquinidine, and epiquinine in order to contact the Therapeutic Trials Committee about trials. Prof. Robert Robinson moved to the Dyson Perrins laboratory in Oxford in 1930 and prepared further analogues of Plasmoquine and Atebrin. C. H. Browning and colleagues in Glasgow and Dr E. E. Turner at Bedford College for Women prepared further antimalarials.

Both quinidine sulphate and dihydroquinidine sulphate were sent to Dr Wayne in Sheffield for testing; a Dutch group had shown that it was impurities of the latter that were active. Henry felt that “Dutch evidence should provide a sufficient foundation in this case for Burroughs Wellcome to proceed without waiting for trials by the TTC”.¹³⁹

It should be clear from the previous account that from the end of the insulin work until the outbreak of the Second War, Burroughs Wellcome had a wide range of products in development. The STC continued to debate whether to remain a ‘Universal provider,’ or whether to concentrate on synthetics, biologicals, vitamins or tropical medicine.

Probably the scale of their development work has been previously underestimated because many of their drugs were aimed at tropical medicine, or were hormonal or vitamin preparations that have since been replaced. I have tried to show how the clinicians, Trevan and Wenyon took a lead role in establishing clinical tests, though with limited success in the UK until the TTC was established. Collaborations with the Chemotherapy Committee were more successful but primarily regarding overseas studies in tropical diseases.

¹³⁶ Sir Charles Harrington, “Harold King” (1956): 161.

¹³⁷ J. A. Goodson, T. A. Henry, J. W. S. MacFie, “The Action of the Chinchona and Certain Other Alkaloids in Bird Malaria” Biochemical Journal (1930): 874-90; STC Meeting, (13 March 1936), WF: STC S/G/49.

¹³⁸ STC Meeting, (28 May 1936), WF: STC S/G/49.

¹³⁹ STC Meeting, (19 November 1937), WF: STC S/G/49.

Burroughs Wellcome continued to release a stream of new products from the establishment of the STC until the outbreak of World War Two. A total of 62 separate product launches took place in the period 1925 to 1939 though few of these were synthetics. These included various formulations of insulin, hormone extracts, purified vitamins, and inorganic preparations, together with purified alkaloids

At the start of 1937 there was an important request to Burroughs Wellcome from the War Office for a list of possible British substitutes for foreign synthetic drugs. The Government had clearly learned a lesson from the problems faced at the outbreak of the First World War and were making early preparations in case of further hostilities. Burroughs Wellcome reviewed the list at the STC of 22 January 1937 and broke the list into classes of drugs and the equivalent that Burroughs Wellcome could offer.¹⁴⁰

The government was interested in analeptics of which Burroughs Wellcome could supply Coramine and Icoral; Local anaesthetics (Percaine); Pyelographic substances (Perabrodi; Hypnotics (Evipan-Na, Avertin, Pentothal- Na); Antimalarials (Atebrin and Plasmoquine). Research was ongoing for new analeptics, hypnotics and antimalarials though it was not possible to say that they could prepare commercially practicable substitutes. They commented that: “all drugs in the list are patented and manufacture would no doubt be taken up if licenses to manufacture could be secured by negotiation, with the patentees or if patentees were compelled by appropriate legislation to grant licenses. Such a procedure would probably be too slow to be useful. They made it clear however that it was most desirable that in the event of War, manufacturers should have had experience in the production of essential drugs, which are at present imported. It seemed clear that the War Office would prefer to deal with a single organisation in this matter and the Committee (STC) are of the opinion that Messrs. B. Wellcome & Co. might suggest that the War Office should provide at once a ‘shadow’ factory at Dartford with a small staff of chemists to work out all the processes for the manufacture”. Burroughs Wellcome further suggested that if this was not acceptable, the National Chemical Laboratory at Teddington engaged in long-term research, was therefore technically capable and could be placed at the disposal of manufacturers through the ABCM. This was a development of a procedure already put in operation for an entirely new drug recently discovered. Either would be quicker than a third

¹⁴⁰ STC Meeting, (22 January 1937), WF: STC S/G/49.

alternative which would be more comprehensive. Several official organisations are already concerned with this matter viz. the MRC, the TTC, the Chemotherapy section of the National Chemical Laboratory at Teddington. These three bodies might in consultation decide what imported drugs are really essential, not only for the War Office, but for the country as a whole. When this preliminary work has been done consultations might be extended to the ABCM to decide how manufacture of these essential drugs could best be undertaken.¹⁴¹ The War Office replied that Pentothal could probably be supplied by BDH.

At the STC of 29 September 1939, the STC considered the list of 40 German drugs and decided which to concentrate on with a view to manufacture over the next 3 months.¹⁴² There were also some that were not considered worth manufacturing.¹⁴³

Regarding antimalarials, Atebrin was to be left to ICI but Plasmoquine to could be made if supplies of 8-aminoquinoline were available and some drugs would only be attempted if raw materials could be obtained. Ephedrine could be made synthetically if the natural base was obtainable or it could be fermented with external help. Phenothiazine could be made if supplies were available from ICI. Phaodorm and Uroselectan needed further work at the WCRL and Burroughs Wellcome planned to speak to Corey Mann regarding preparation of Solganol B.

Robinson collaborated with several pharmaceutical firms, having joined the ICI research council as early as 1927.¹⁴⁴ He worked on antimalarials with Pyman of Boots in the lead up to the War and collaborated with Hoffman la Roche and Sandoz, and with

¹⁴¹ C. M. Wenyon to AMD3, War Office, STC Meeting, (9 February 1937), WF: STC S/G/49.

¹⁴² These were adrenaline, arecoline, Atebrin, Avertin, cardiazole, Doryl (carbaminoylcholine chloride; or intermediates to prepare it), Epanutin, Ephedrine synthetic, Eumydrine, Evipan, Fouadin, Hepaprin, Neostibosan, Pantocaine (Decicaine), Phanodorm, phenobarbitone, phenothiazine, Plasmoquine, progesterone, Prominal, Solganol, Solganol B, Solustibosan, Tutocaine, Uroselectan, STC Meeting, (29 September 1939), WF: STC S/G/49.

¹⁴³ Adalin (carbromalium BP), ascorbic acid, Butolan, Icoral, Lopion, Moogrol iodinised, Oestrodinol, Oestrone, Pentothal (Abbott), Perabrodil, Rivanol, Surfén, Zephiran, *ibid.*

¹⁴⁴ Trevor I Williams, Robert Robinson, Chemist Extraordinary (Oxford: Clarendon Press, 1990): 95-6, 104-5. Robinson continued to consult for I.C.I. until he retired in 1955.

Kemball Bishop of Bromley from 1938 to make citric acid and tartaric acid by fermentation.

7.7 Conclusions.

Burroughs Wellcome underwent profound changes in the interwar period and lost ground on its major competitors in Britain, particularly British Drug Houses. This was because of the significant staff losses, partly due to a policy of following medical advances rather than focusing on their own research, and partly due to their insularity. Henry Wellcome's focused more on his travels and collecting medical artifacts. However both Henry Wellcome and H. A. D. Jowett died in 1936.¹⁴⁵ Morale, like wages was low and this worsened after the crippling duties payable after Wellcome's death in 1936.¹⁴⁶ George Pearson, who had been General Manager since 1905, and Assistant Governing Director from 1924, took over as Governing Director - his iron discipline and unimaginative and overcautious nature prevailed, although he was a "very distinguished member of the (Pharmaceutical) Society" and was also an active member of the Society of the Chemical Industry.¹⁴⁷ He retired in 1940 after 45 years service and in 1941 Trevan became head of the WPRL succeeding R. A. O'Brien, and A. C. White took over his role as head of the pharmacology department.¹⁴⁸

Dale later wrote to Elliott: "There is still much to be done to make good the long years of neglect by Wellcome and by whom he appointed and left in charge and to catch up with missed opportunities".¹⁴⁹ Professor Elliott thought the company "ought to be emphasising research." In 1938 he wrote: "special men and especially (Sir) Andrew Balfour were always eager to keep themselves and their Bureau (of Scientific Research)

¹⁴⁵ G. H. Lyall, H. H. Dale, L. C. Bullock, M. Prince, T. R. Elliott, "The Will of the Late Sir Henry Wellcome" The Lancet (1937): 289.

¹⁴⁶ A. R. Hall, B. A. Bembridge, Physic and Philanthropy: the Wellcome Trust 1936-86 (Cambridge: Cambridge University Press, 1986).

¹⁴⁷ "Obituary, G. E. Pearson" Chemist & Druggist 155.2 (7 April 1951): 433; Extracts from a pharmacy journal in WF: E2 PF; "Obituary" The Times (31 March 1951); "Obituary" Pharmaceutical Journal 166 (7 April 1951): 27-28.

¹⁴⁸ J. H. Gaddum, "John William Trevan" (1957): 275.

¹⁴⁹ H. H. Dale to T. R. Elliott, (10 December 1957), in H. Dale Archives at the Royal Society Memoirs, HD 36/4.26.

dissociated in the public eye from the commercial side”; These were “undistinguished years”.¹⁵⁰ However it was not all bleak and some progress was made. I have demonstrated the significant efforts that went into developing synthetic drugs. Burroughs Wellcome’s approach could be classed as a ‘fast follower’. They kept a close watch on the medical literature and sought feedback from the medical profession and improved upon German drugs, particularly if a valid patent was not in place. The drugs produced were more active, more soluble, with less side effects or were easier to administer. The modified drugs were patented where possible, the manufacture of some were simply copied and produced under license. The advances in their chemical understanding to achieve this should not be underestimated, but Burroughs Wellcome never threatened to establish empiric research on the German scale. By preparing a series of similar drugs, observations were made on structure-function activities. Clinical trials were established, though it was more difficult in the Britain than in the tropics, and many advances were aimed at Tropical Medicine, always an interest of Wellcome and Wenyon, and of increasing strategic importance as the Second World War threatened. By the end of this period chemical laboratory facilities had expanded significantly and so to had the manufacturing capacity of firms such as Burroughs Wellcome, Boots, Glaxo, Allen & Hanbury’s and British Drug Houses.

¹⁵⁰ D. J. Jeremy (ed.), “H. S. Wellcome” Dictionary of Business Biography 6 (London: Butterworths, 1986): 36.

CHAPTER EIGHT: The Therapeutic Trials Committee of the MRC.

8.1 Introduction.

In previous chapters I have shown that a significant problem for the British pharmaceutical firms had in having their novel drugs tested clinically. Chapter 6 emphasised repeated ABCM campaigns to the MRC from 1922 to 1930 for a means of performing clinical trials of pharmaceutical firms' drugs, while the MRC tested insulin and other drugs from abroad. The MRC tested drugs during the Great War (chapter 4) and then coordinated biological standardisation of drugs (chapter 5). Chapter 7 exemplified the difficulties that Burroughs Wellcome encountered in having new drugs tested in Britain, most of their successful clinical studies being in tropical medicine centres overseas.

The MRC had difficulties in collating clinical responses to Salvarsan, due to the variability of the drug supplied, and the circumstances of wartime record keeping. In the second Salvarsan Committee from 1918, the MRC clearly defended British preparations in comparison with German competitors, to ensure British production of Salvarsan. It was the same with insulin, excluding competitive threats from Eli Lilly of America and Leo of Denmark. Stimulation of the British ethical pharmaceutical industry went hand in hand with the MRC aim of regulating drug quality and evolving a system of clinical research in Britain. They were more comfortable when a drug such as insulin was standardised and evaluated in the laboratory, and glucose levels were measured as a signal of efficacy in clinical studies in their own research centres.

Liebenau argued that the development of insulin was symbolic of the changing industry-government relations and part of an MRC aim to regulate the British pharmaceutical industry.¹ Valier also referred to this as “symbolic of the changing relationship between government and industry” and suggested that it was the wartime shortages of drugs and the unique opportunity of insulin that led the MRC “to abandon its non-interventionist position with respect to industry, and take on a regulatory and supportive role”.² However, she remarks that this “new ethos of interventionism was first

¹ Jonathan Liebenau, “The MRC and the Pharmaceutical Industry: The Model of Insulin” in Joan Austoker and Linda Bryder (eds.), Historical Perspectives on the Role of the MRC (Oxford: Oxford University Press, 1989): 163-80.

² Helen K. Valier. “The Politics of Scientific Medicine in Manchester c 1900 – 1960”: 148 (University of Manchester: PhD. Thesis, 2002).

employed in relation to insulin,” whereas I would emphasise further that this had already begun in depth with Salvarsan and was part of a more general campaign to ensure that only scientifically proven drugs were marketed.

Whereas insulin may have provided a good model for further MRC - led studies, it did not provide a good model for British pharmaceutical firms to get their own novel, sometimes synthetic products tested. Indeed insulin pre-occupied both the British pharmaceutical industry and the MRC for several years, and seems to have inhibited the testing of other drugs. Moreover, the MRC and industry approached clinical testing from different perspectives. The MRC felt that their control of the insulin patents prevented ‘commercialisation’ of insulin.³ The British firms on the other hand wanted their drugs tested so they could commercialise them.

British companies clearly had difficulty in arranging clinical trials of their own products, as previously highlighted by George Pearson of Burroughs Wellcome in 1922. The establishment of the MRC Chemotherapy Committee in 1927 did not help the pharmaceutical firms as it focused on collaboration with the DSIR and on tropical medicines, which were among the few drugs that Burroughs Wellcome managed to get tested in the colonies as described in chapter 7.⁴ In the 1920’s, British firms that could not get their new products clinically tested, depended on whatever affidavits they could get. The following example of trichlorophenylmethyliodosalicyl (more widely known as the antiseptic T.C.P) from British Alkaloids Limited was typical:

“The preparation is testified to by many members of the medical profession as being non- toxic and analgesic and a useful application as a gargle or spray in affections of the nose or throat and as a lotion in wounds and scalds as well as in eczema, chilblains and haemorrhoids”.⁵

This above case is however, unusual, as the drug succeeded due to advertising to the public, whereas a drug marketed to physicians would have failed without supporting publications.

³ “Patents and Designs Bill” *British Medical Journal* (11 June 1931): 1107.

⁴ The Chemotherapy Committee, established jointly with the DSIR included Thomas Henry of Burroughs Wellcome, Frank Pyman of Boots and J. Davidson Pratt, the secretary of the ABCM: Joan Austoker and Linda Bryder, “The National Institute for Medical Research” in Joan Austoker and Linda Bryder (eds.), (1989): 45.

⁵ “TCP” *Lancet* (11 January 1930): 114.

This chapter explores the experiences of the Therapeutic Trials Committee (TTC) from its establishment in 1931, both from the MRC perspective, and from the viewpoint of the pharmaceutical firms, and especially Burroughs Wellcome. It has been possible to gain an understanding of the functioning of the Therapeutic Trials Committee from TTC Minutes, MRC Minutes, the personal correspondence of the committee members, Elliott, Dale, and Green,⁶ TTC files on individual drugs, published reports, the British Pharmacopoeia, company histories and primary sources at Burroughs Wellcome, particularly the Scientific & Technical Committee (STC) minutes. A synthesis of these diverse sources allowed me to follow the progress of most drugs examined, both from the TTC perspective and that of the company providing the drug, and thereby giving an insight into the state of British drug development, whereas previous research has focussed only on the major drugs.

This chapter examines the types of compounds put forward, and assesses which British and foreign firms were most active in providing drugs for the TTC. It gives an insight into how the TTC selected drugs for clinical trial and how they organised the trials. Three themes emerge, the differing emphasis placed on synthetic chemistry between firms; the continuity of testing within given therapeutic fields, both in terms of the clinical investigators and the evaluations performed; and the failure of a high proportion of the TTC studies. The example of organotherapy shows how the TTC pursued the MRC interest in this therapeutic approach, which initially relied on biological standardisation of the drugs, but subsequently extracts were replaced by synthetic versions. Notable also was the change around 1935, as a result of the Bayer's discovery of Prontosil, when the realisation that the active ingredient was not patent-protected led to more firms adopting synthetic drugs and also to their increased acceptance by physicians, keen to obtain samples of these powerful new therapies.

The pressure from the ABCM for the proposed Therapeutic Trials Committee paid off in 1931 at a time of increasing Government receptiveness to the need to exclude ineffective medicines, and to give precedence to the scientifically validated drugs of ethical

⁶ F. H. K. Green was the Secretary of the TTC. "Francis Henry K. Green, 1900-1977 Obituary" *Lancet* (19 November 1977): 1067.

pharmaceutical manufacturers.⁷ Attempts to control of the claims made by manufacturers, seen first in the campaigns against patent medicine manufacturers, and captured in the Therapeutic Substances Acts of 1925 and 1927, continued the trend of Government intervention, requiring standardisation of the potency of a new era of biological drugs, including vitamins, organotherapy extracts, hormones, antitoxins and vaccines. This had the impact of driving ever more complex methods of manufacture and control.

The TTC was established at a time of increasing drug legislation, in the same week as the first draft of a further revision of the Therapeutic Substances Regulations was published.⁸ The 'Proprietary Medicines Bill' in May 1931 continued the fight against false testimonials by patent medicine manufacturers.⁹ The Consumers Council Bill relating to the pricing of drugs, and especially imports, was also before Parliament, and the Pharmacy and Poisons Bill (concerning licensing of pharmacists) was in the committee stage in the Lords, having been introduced on 17 December 1930.¹⁰

The TTC was also established during a period of poor trade balances, unemployment, increased nationalism and threats of tariffs. By 19 September 1931 foreign credits were exhausted and the gold standard was abandoned.¹¹ In the midst of the economic uncertainty, with the pound uncompetitive for exports, the Government fell. The resulting devaluation and high fixed exchange rate led to lower export prices, and raised the price of imports. The medical literature called for a strong British Pharmaceutical Industry and some papers were simply signed 'Anti-foreign'. J. Davidson Pratt of the ABCM

⁷ The MRC announced a meeting with representatives of the ABCM: (16 January 1931), MRC Minutes 1523/15: 4.

⁸ The Therapeutic Substances Regulations were issued on 25 July 1931 and presented to the House of Commons on 14 September; "National Economy Bill" British Medical Journal (19 September 1931): 551.

⁹ The War postponed legislation from the Select Committee report of 1914 and a Proprietary Medicines Bill introduced in 1920 was withdrawn in the House of Lords: "Medical Notes in Parliament (Proprietary Medicines Bill)" British Medical Journal (25 July 1931): 168; "National Health Insurance" British Medical Journal (28 November 1931): 1016; T. Hynes, "The Patent Medicine Stamp Duty; its Origin and History" British Medical Journal (9 January 1932): 32-33.

¹⁰ "Consumers Council Bill" British Medical Journal (4 April 1931): 607; "Poisons and Pharmacy Bill" British Medical Journal (4 April 1931): 607.

considered that it was the most difficult period ever faced, with a trade deficit of £9m. He called for further protection for fine chemicals, as given by the Dyestuffs Act for the £23 million of dyes imported into the Empire.¹² The Pure Food Council, British Medical Association, Pharmaceutical Society and Proprietary Medicines Manufacturers met to discuss the need for a registry of proprietary drugs, medicines, and methods of treatment.¹³ However, in the growing economic gloom, the possibility of enforced regulation of drugs was dropped to allow the whole session of Parliament to be devoted to the National Economy Bill.¹⁴ Thus, the collaboration of representatives of the industry and the MRC was part of much broader encouragement of the infant British Industry and more followed such as the Import Duties Bill introduced by Chamberlain in February 1932.¹⁵

In contrast to increasing government influence on the claims, strength and variability of medicines, some influential clinicians such as Lord Dawson, President of the Royal College of Physicians, strongly advocated that Whitehall should play no part in drug regulations, leaving doctors to prescribe, as they wanted. The quarrels that Lord Dawson and Lord Moynihan, Presidents of the Royal College of Physicians and of Surgeons respectively, had with the MRC were documented previously. Moynihan did not think MRC researchers had enough clinical judgment skills. However, Fletcher at the MRC insisted that the TTC did not aim to tell doctors which therapies to use, only to test novel drugs to see if they had clinical utility and that they were safe to prescribe. Whether they were then prescribed was a matter for the doctors themselves and the firms promoting the

¹¹ “The Dyestuffs Act” *Chemist & Druggist* 113.2 (18 October 1930): 475; “ABC: Dyes and Textiles”(18 October 1930): 486; A. J. P. Taylor, *English History 1914 - 1945* (Oxford: Clarendon Press, 1988): 283-97.

¹² J. Davidson Pratt, *Chemist & Druggist* 114.2 (31 October 1931): 551; *Chemist & Druggist* 114.2 (26 December 1931): 757. The growth in Chemical industries since the War was in the ratio U.S. 6.3, Germany 5.2, and France 4.8 compared with Britain 2.1 and world trade rose from £11.5 m in 1913 to £23 m in 1928; L. F. Haber, *The Chemical Industry 1900 – 1930: International Growth and Technological Change* (Oxford: Clarendon Press, 1971): 1, 7.

¹³ ABCM: *British Chemicals: their Manufacturers and Uses* (London: ABCM, 1927, 1929, 1931).

¹⁴ A. J. P. Taylor, (1988): 321-50.

¹⁵ A. J. P. Taylor, (1988): 330.

products. In an attempt to bring the Royal Colleges closer to their line of thinking, Fletcher co-opted Lord Dawson of Penn onto the main committee of the Medical Research Council.

8.2 The Therapeutic Trials Committee 1931-1939.

The Therapeutic Trials Committee has received limited attention previously. Whether this is due to the number and complexity of drugs tested or the state of the files is not clear.¹⁶ The TTC comprised mostly doctors that had been supported by the MRC throughout the 1920's. The Chairman was Professor Thomas Renton Elliott of University College Hospital, London. His close friend, Henry Dale, the Director of the National Institute of Medical Research, represented the Chemotherapy Committee and provided an excellent link between the MRC and the industry, after working at Burroughs Wellcome and collaborating with industry on the standardisation of Salvarsan and other drugs; Professor F. R. Fraser (later Sir Francis) of the Clinical Medicine laboratories at St. Bartholomew's Hospital, London and Fellow of the Royal College of Physicians¹⁷ had collaborated with both Dale and Elliott on a committee arranging trials in pernicious anaemia. Fraser was an expert in the structure-activity relationships of alkaloids.¹⁸ He was a member of the Pharmacopoeia Commission from 1928, remaining a member until October 1944.¹⁹ Frank H. K. Green, previously a recipient of an MRC grant for research at St. Bartholomew's had been a member of the MRC since 1929. He would have been a consultant but for his bronchitic asthma, so a desk job as Secretary of the TTC was ideal.²⁰ These four chose the remainder of the committee, which included prominent figures from many fields of medicine: Professor Arthur W. M. Ellis of the London Hospital; Dr John A. Ryle, who had a private clinic in Wimpole Street (later Sir John Ryle, Regius Professor of Physic at Cambridge and Oxford)²¹; Sir John W. Thomson-Walker, an important Harley

¹⁶ I reviewed the files at the MRC buildings just before the move to the PRO and at a time when many files were being shredded.

¹⁷ "Retrospect on 40 years of Practice: BMA Presidential Address, British Medical Journal (29 July 1939): 209.

¹⁸ MRC Minutes II, (16 July 1920): 114; MRC Minutes II, (15 July 1927): 156.

¹⁹ British Pharmacopoeia (London: General Medical Council, 1948): viii – ix.

²⁰ Maisie Fletcher, The Bright Countenance: a Personal Biography of Walter Morley Fletcher (Hodder & Stoughton, 1957): 323; F. H. K. Green, "Clinical Evaluation of Remedies in Britain", Brit. Med. Bulletin 2 (1944): 58–60.

²¹ Joan Austoker and Linda Bryder (eds.), (1989): 76, 214, 224; M. W. Weatherall, Gentlemen, Scientists and Doctors: Medicine at Cambridge 1800 – 1940 (Cambridge: Boydell Press, 2000): 277-8.

Street figure and a senior urologist at Kings College and surgeon at St. Peter's Hospital, London.²² Sir Edward Farquhar Buzzard, a neurologist and successor to William Osler as Regius Professor of Medicine at Oxford; Professor D. P. D. Wilkie, a general surgeon and urologist from Edinburgh; Sir Thomas Lewis, the eminent cardiologist of University College Hospital, London; Sir John H. Parsons CBE, President of Ophthalmology at the BMA in London and later in Birmingham and Mr Wilfred Trotter, a prominent Harley Street and UCH surgeon.²³ Over the next years further experienced research doctors were added as others retired.²⁴ Edward Mellanby of Sheffield joined and was to become the new Secretary of the MRC,²⁵ and Thomas Watts Eden was one of the foremost gynaecologists in London and had helped to found the British (later Royal) College of Obstetricians and Gynaecologists in 1929, and in 1930 he was President of the Royal Society.²⁶

The TTC met for the first time on 6 March 1931 and sent out notes to pharmaceutical firms and other interested parties entitled "Conditions under which the TTC may be prepared to undertake clinical trials of new remedies of British or foreign origin, submitted by the manufacturers".²⁷

²² MRC Minutes, (13 March 1931): 33; J. W. Thompson-Walker, "The Part of the Practitioner in the Treatment of the Pre-Operative Stage of Enlarged Prostate", British Medical Journal (15 January 1921): 71.

²³ Trotter was a pupil of Sir Victor Horsley. He was a surgeon at UCH from its opening in 1906: W. R. Merrington, UCH and its Medical School (London: Heinemann, 1976): 47,102; MRC File 1523/1; J. H. Gaddum, "Wilfred Batten Lewis Trotter." Biographical Memoirs of Fellows of the Royal Society 3 (1957): 273-88.

²⁴ From January 1934 Fred Menzies, Medical Officer of Health, London County Council, and Dr. Thomas Carnwath, a senior medical officer in the Ministry of Health were added. Linda Bryder, "Public Health Research and the MRC" in Joan Austoker and Linda Bryder (eds.), (1989): 59-82; From June 1934, Professor A. J. Clark was added: D. H. Clark, Alfred Joseph Clark 1885 – 1941, a Memoir (Glastonbury: C. & J. Clark, 1985); MRC Minutes II, (29 October 1931): 128; Helen K. Valier, (University of Manchester: PhD thesis, 2002).

²⁵ Sir Henry Dale, "Edward Mellanby." Obituary Notices of Fellows of the Royal Society 1 (1955): 193-222.

²⁶ "Obituary of Thomas Watts Eden (8 May 1864- 22 September 1946)" British Medical Journal (5 October 1946): 517.

²⁷ The Therapeutic Trials Committee. "Facilities for the Clinical Testing of New Remedies", (6 March 1931), MRC File 1523/1 (TTC).

“The new committee would be empowered to assign the submitted remedies for trial by approved workers in the clinical field and would receive and publish their reports in suitable medical journals”.²⁸

Notices also appeared in *The Telegraph*.²⁹ *The Times* recorded that:

“The MRC announce that they have appointed a Therapeutic Trials Committee, as follows, to advise and assist them in arranging for properly controlled trials of new products that seem likely on experimental grounds to have value in the treatment of diseases”.³⁰

One week later a long article appeared in the *British Medical Journal* reinforcing not only the functions but also the need for the newly constituted committee.

“A sign of the times is the setting up of the Therapeutic Trials Committee. Until now it has been left to the manufacturers to arrange as they thought fit for clinical trials, with the attendant difficulty of not always being able to ensure the necessary tests being conducted in a sufficient number of cases. As a rule I believe it is the custom for free samples to be supplied to such private practitioners as are willing to accept them, and to rely upon those practitioners to make use of them in cases thought to be suitable. But what happens I imagine is that in many instances the samples are only tried by way of experiment, when the ordinary remedies have failed in particular cases. Evidence of this sort of thing can be furnished by many chemists who carry on business in districts where doctors fond of trying new products alleged to possess remedial properties are in practice. Sometimes good luck attends the empirical trials, but more frequently it does not, and an element of uncertainty seems to attach itself to the results obtained by such happy-go-lucky clinical trials so-called. More systematic methods doubtless characterise the procedure adopted by some manufacturers of new products offered for the treatment of disease, but it seems all to the good that opportunity should now be provided for arranging properly controlled clinical tests. The new committee is a strong one, including individuals of the highest reputes and both medicine and pharmacy ought to benefit by its existence”.³¹

This definition of the TTC was broader than that interpreted by Valier who wrote that it was set up “to ensure that potentially useful *synthetic* products were quickly recognised”.³²

²⁸ “Clinical Trials of New Remedies” Lancet (8 August 1931): 304.

²⁹ Telegraph (31 July 1931). Cutting in MRC File 1523/1 (TTC).

³⁰ Times (31 July 1931). Copy in MRC File 1523/1 (TTC).

³¹ “Clinical Trials of New Remedies” British Medical Journal (8 August 1931): 251-2.

³² Helen K. Valier. (University of Manchester: PhD thesis, 2002): 168.

I will show that although some drugs were synthetic, and some were novel in other ways, the therapies tested were often not new, some dating back to the previous century, and neither were they as open to “foreign” drugs as suggested above, at least initially. Many of the drugs tested were British versions of foreign drugs. In fact the clear phrasing of their remit immediately placed the TTC in a dilemma. Their very existence was due to pressure from the ABCM to assist British firms, and yet just before the TTC was formed, one of the members of the Chemotherapy Committee, C. H. Andrewes (later Sir Christopher)³³ received a request from the German firm, Schering for help in arranging tests of a new drug called 'Solganol B' or aurothioglucose, a gold-based drug.³⁴

In the belief that gold had an antiseptic and anti-tubercular activity, Solganol had been given to 39 German patients with underlying complaints attributed to infections. However, because several who also had rheumatoid arthritis experienced a relief of joint pain, Schering decided to explore this further.³⁵

Schering had independently approached a Dr. William Robertson Snodgrass at Glasgow Royal Infirmary, who agreed to treat 30 cases for them. On hearing of this, the Professor of Bacteriology, C. H. Browning³⁶ at the University of Glasgow suggested that Snodgrass might be invited to submit his request instead to the TTC, but secretary F. H. K. Green³⁷ considered: “it was hardly fair to the ABCM that the first activity of the new committee should be the acceptance of a report on the German drug”.³⁸ Dale commented:

³³ Christopher Andrewes was the son of Sir Frederick Andrewes, and performed cancer research under William Gye at the NIMR. After working on dog distemper virus, he was one of a group that isolated the influenza virus in 1933: Joan Austoker, Linda Bryder in Joan Austoker and Linda Bryder (eds.), (1989): 41-44.

³⁴ C. H. Browning to F. H. K. Green, (27 February 1931) MRC File 1523/1 (TTC). Schering had already tested an antibacterial, Neotropin; Walter Sneader, Drug Discovery: the Evolution of Modern Medicines (Chichester & London: John Wiley, 1985): 90.

³⁵ W. Sneader, (1985): 90.

³⁶ C. L. Oakley, “Carl Hamilton Browning, (1881 – 1972)” Biographical Memoirs of Fellows of the Royal Society 19 (1973): 173–215. Cyril L. Oakley, a physician from UCH, where Burroughs Wellcome had drugs tested, joined the WPRL in 1934 to work as an experimental pathologist under Glenny.

³⁷ F. H. K. Green to C. H. Browning, (3 March 1931) MRC File 1523/1 (TTC).

³⁸ F. H. K. Green to H. H. Dale, (3 March 1931), Thomas Renton Elliott Files, “Therapeutic Trials Committee (TTC) 1933-43”, Wellcome Institute, WI: GC/42, 13/1.

“it was of course very stupid of Browning to bring that suggestion to us via the firm in question”.³⁹

Given the inauspicious start with Snodgrass, the Therapeutic Trials Committee set down operational rules on how they proposed to work. Dale pointed out that the committee was “likely to be asked to arrange trials of many drugs which were merely modifications of existing remedies, solely in order that their reports might be quoted as propaganda,” and he felt the TTC should only select “new remedies likely (on the basis of experiments) to advance therapeutics”.⁴⁰ This would discourage speculative approaches such as by the Research Association of British Rubber Manufacturers in Malaya, to have Querbrachitol tested, when in the absence of data “It occurred ... that this product might possess some properties of use” - it was rejected.⁴¹

Ellis suggested that in order to avoid future controversy, studies should be performed at more than one centre; those where the MRC already funded work and where they had trained staff in place.⁴² The TTC insisted that the manufacturing firm provided all available information on a new drug on a confidential basis, and they provided a standard form to collect this. They also insisted that they were solely responsible for studies and that the company could not attempt to set up their own studies in parallel. In return the TTC offered timely completion of the study, which if successful, would be published in a reputable journal as a seal of approval.

8.3 Clinical Trials Established by the Therapeutic Trials Committee.

The TTC met formally on only ten occasions between 1931 and 1939, which perhaps highlights both the scarcity of significant clinical developments during the period, but also the importance of the intervening minutes and correspondence on which I base my

³⁹ H. H. Dale to F. H. K. Green, (27 February 1931), MRC File 1523/1 (TTC).

⁴⁰ First meeting of the TTC, (8 July 1931), MRC File 1523/15 (TTC).

⁴¹ “Querbrachitol, (1-methyl inositol)”, MRC File 1523/15 correspondences from 17 March 1932 to 26 October 1933.

⁴² This is clear from a comparison of the files of the TTC and the MRC Minutes from the previous years. MRC Files 1523/1 and 1523/15.

assessments. Between meetings, progress was coordinated between members by the secretary Green, who also corresponded with individual firms. After the initial decision not to arrange a study on behalf of Schering, there appears to have been a clear policy of preferential treatment for British firms. The first twelve substances investigated were all British and only two of the first 26 tested were German.⁴³ In 1934 Green wrote to Elliott:

“Although it might perhaps be thought desirable to explore the supposed action of bee-venom in 'rheumatic' conditions, I imagine that the Committee would hardly want to arrange for tests of the bee venom in the form of a German ointment?”

He was correct for Elliott replied:

“Sorry, you can't sting me into any enthusiasm for this quest!”⁴⁴

The major British firms all turned immediately to the TTC for testing of their drugs. Ten drugs were put forward to the first meeting of the TTC in July 1931, and included four from Boots, three from Burroughs Wellcome and two from May & Baker; who along with Allen & Hanbury's were four of the five principal British firms.⁴⁵ The other major firm, British Drug Houses, submitted their Oestrin preparation and followed with three drugs for the next meeting of the TTC in January 1932.⁴⁶

The committee accepted 8, but rejected 2 of the initial ten drugs as being unworthy of testing. The successful agents included two synthetic antiseptics from Boots, but the others were all derivatives of natural products. No reasons were given for rejecting Propyl guaiacol from Boots and Parosan from May & Baker, although the former represented a new synthetic version of a compound first described in 1887, when it was isolated from beechwood tar.⁴⁷ Parosan is not mentioned in Slinn's book on May & Baker or in the British Pharmacopoeia of 1948, so it appears not to have been developed. Of the drugs offered to the Committee, it appears that they gave priority to those that could be assayed

⁴³ The TTC examined 59 remedies between 1931-9; TTC Minutes 1- 10, MRC File 1523/15. Further compounds were forwarded but not discussed at the main meetings.

⁴⁴ F. H. K. Green to T. R. Elliott (25 June 1934); T. R. Elliott to F. H. K. Green (27 June 1934), T. R. Elliott Files “TTC 1933-34” WI GC/42.

⁴⁵ TTC Minutes 1, (8 July 1931), MRC File 1523/15.

⁴⁶ TTC Minutes 2, (15 January 1932), MRC File 1523/15.

⁴⁷ Neither of these drugs appears in the British Pharmacopoeia of 1948 and they were presumably not marketed. (London: British Pharmacopoeia, 1948).

biologically and for use in indications in which they had expertise, such as organotherapies as described below. Another reason for selecting organotherapies, as a case study is that work in parallel suggested that, once the active hormone was identified, it could be synthesised and thereby offer a pure version of the human hormone, rather than relying on extracts from tons of animal organs, and these developments in turn stimulated drug synthesis in British pharmaceutical firms.

8.4 Collaboration in Organotherapy and Vitamins Leads to Increased Capacity.

Several authors have addressed the development of organotherapy.⁴⁸ The term applied to the use of extracts from various animal tissues and glands that were given to replace deficiencies in diet or metabolism, and it was analogous to the extraction of alkaloids from plants. Organotherapy became popular at the end of the nineteenth century with extracts of testes, adrenal glands, pancreatic glands, and ovaries, following the discovery of the benefits of thyroid extracts in 1874.⁴⁹ Natural thyroid hormone deficiency and the problems seen after thyroidectomy could be distinguished, and the potential benefits of iodine were noted, well before Kendall described thyroxin in 1915, and before Harrington synthesised the hormone in 1926.⁵⁰

American pharmaceutical firms such as Armour advertised an extensive range of organotherapies in 1918.⁵¹ A report in 1919 had indicated the potential role of pituitary extracts for treating menstrual migraines, and yet preparations were of variable strength.⁵² Organotherapy was stimulated further by the discovery and success of the pancreatic hormone insulin, by the demonstration that cod liver oil prevented the bone disorder rickets, and the use of liver extracts for pernicious anaemia, all of which were investigated by the

⁴⁸ M. Borrell, "Organotherapy and the Emergence of Reproductive Endocrinology" *J. Hist. Biol.* (1985) 18: 1-30; M. Borrell, "Organotherapy, British Physiology, and Discovery of the Internal Secretions" *J. Hist. Biol.* (1976) 9: 235-68; *British Medical Journal* (6 February, 1915): 243-247; E. C. Dodds, "The Hormones and their Chemical Relations" *Lancet* (19 May 1934): 1048-54; Sir Humphrey Rolleston, "The History of Organotherapy" *British Medical Journal* (15 May 1937): 1033-36; Sir W. Langdon-Brown, "Recent Advances in Organotherapy" *Pharmaceutical Journal* 141 (30 July 1938): 93.

⁴⁹ W. Sneader, (1985): 192.

⁵⁰ C. Harrington, G. Barger, "Chemistry of Thyroxine. (III) Constitution and Synthesis of Thyroxine" *Biochemical Journal* 21 (1927): 169.

⁵¹ The substances and gland preparations included bronchial, cardin, cerebrenin, corpus luteum, duodenal, lymphatic, mammary, orchitic, ovarian, pancreas, parotid and pineal *Chemist & Druggist* (6 July 1918) suppl. V.

MRC.⁵³ Each new hormone was examined in a similar fashion. Firstly extracts were made of variable quality, and then improved methods of extraction were identified, the substance was crystallised if possible and in the course of a decade, synthetic drugs were made, rapidly superseding the extraction of tens of thousands of tissue samples to produce a single gram of material.⁵⁴

Walter M. Fletcher set up a Sex Hormones Committee within the Chemotherapy Committee in 1930, including Dale, Watts Eden and Ellis.⁵⁵ Organotherapy was within the ‘comfort-zone’ of the MRC, because the organ extracts had to undergo biological standardisation in their laboratories. Harold King at the NIMR investigated the chemical structure of the hormones, just as George Barger had with thyroxine in 1927.⁵⁶ Because the MRC already supported research in organotherapy, the TTC had no difficulty in arranging studies.

One of the original departments of the NIMR, the Department of Applied Physiology and Endocrinology headed by Sir Leonard Hill had ceased to exist when he retired in 1930.⁵⁷ From July 1932 a sub-department studying the Physiology of Sex Hormones was established under Alan Parkes (later Sir Alan), who had previously collaborated with Guy Marrian at UCH⁵⁸ and also with Professor E. C. (Later Sir Charles) Dodds on hormones.⁵⁹

⁵² W. Sneader, (1985): 96, 166, 334.

⁵³ J. Barnes, M. J. Brady, G. M. James, “The Comparative Value of Irradiated Ergosterol and Cod Liver Oil as a Prophylactic Antirachitic Agent when Given in Equivalent Dosage According to Rat Units of Vitamin D” American Journal of Diseases of Childhood (1930) xxiv 45.A.; Walter Sneader, (1985): 193.

⁵⁴ H. E. Dale, “The Chemistry of Sex Hormones” Pharmaceutical Journal (27 April 19139): 432-34.

⁵⁵ TTC Minutes 2 (18 January 1932); MRC Minutes II, (16 May 1930): 87. Dr F. H. A. Marshall was chairman, with Dr. V. Korenchevsky and Dr A. J. Parkes. MRC Minutes II, (20 June 1930): 112 and (4 June 1931): 91.

⁵⁶ Walter Sneader, (1985): 209.

⁵⁷ Joan Austoker, Linda Bryder in Joan Austoker and Linda Bryder (eds.), (1989): 48-9.

⁵⁸ A. J. Parkes, “The Rise of Reproductive Endocrinology 1926-40” Journal of Endocrinology 34 (1966) xx- xxxii; H. H. Dale, “NIMR” in Dale Archives, Royal Society, HD 47.13.144.

⁵⁹ Dodds was Prof of the University of London: MRC Minutes II, (30 April 1926): 74: E. C. Dodds, “Synthetic Oestrogens” Endeavour (1947): 145-7; E. C. Dodds, L.

Burroughs Wellcome took an early interest in organotherapy and was, like many firms involved in the insulin studies. They had already placed their thyroxine preparation on the market in September 1926.⁶⁰ Burroughs Wellcome's anterior pituitary lobe preparation, neo-Infundin, was marketed in 1931 and was claimed to be free from the pressor principles associated with earlier extracts.⁶¹ The first hormone submitted to the TTC by Burroughs Wellcome was Progesterone, which had been isolated in 1929.

The New York house of Burroughs Wellcome at Tuckahoe, established in 1906, prepared a further extract from the brain's anterior pituitary lobe for Dr. Lees to test at the WPRL.⁶² By 1933 several companies sold preparations of anterior pituitary lobe extract. Because of the rapid developments in organotherapy, a section of hormone physiology was created at the Burroughs Wellcome site at Beckenham and further organ extracts were made. Jowett prepared a duodenal extract using a process devised by Trevan.⁶³ Prof. C. C. Lambie, by now at the University of Sydney was invited to the WPRL to describe his work on thyrotropic hormone.⁶⁴

8.4.1 Oestrin

At the first meeting of the TTC it was proposed to evaluate Oestrin from British Drug Houses, in collaboration with members of the Sex Hormones Committee, including T. Watts Eden. Oestrin was an ovarian follicular hormone extract, first described in America in 1923 by Edgar V. Allen of Colorado and Edward Adelbert Doisy.⁶⁵ Parke Davis supported Doisy, and he isolated the crystalline hormone in 1924. The MRC had supported ovarian hormone research since the early 1920's, culminating in the detection of ovarian

Goldberg, W. Lawson, R. Robinson, "Oestrogenic Activity of Certain Synthetic Compounds" Nature (1938) 141: 247.

⁶⁰ Mr. Hogg, "History of the Works" (1907) III, WF: S/G/145.

⁶¹ "Preparations & Appliances: Neo-infantine" British Medical Journal (7 March 1931): 406.

⁶² STC Meetings, (12 July 1935) and (19 November 1937), WF: STC S/G/49.

⁶³ STC Meeting, (29 May 1936), WF: STC S/G/49.

⁶⁴ STC Meeting, (24 May 1937), WF: STC S/G/49.

⁶⁵ E. V. Allen, E. A. Doisy "An Ovarian Hormone: Preliminary Report of its Localization, Extraction and Partial Purification and Action in Test Animals" J. American Medical Association 81 (1923): 819-21; E. V. Allen, E. A. Doisy, "Isolation of the Active Principle of the Ovarian Hormone (Oestrin)" J. Biological Chemistry 61 (1924): 711-723.

hormones in the urine of pregnant women by Guy Marrian at University College Hospital.⁶⁶ Charles Dodds of the Courtauld Institute of Biochemistry at the Middlesex Hospital in London, who had been involved in the early production of insulin and also had collaborated with the Burroughs Wellcome STC regarding Oestrin (chapter 7), showed that oestrus was caused by Secretin, extractable from ovarian tissue, which if injected into ovariectomised animals caused an artificial oestrus. For a while the urine of pregnant women and mares was the chief source of Secretin, allowing commercial production of crystalline extracts, which were used to treat ovarian dysfunctions such as menopausal disorders, amenorrhoea, and menstrual headaches. The Dutch firm Organon published the first patents for methods of extraction on 28 May 1927, followed in November by Soci  t   Chemical Industrie of Basle (CIBA) with Parke Davis, Schering Kahlbaum and IG Farben soon competing.⁶⁷

Because observations of the clinical utility of organ extracts were published openly, any firm with appropriate facilities could attempt production although each would guard the methods of extraction. This led to a situation whereby the several extracts appeared simultaneously, that could only be differentiated biologically in terms of ‘rat units,’ defining the amount of an extract bringing about oestrus or abortion.⁶⁸ From 1931, both the American firm of Parke Davis and the German firm, Schering commercially produced oestrone and related hormones.⁶⁹ Oestrin was shown to help 23 out of 25 women with menstrual migraine in an independent clinical study in 1932.⁷⁰ Dr. John Chassar Moir, who had been funded by the MRC and collaborated with Dale in refining ergot, took up the TTC work on Oestrin and other organ extracts. Moir had trained in Vienna, Berlin and Johns Hopkins in the USA, and performed research in Edinburgh before taking a post at UCH in 1930.⁷¹

The MRC Sex Hormones committee recommended to the TTC that standards should be defined and that clinical trials be arranged for Oestrin and for “some British firm

⁶⁶ J. K. Grant, “Guy Frederick Marrian (1904-81)” Biographical Memoirs of Fellows of the Royal Society 28 (1982): 347-78.

⁶⁷ STC Meeting, (19 May 1933), WF: STC S/G/49.

⁶⁸ “Clinical Effects of Ovarian Hormone” Lancet (15 March 1930): 586.

⁶⁹ W. Sneader, (1985): 193-4.

⁷⁰ A. P. Thompson, “A Contribution to the Study of Intermittent Headache” Lancet (30 July 1932): 229-235.

⁷¹ “Obituary. John Chassar Moir” Lancet (10 December 1977): 1240.

to undertake its production” and BDH submitted their version.⁷² Dodds reported favourable clinical outcomes in his studies, which encouraged him to attempt the identification and synthesis of Oestrin.⁷³ In the summer of 1932, the MRC collaborated with the League of Nations to establish International Standards Units for oestrogenic hormones and Alan Parkes’ department performed many studies of sex hormones preventing fertility.⁷⁴ With a biological test in place to measure the overall activity, the race began to define the active substance within the extracts.⁷⁵

Having followed the development of thyroxine, Burroughs Wellcome decided to “keep a watch on the possibilities of synthetic oestrogenic compounds of this type”.⁷⁶ In 1932 Rosenheim and King proposed that oestrogens had a structure similar to ergosterol, and Dodds established the relationship between the essential parts of the chemical structure and oestrogenic activity, finding potent activity in anol, which was cheaply prepared from natural oils. Burroughs Wellcome’s STC supported the production of extracts of Oestrin at Dartford, where the first experimental batch was produced in December 1934.⁷⁷ Oestrin given orally was a successful product for Burroughs Wellcome and other firms, but they also provided Dodds with large quantities of material to try to synthesise it.⁷⁸

By 1937 a series of firms were selling oestrogenic hormones based on either ketohydroxyoestrin such as Schering’s Progynon and Parke Davis’ Theelin and Oestroform from BDH, or preparations based on oestadiol benzoate in which case the letter B was added by BDH and Organon produced Oestroform-B. Boots produced Ovostab and Ovostal.

Dodds then collaborated with Sir Robert Robinson, the Waynflete Professor of Chemistry in Oxford and advisor to industry, who suggested that stilbenes, 2-3 times more potent than oestrone were formed by the condensation of two anol molecules and thus the

⁷² MRC Minutes III, (13 March 1931): 39.

⁷³ E. C. Dodds, F. Dickens, S. Wright, “Observations upon the Preparation of the Ovarian Hormone” *Biochemical Journal* 19 (1925): 853-59; E. C. Dodds, J. D. Robertson, “Clinical Experiments with Oestrin” *Lancet* I (1930): 1390-2.

⁷⁴ J. Austoker, L. Bryder, in Joan Austoker and Linda Bryder (eds.), (1989): 49.

⁷⁵ Oestrin is still used in its modern form as oestrogen, R. E. Jowett, “Some Unusual Experiences with Oestrin Therapy” *J. Laryngol. Otol.* 82 (1) (1968): 69-71.

⁷⁶ STC Meeting, (19 May 1933), WF: STC S/G/49.

⁷⁷ STC Meeting, (14 December 1934), WF: STC S/G/49; MRC Minutes II, (26 June 1931): 91.

synthetic substitutes stilboestrol, hexoestrol and dienoestrol, were prepared in January 1938.⁷⁹

Within weeks of Dodds discovery, Burroughs Wellcome synthesised diethylstilboestrol on a commercial scale, and Boots and BDH soon also prepared it and both of their preparations were accepted for trial by the TTC in July 1938 at UCH, the Postgraduate Medical School and Guy's in London and the Royal Maternity Hospital in Edinburgh.⁸⁰ Dr. P. M. F. Bishop at Guy's Hospital was a lecturer in chemical physiology, Muriel Boycott at UCH had been a BDH sponsored research fellow since October 1937, and S. Zuckerman was from the Department of Pathology in Oxford. Their multicentre clinical study demonstrated that stilboestrol dipropionate (BDH & Boots) and hexoestrol (Boots) were both highly active, with stilboestrol being most active, although hexoestrol was given at a low dose in a series of 152 cases.⁸¹ The early success of Oestrin extracts in TTC trials clearly encouraged attempts to synthesis the hormone and the early availability of synthetic versions stimulated the TTC to examine several further preparations, this time showing clear benefits and a clear case of successful industry collaboration with academia and the TTC. The TTC helped to organise the trials but also endorsed the products. The synthetic preparations could be given by injection and their decreased cost compared to

⁷⁸ R. A. O'Brien to H. A. D. Jowett, (26 May 1925), WF: STC S/G/49.

⁷⁹ S. A. B. Kipping, Chemistry and Industry (25 February 1963): 304; W. Sneader, (1985): 196, 201, 336, 340; Lord Todd, J. W. Cornforth, "Robert Robinson" Biographical Memoirs of Fellows of the Royal Society 22 (1976) 415-527; STC Meeting, (31 January 1939), WF: STC S/G/49; E. C. Dodds, W. Lawson, "A Simple Aromatic Agent with an Activity of the same Order as that of Oestrone" Nature 139 (1937): 627; E. C. Dodds, L. Goldberg, W. Lawson, R. Robinson, "Oestrogenic Activity of Certain Synthetic Compounds" Nature 141 (1938): 247-48.

⁸⁰ TTC Minute 9, (14 July 1938), MRC File 1523/15 W. R. Winterton, T. N. MacGregor, "Clinical Observations with Stilboestrol (Diethylstilboestrol)" British Medical Journal (7 January 1939): 10-12; "A New Synthetic Oestrogen" British Medical Journal (7 January 1939) 23-34; Alfred A. Loewer, "Therapeutic Trials of Diethylstilboestrol" British Medical Journal (7 January 1939): 13.

⁸¹ P. M. F. Bishop, M. Boycott, S. Zuckermann, "The Oestrogenic Properties of Stilboestrol (diethylstilboestrol)" Lancet (7 January 1939): 5; P. M. F. Bishop, R. K. Bowes, M. Boycott, R. Kellar, T. N. MacGregor, B. C. Markers, "Oestrogenic Properties of Stilboestrol dipropionate and Hexoestrol" Lancet (6 April 1940): 629-633; "Synthetic oestrogens" British Medical Journal (25 February 1939): 351.

extracts, promised early success and it was not long before Boots, BDH and Oxo joined Burroughs Wellcome in manufacturing stilboestrol ampoules and tablets.⁸²

8.4.2 Suprarenal Cortical Extract (Cortin).

Adrenocortical steroids had been first described in America in 1927, but the clinical potential only became evident after stronger preparations were extracted using benzene and Parke Davis was first to prepare a commercial version.⁸³ Towards the end of 1933, Organon of Oss in Holland approached the TTC to perform the first UK trials of suprarenal cortical extract on patients with Addison's disease, a deficiency disease first described by Thomas Addison in 1855.⁸⁴ The TTC were concerned that suprarenal cortical extracts called Eucortone (Allen & Hanbury's) and Eschatin (Parke Davis) were already on the market and both were expensive.⁸⁵ Organon's version was an unpatented preparation with an improved biological standardisation. In this case, rather than promote the British firm as they so often did, the Committee took the view that it would be advantageous to everyone if a cheaper version were allowed on the market. The Committee arranged for trials of the Organon extracts to be performed at the Royal Free Hospital in London, and in Aberdeen and Manchester.⁸⁶ Despite all of the concerns that the MRC had with Manchester, it was Wilkinson with 8 cases that contributed the most patients.⁸⁷ Although Organon's Cortin was cheaper, the committee were concerned about starting a patient off on Cortin in a trial, and then having to switch to more expensive marketed preparations:

“If we start a patient successfully with our free extract, at what cost will maintenance treatment be provided? We can't drag a patient from the pit and

⁸² “Sex Hormones: Standardised Commercial Preparations”, Pharmaceutical Journal 142 (27 April 1939) 436-442.

⁸³ W. Sneader, (1985): 221.

⁸⁴ Sir John Conybeare (ed.), A Textbook of Medicine (Edinburgh, E. S. Livingstone, 9th edition 1949): 257-8.

⁸⁵ T. R. Elliott File, WI GC/42; Eucortone, Corton (A&H): extract of adrenal cortex for the treatment of Addison's disease and other conditions highly active, highly purified (London: Allen & Hanbury's, 1938)- advertisement at Wellcome Institute QV26 1938A42e.

⁸⁶ TTC Minutes 5, (5 March 1934), MRC File 1523/15.

⁸⁷ F. H. K. Green to T. R. Elliott, (20 December 1933), T. R. Elliott Files, WI GC/42 TTC 1933-34; TTC Minutes 5, (5 March 1934), MRC File 1523/15.

then leave him to slide back. Yet the hospital might not relish this aftermath of the investigation”.⁸⁸

In February 1934 a conference was held to discuss the clinical trials of suprarenal cortex extracts and the Committee decided to do what the MRC did best, to perform comparative laboratory tests of potency on the three available preparations.⁸⁹ While the intention of providing a cheaper product was laudable, the study struggled to recruit sufficient patients with only 14 cases treated from 12 different London hospitals during the whole of 1933.⁹⁰ In order to find further clinical cases to treat, advertisements were placed in the *Lancet*, *British Medical Journal*, *Clinical Journal* and *Practitioner*. Data were collected on dose, pigmentation, muscular weakness, digestive symptoms, history of cases, loss of weight and specified clinical and pathological tests.⁹¹ Edward Mellanby chaired a second conference on the role of Cortin in Addison's disease in July 1936, but the study was still a failure with only 20 cases treated. Murray Lyon, who had treated 4 cases concluded: “the results as far as they go do not seem to be encouraging but they do not go far” and Elliott who had only one case commented tamely: “his results do not show that Cortin is useless”.⁹² The Cortin studies can therefore at best be classed as inconclusive, and the performance of the TTC in recruiting cases was poor and although further trialists were contacted, it was too late.⁹³ Perhaps the MRC felt an obligation to study the Organon drug, having refused an import

⁸⁸ T. R. Elliott to F. H. K. Green (21 December 1933), T. R. Elliott Files, WI GC/42 TTC 1933-34.

⁸⁹ “Clinical Trials of Extracts of Suprarenal Cortex” (6 February 1934), T. R. Elliott Files, WI GC/42, TTC 1933-34, 13/1.

⁹⁰ F. Menzies (London County Council) to T. R. Elliot (23 March 1934), T R Elliott Files, WI GC/42, 13/1 TTC 1933-34; Clinical trials of extracts of suprarenal cortex, conference; Simpson had already published experimental studies using rats: S. Levy Simpson, A. Kohn-Speyer, V. Korenchevsky, “The Adrenal Cortex and Sex” *Lancet* (25 November 1933): 1194.

⁹¹ MRC Clinical Trials of Cortin, first conference (6 February 1934), T. R. Elliott Files, WI Contemporary archive, 13/1 TTC correspondence.

⁹² The quote is from T. R. Elliott to F. H. K. Green, 12 March 1936); TTC Meeting 7, (11 February 1937), MRC File 1523/15; Elliott treated 1, Levy Simpson 6, Murray Lyon 4, Wilkinson 9, T. R. Elliott Files, WI GC/42 TTC 1933-34; *Society of Therapy and Pharmacology* (1937): 1141 - 1145.

⁹³ F. H. K. Green to T. R. Elliott, (30 April 1934): T. R. Elliott Files, WI GC/42, TTC 1933-34.

license of that firm's insulin in October 1923.⁹⁴ The failure of the study may be ascribed to the relative rarity of the types of patients required, but the results that were available were not stunning and this almost certainly reflected the quality of the extracts provided. It would be a further 20 years before the complex chemistry of the adrenocortical steroids was fully resolved.

8.4.3 Progestational Agents.

Organon approached the committee to study its Progestin extract, trade marked 'Hombreol', having already independently approached a surgeon, Mr. Victor Dix at the London Hospital, to perform a study in prostatic cases.⁹⁵ The TTC arranged further studies through its sub-committee members A. S. Parkes and Chassar Moir, but it was "difficult to collect adequate data". Hombreol was also studied at Guy's Hospital,⁹⁶ and St. Bartholomew's in London, Edinburgh, Manchester, in patients suffering repeated abortion, prostatic cases, and chronic interstitial mastitis.⁹⁷ Once more overall results⁹⁸ were inconclusive, but the Edinburgh data was at least submitted to the *British Medical Journal*.⁹⁹ By 1934 the active principle progesterone had been isolated, but it had to be injected in large quantities to be active and it was several more years before a synthetic route was derived.

Meanwhile, by the time of the seventh TTC meeting on 11 February 1937, a more purified Swiss version of testicular hormone was available as 'CIBA 2020', and it was decided to abandon Organon's 'Hombreol' in favour of this. CIBA had been in the hormone field since 1913, when they first prepared ovarian extracts.¹⁰⁰ There were already at least 4 preparations on the market (Proluton from Schering, Progestin from Organon and BDH, and Lutren from Bayer). Nevertheless Organon still sold Neohombreol, from May 1942. CIBA 2020 was forwarded to the London Hospital, St. Bartholomew's, and to

⁹⁴ Jonathan Liebenau, Medical Science and Medical Industry. The Formation of the American Pharmaceutical Industry (Basingstoke: MacMillan, 1987): 176-7; MRC File, 1092/35 Organon.

⁹⁵ TTC Minutes 6, (28 February 1936), MRC File 1523/15.

⁹⁶ TTC Minutes 8, (7 February 1938), MRC File 1523/15.

⁹⁷ Miss A.N. MacBeth to F. H. K. Green (29 July 1938), T. R. Elliott Files, WI GC/42 TTC 1935-42; TTC Minutes 6, (28 February 1936) MRC File 1523/15.

⁹⁸ TTC Minutes 5, (5 March 1934), MRC File 1523/15.

⁹⁹ TTC Minutes 6, (28 February 1936), MRC File 1523/15.

¹⁰⁰ W. Sneader, (1985): 193.

Oxford where Prof. J. A. Gunn performed physiology experiments to confirm its powerful pressor effect and found adrenalin-like effects on the intestine and rabbit uterus.¹⁰¹ Publication of his study was held up at the end of 1937 until CIBA made decisions on a name for the drug, and whether they would market it, as there had been some minor safety issues.¹⁰² By the following year a study of 150 patients had been completed in London confirming the sharp rises of blood pressure and also utility in asthma patients.¹⁰³ Schering Kahlbaum, at the forefront of attempts to synthesise the hormone, sent to the TTC their male hormone extract, Proviron, for the treatment of bilateral orchidectomy, premature senility, and impotence. However over a period of 2 years, only one case was secured from 2 centres and although two further centres were added eventually this study was also abandoned.¹⁰⁴

In conclusion, despite the TTC having a major interest in organotherapy, they failed to establish successful clinical trials with several organ extracts. All preparations sent to them were accepted for evaluation, even when alternative versions were already available commercially. The TTC did not adhere to their promise to examine only novel agents and on several occasions tested preparations simply to ensure that a British version was available, while allowing testing of 'foreign' preparations from Organon of the Netherlands and CIBA of Switzerland when they thought this would reduce prices. The TTC recognised the problems with early extracts being of variable and often weak potency and they were flexible in their approach to evaluating new extracts that offered greater potency. Their only real success was with oestrone, and this correlated with the parallel development of the understanding of the active ingredients and ultimately with their synthesis and manufacture by pharmaceutical firms.

8.4.4 Pernicious Anaemia.

¹⁰¹ TTC Minutes 9, (14 July 1938), MRC File 1523/15 Gunn was still testing it in 1939, TTC Minutes 10, (28 March 1939).

¹⁰² F. H. K. Green to T. R. Elliott, (13 October 1937) and T. R. Elliott to F. H. K. Green (15 October 1937), T. R. Elliott Files, WI GC/42 TTC 1935-42.

¹⁰³ The continued use of the code name was understandable in the light of the chemical name trimethoxybenzyl-dihydroimido-azol hydrochloride. "Preparation 2020 for raising Blood Pressure", *Pharmaceutical Journal* 140 (26 February 1938): 211.

¹⁰⁴ TTC Minutes 4, (undated, 1933); TTC Minutes 5, (5 March 1934); TTC Minutes 6, (28 February 1936), MRC File 1523/15.

In 1926 two American scientists discovered that in pernicious anaemia, raw liver could cure a previously fatal disease, and while it was undesirable to give the large quantities of liver extract required, this was attempted while the active principle was sought. Glaxo licensed an extraction process developed in Norway in 1936, resulting in the marketing of Examen.¹⁰⁵ Burroughs Wellcome made liver extracts commercially from December 1927, and being unable to decide upon clinical tests they contacted the Chemotherapy Committee, and then directly approached the Association of Clinical Pharmacologists. As a result, and as described in the previous chapter, the MRC became involved in studying liver extracts for pernicious anaemia in 1928. Burroughs Wellcome produced a more concentrated form in May 1932 and took part in their first Pernicious Anaemia Conference on 5th January 1934, involving Allen & Hanbury's, Boots, British Drug Houses, Burroughs Wellcome, Oxo and Glaxo. Given the previous conflicts on this project, the TTC maintained that doctors preferred to receive samples via the MRC, rather than dealing directly with a firm.¹⁰⁶ Despite this, Wilkinson in Manchester continued to test both stomach and liver preparations by dealing directly with Boots. Meanwhile, the Association of Clinical Pathologists, that had tried to collaborate with the MRC became frustrated with them, and turned to using what they regarded as a superior German preparation. A number of commercial liver preparations were available up to the outbreak of the Second World War in a market dominated by British and American firms.¹⁰⁷

8.4.5 Vitamins.

While Glaxo embraced vitamins immediately, it will be recalled that Burroughs Wellcome was more circumspect until they manufactured Calciferol from September 1932. Many of the early preparations used fish livers as the source of vitamins.¹⁰⁸ By the early 1930's interest was rekindled after a series of studies led to the discovery of the chemical structure of vitamin C as ascorbic acid, allowing synthesis and thereby avoiding the variable nature of extracts. Yet when commercial production of synthetic vitamin C was achieved by Hoffman la Roche of Switzerland,¹⁰⁹ and they approached the TTC in 1934, Elliott argued

¹⁰⁵ R. P. T. Davenport-Hines, Judy Slinn, *Glaxo: A History to 1962* (Cambridge: Cambridge University Press, 1992): 176.

¹⁰⁶ Helen Kathryn Valier, (University of Manchester: PhD thesis. 2002): 180.

¹⁰⁷ "Commercial Liver Preparations" *Pharmaceutical Journal* 142 (11 March 1939): 169.

¹⁰⁸ "The Cod Liver Industry" *Pharmaceutical Journal* 141 (19 November 1938): 529.

¹⁰⁹ Walter Sneader, (1985): 234.

that ascorbic acid, in the form of fruit, had been used for years and he did not consider that the synthetic agent was any different so the TTC did not pursue any studies. Yet, when Green later received a case report of the first patient treated in the UK, he was at least in favour of publication if only for its historic interest and so too, was Mellanby.¹¹⁰ Elliott argued that Calciferol, (vitamin D₂) could also be considered synthetic, though it did not originate from elementary substances. Meanwhile, Burroughs Wellcome decided to manufacture the synthetic vitamin and issued supplies in September 1934.¹¹¹ Then it was recognised that irradiated milk offered the best administration of vitamin D.¹¹² Szent-Gyorgy's vitamin P (citrin) was also prepared¹¹³ and sent to Dr. MacFarlane and Dr. Sylvester Zilva at the Lister Institute for experimental work.¹¹⁴ Prof. Noah Norris compared vitamin D₃ and calciferol in human rickets without showing any differences, although as Dale showed the former appeared a hundredfold more active in laboratory tests.¹¹⁵

By 1939 British firms were manufacturing the whole range of vitamins in a variety of presentations. Vitamin A was produced as capsules, tablets and in a parenteral form. Burroughs Wellcome made vitamins A, B₁, B₂, C, and D. British Drug Houses made A, B₁, B₂, C, D, E and combinations. Allen & Hanbury's made vitamins A, B₁, B₂, C, D, and combinations, and Glaxo made the whole range and also vitamin P. May and Baker made only vitamin A.¹¹⁶

8.5 Prontosil: a New Era of Chemotherapy.

In 1935 Dr. Gerhard Domagk, director of the Bayer Research laboratories in Elberfeld, reported the discovery of the first effective sulphonamide antibacterial, with

¹¹⁰ F. H. K Green to T. R. Elliott (19 February 1935), T. R. Elliott Files, WI GC/42 TTC 1935-42.

¹¹¹ STC Meeting, (19 May 1933), WF: STC S/G/49.

¹¹² "Dosage of Vitamin D" British Medical Journal (17 November 1934): 907.

¹¹³ STC Meeting, WCRL Report, (22 January 1937), WF: STC S/G/50.

¹¹⁴ STC Meeting, (22 January 1937), WF: STC S/G/50; F. H. K. Green to T. R. Elliott, (19 February 1935), T. R. Elliott Files, WI GC/42 TTC 1935-42.

¹¹⁵ H. H. Dale to F. H. K. Green (8 July 1938), T. R. Elliott Files, WI GC/42 TTC 1935-42

¹¹⁶ "The Vitamins (VI): the Potency of Commercial Preparations" Pharmaceutical Journal 142 (21 January 1939): 54-59.

promising activity against streptococcal infections.¹¹⁷ Henry Dale was “probably the first person from this country to meet Domagk at Bayer, and to share his finding before publication, which was delayed for a year”.¹¹⁸ After the TTC had focussed for four years on British drugs, the scientific and medical promise of Prontosil outweighed its German origins, but the Committee still debated who should test it. According to their records, the Therapeutic Trials Committee were approached by Colebrook from Queen Charlotte’s Hospital in London, who wanted to be the first and only person in the UK to work on Prontosil.¹¹⁹ In another version Dale:

“Succeeded in persuading the highly sceptical Colebrook to undertake such a controlled trial of its action on patients in his Puerperal Fever Unit, as would convincingly determine whether the substance was clinically effective, and finally having had the chance, Colebrook confessed it was rather better than anything that he tried”.¹²⁰

Dale was “astounded to hear the story that he (Colebrook) had taken the initiative and gone over to Elberfeld” and corroborated his version with Frank Green.¹²¹ Nevertheless, the Committee agreed to allow Colebrook to investigate Prontosil even though Elliott remarked: “we will never get convincing clinical evidence when a report is made by only one man”.¹²²

Prof. Charles Cyril Okell,¹²³ Professor of Bacteriology at UCH since 1930, having worked in the laboratories of Burroughs Wellcome, noted that “Hopeful” results on

¹¹⁷ Domagk (1895-1964) qualified in medicine in 1921 and trained as a bacteriologist. He was appointed as Director of Research at IG Farben in 1927: R. A. Kyle, M. A. Shampo, “Gerhard Domagk” *JAMA* 247 (14 May 1982): 2581.

¹¹⁸ H. H. Dale to A. Landsborough Thompson, (17 February 1967), 93 HD 47.5.151.

¹¹⁹ F. H. K. Green, G. Covell, “Medical Research”, chapter 7 in A. S. MacNalty (ed.), *History of the Second World War* (London: HMSO, 1953): 258-271; E. J. Lowbury, “Leonard Colebrook (1883-1967)” *British Medical Journal* 287 (1983): 1981-3; J. L. Turk, “Leonard Colebrook: the Chemotherapy and Control of Streptococcal Infections” *J. Roy. Soc. Med* 87 (December 1994): 727-28.

¹²⁰ H. H. Dale to A. Landsborough Thompson, (17 February 1967), Dale Archives, Royal Society, 93 HD 47.5.151.

¹²¹ H. H. Dale to A. Landsborough Thompson, (17 February 1967), Dale Archives, Royal Society, 93 HD 47.5.151.

¹²² T. R. Elliott to F. H. K. Green, (8 May 1935), T. R. Elliott Files, WI GC/42 TTC 1935-42.

¹²³ “Charles Cyril Okell, Obituary” *British Medical Journal* (18 February 1939): 362.

Prontosil had been reported from Germany.¹²⁴ He explained to Green that the German work was not “a sudden skyrocket but had been burning steadily for some time”.¹²⁵ Early in 1935, Bayer told Dale that they were ready to supply Prontosil to the MRC and had Okell not fallen ill, he would probably have been testing Prontosil ahead of Colebrook.

Having established the initial main study with Colebrook, the Committee was inundated with requests for Prontosil, and they accepted them all except one from a Dr. A. H. Douthwaite, of Harley Street who wished to perform a clinical study of streptococcal arthritis after hearing a lecture on Prontosil by Prof. Heinrich Hörlein, the Head of Bayer Pharmaceuticals.¹²⁶ Elliott recommended that Douthwaite should not be supplied: “He is a man with brains and perhaps a critical judgement; but has been spoiled by success in practice. He writes too publicly; everything that he touches is the right thing because the king has touched it”.¹²⁷ Prof. C. H. Browning in Glasgow investigated Prontosil, and Dr. Alexander Joe at the North West Fever Hospital (in Edinburgh,) treated cases of erysipelas and scarlet fever, though with “discouraging” results. London’s two fever hospitals treated cases of gonorrhoea with Bayer’s Uleron formulation of Prontosil.¹²⁸ In March of 1936, Green contacted W. R. Snodgrass in Glasgow,¹²⁹ and he treated 60 erysipelas cases, while Prof. Ellis agreed to treat cases of arthritis.¹³⁰ Wilkie showed “remarkably good results in some cases”.¹³¹

¹²⁴ Prof. Okell drew attention to a paper in Deutsche Med. Woch: T. R. Elliott to F. H. K. Green, (8 May 1935), T. R. Elliott Files, WI: GC/42 1933-43.

¹²⁵ T. R. Elliott to F. H. K. Green, (8 May 1935), T. R. Elliott Files, WI GC/42 TTC 1935-42.

¹²⁶ F. H. K. Green to T. R. Elliott, (7 October 1935), T. R. Elliott Files, WI GC/42 TTC 1935-42. Hörlein took charge of Bayer’s pharmaceutical department in 1910 and he had engaged the scientists Roehl and Domagk who continued Bayer’s tradition of discovery. From Germanin to Acylureidopenicillin (Leverkusen: Bayer, 1980): 13-32.

¹²⁷ T. R. Elliott to F. H. K. Green, (10 October 1935), T. R. Elliott Files, WI GC/42 TTC 1935-42.

¹²⁸ TTC Minutes 8, (7 February 1938), MRC File 1523/15; “Treatment of Syphilis” Lancet (25 September 1937): 759-60.

¹²⁹ F. H. K. Green to T. R. Elliott, (9 March 1936), T. R. Elliott Files, WI GC/42, TTC 1935-42.

¹³⁰ TTC Minutes 6, (28 February 1936), MRC File 1523/15.

¹³¹ TTC Minutes 7, (11 February 1937), MRC File 1523/15.

Thomas Henry made Prontosil at the WCRL for trial at WPRL, and a patent search was set underway to see whether it was protected.¹³² Although it was a simple derivative of a dye intermediate: “even if it proved to be unprotected Burroughs Wellcome doubted whether it could be manufactured successfully in competition with a dye-works, and there was evidence already of Roche patent activity”.¹³³ However, J. Tréfouël at the Pasteur Institute showed that the colourless para-aminobenzenesulphonamide was the active part of ‘Prontosil,’ and as it had been described in 1908, it was unprotected by patents.¹³⁴ A large batch of this base compound was made at Dartford by a process supplied by the WCRL, for tests on larger animals, for clinical trials, and as a starting point for preparing further similar synthetic derivatives.¹³⁵ The first of these to be offered for testing was diaminodiphenylsulphone.¹³⁶ Burroughs Wellcome offered ‘British-made’ Prontosil to the TTC “as the matter was urgent, in view of possible similar action by another firm”- Trevan suggested that if the trial were agreed, full details of the pharmacological results at the WPRL would be supplied.¹³⁷ On 1 October 1935, they heard that the TTC were already examining material from another source (Bayer). G. A. H. Buttle, who worked under Trevan at the WPRL, sent a letter to the Secretary of the TTC regarding preliminary experiments with Prontosil in meningococcal bacteria (a cause of meningitis).¹³⁸ Burroughs Wellcome advertised that they had prepared Prontosil, and contrary to their usual experiences of difficulties in arranging trials, they set up a policy for dealing with an anticipated rush of external requests:

- a) Those coming from GPs and men of no outstanding importance – a letter would be sent advising that the preparation was under clinical trial by the TTC and would not be made available until their report is published.

¹³² STC Meeting, (12 July 1935), WF: STC S/G/50.

¹³³ IG patent 430,580 was possibly anticipated by Ro 149,428, STC Meeting, (15 November 1935), WF: STC S/G/49.

¹³⁴ M. Weatherall, In Search of a Cure: a History of Pharmaceutical Discovery (Oxford: Oxford University Press, 1990): 150 – 153.

¹³⁵ STC Meeting, (13 March 1936), WF: STC S/G/50.

¹³⁶ Report of WCRL, (January 1937), WF: STC S/G/50.

¹³⁷ STC Meeting, (29 May 1936), WF: STC S/G/50.

¹³⁸ G. A. H. Buttle, R. A. Q. O’Meara, “The Mode of Action of betaaminobenzenesulphonamide and Prontosil in haemolytic Streptococcal Infections” Lancet (5 December 1936): 1323-26.

- b) Men considered by the Director of the WPRL to be of sufficient importance were to receive specimens with introduction regarding dosage etc. direct from the WPRL who were to maintain a list of those supplied.

Given the intense interest in Prontosil, it was frustrating for the TTC to wait so long for the results from Colebrook. Dr. R. M. Fry who collaborated with Colebrook sent in a summary report of the first 36 cases of haemolytic streptococcal infection. Few patients on Prontosil died of their infections, but in large doses it was associated with some adverse effects, and as a result the TTC advised not to use Prontosil prophylactically. Almost a year after beginning his studies on Prontosil, Colebrook sent in the report, which would eventually herald the dawn of the new chemotherapeutic era.¹³⁹ However, the initial paper was not well written and provoked significant debate at the TTC, incurring further delays.

Dale discussed the paper with Andrewes and King and resolved several errors.¹⁴⁰ Elliott wrote: "I don't find the whole paper well written and do not think it will do much more than incite some other investigator to try the substance", and yet he supported publication in the hope that further evidence would confirm that "the substance is unquestionably useful".¹⁴¹ A further draft of Colebrook's paper was forwarded from Elliott to Green and was discussed at a meeting of the TTC in December 1936.¹⁴² Elliott had already sent his comments directly to Green:

"Since Mellanby is satisfied with this paper I agree to its immediate publication. I wasn't much impressed by the first paper, and I regretted the outburst of excitement in the public press about the discovery, which was only an extension of the German work. Some of the cases in the second paper are indeed certainly most striking. But, the writing, with its italics and excited adjectives, reminds me of Queen Victoria's 'Leaves from a highland diary' – after which page 10 drags one down with a sad bathus. (Sic). This page 10 must be re-written. I remain a little sceptical, and I wonder whether

¹³⁹ T. R. Elliott to F. H. K. Green, (8 May 1936), T. R. Elliott Files, WI GC/42 TTC 1935-42.

¹⁴⁰ F. H. K. Green to T. R. Elliott, (22 May 1936), T. R. Elliott Files, WI GC/42 TTC 1935-42.

¹⁴¹ T. R. Elliott to F. H. K. Green, (29 May 1936), T. R. Elliott Files, WI GC/42 TTC 1935-42.

¹⁴² L. Colebrook to F. H. K. Green, (29 October 1936), F. H. K. Green to T. R. Elliott, (29 October 1936), T. R. Elliott Files, WI GC/42, TTC 1935-42.

the treatment is any better than that by Glycerine which Dr. Colebrook, I think, formerly advocated".¹⁴³

The parting line made it clear that, despite having a new substance with unparalleled activity in the laboratory, and despite the delay and multiple efforts to write the paper, it had been impossible to design and perform a clinical trial, which conclusively showed the benefit of Prontosil. Colebrook's trial was finally published, and soon other Prontosil reports appeared.¹⁴⁴ Gradually a positive consensus of its remarkable activity emerged, opening the way for several firms to produce sulphonamide variants by chemical modification, including American Cyanamid, Sharp & Dohme and Merck. Colebrook tested the sulphanilic acid-4-acetanilide (Ilivin) of E. Merck, which was meant to be less toxic.¹⁴⁵ Evans Sons, Lescher & Webb and Burroughs Wellcome also forwarded preparations to the TTC.¹⁴⁶

Green met investigators who noted the alarming adverse effects of cyanosis and thought the drug might be affecting the patient's heart. It became apparent that the new agents though offering great potential, were not the Ehrlich's 'magic bullet' for they had new and hitherto unseen dangers and it was essential that these were objectively assessed.

Colebrook investigated all new sulphonamides and produced a better report of his experience of sulphanilamide for puerperal fever.¹⁴⁷ The promise shown by Prontosil encouraged the Government to invest £30,000 in 1936 in the preparation of chemically

¹⁴³ T. R. Elliott to F. H. K. Green, (28 October 1936), T. R. Elliott Files, WI GC/42, TTC 1935-42.

¹⁴⁴ T. R. Elliott to F. H. K. Green, (12 February 1937), T. R. Elliott Files, WI GC/42, TTC 1935-42. L. Colebrook, M. Kenny, "Treatment of Human Puerperal Infection and of Experimental Infections in Mice with Prontosil" Lancet (6 June 1936): 279; "Treatment with Prontosil of Puerperal Infections due to Haemolytic Streptococci, Lancet (5 December 1936): 1319-22.

¹⁴⁵ TTC Minute 9, (14 July 1938), MRC File 1523/15.

¹⁴⁶ TTC Minutes 8, (7 February 1938), MRC File 1523/15.

¹⁴⁷ F. H. K. Green to T. R. Elliott, (18 October 1937), T. R. Elliott Files, WI GC/42, TTC 1935-42.

unique sulphonamides, and research in chemotherapy was expanded at the NIMR.¹⁴⁸ The MRC conclusions were that:

“Results of practical value had so far been meagre when compared with the work done in Germany on a large scale over a longer period... effective cooperation was not obtainable in this country. Various proposals for expansion of the scheme were mentioned and particularly one for a central lab for combined chemical and biological investigations supplemented by grants in aid of work at academic centres”.¹⁴⁹

I have described how Burroughs Wellcome began preparing Prontosil as early as 1936. No patent could be traced for the water- soluble sulphonamide, which Burroughs Wellcome also prepared as ‘Soluseptasine’ in 1936.¹⁵⁰ This and similar products appeared in publications as May & Baker also prepared an intramuscular form of Soluseptasine and an oral form, proseptasine.¹⁵¹

“It is the experience of our reps in this country and that in many Institutes that Prontosil and Prontosil album have gained a very strong hold and that in many Institutes supplies sufficient for 1 year have been donated. We hear from our Egyptian depot that solusephasine is being distributed liberally in order to fully establish it in that territory. The competition is making considerable progress as a result of their extended claims”.¹⁵²

The first British firm to market a sulphonamide was May & Baker, where George Newberry,¹⁵³ a graduate of the Royal College of Science who had joined in 1918 prepared Prontosil as M & B 576 in January 1936. By May 1937 Burroughs Wellcome’s Sulph- P, version of Prontosil was being used for otitis media, mastoiditis, rheumatic fever,

¹⁴⁸ MRC Annual Report 1936-7, (1937): 9-15 refers to NIMR 588/6 memo “The Present Position and Future Development of British Research Work in Chemotherapy” (17 March 1936).

¹⁴⁹ MRC Minutes III, (20 March 1936): 47.

¹⁵⁰ G. M. Roberts, “Soluseptasine and Sulphapyridine in Meningitis Due to Pfeiffer Bacillus” *British Medical Journal* (25 November 1939): 1041; “A Table of Sulphonamides”, *Chemist & Druggist* 146.1 (14 September 1946): 336-37; “Soluseptasine” and “Prosephasine” *British Medical Journal* (27 March 1937): 666.

¹⁵¹ STC Meeting, (19 November 1937), WF: STC S/G/50.

¹⁵² STC Meeting, (7 May 1937) WF: STC S/G/50.

¹⁵³ J. Slinn, *A History of May & Baker 1834 – 1984* (Cambridge: Hobson’s Ltd., 1984): 100, 124.

meningococcal meningitis, puerperal sepsis and the soft tissue infection, erysipelas with great success.¹⁵⁴

Arthur J. Ewins and his team synthesised the sulphonamide analogue, M&B 693 in November 1937 and sent a sample to Dr Lionel Whitby, pathologist at the Middlesex Hospital, and Assistant Pathologist at the Bland Sutton Institute and he helped them to select this as their most promising derivative.¹⁵⁵ Samples were also sent to Dr. R. Wien at the pharmacological laboratories of the Pharmaceutical Society for testing in mice, and it was made generally available in September 1938 as sulphapyridine.¹⁵⁶ There was some adverse criticism of M & B 693 by the Americans, but Colebrook resolutely defended the sulphonamides.¹⁵⁷

As regards the testing of Bayer Prontosil, Green recorded in the minutes of the TTC meeting in 1938 that:

“The drugs were now being tested so extensively in various diseases by independent workers throughout the world that their value and limitations were likely to be determined without the Committee taking further initiatives, unless some new and particularly promising variant of sulphanilamide were in due course offered”.¹⁵⁸

Snodgrass had extended his experience to include 360 cases of Scarlet fever treated with sulphanilamide.¹⁵⁹ Fundamental details relating to the dosage were unclear and Colebrook had “no exact information on the incidence of toxic effects” though he had seen two cases of agranulocytosis, or depletion of the white blood cells.¹⁶⁰ “The relation of dosage to

¹⁵⁴ STC Meeting, (24 May 1937), WF: STC S/G/50.

¹⁵⁵ H. H. Dale “Arthur James Ewins”, Biographical Memoirs of Fellows of the Royal Society 4 (1958): 81-91; L. E. H. Whitby, Lancet (26 May 1938).

¹⁵⁶ J. Slinn, (1984): 122 – 125; H. J. Barber, Historical Aspects of Chemotherapy: Six Essays (May & Baker, 1978): 27.

¹⁵⁷ P. H. Long in Iago Galdston, Behind the Sulfa Drugs. A Short History of Chemotherapy (New York: Appleton-Century, 1943); P. H. Long, E. A. Bliss, The Clinical and Experimental use of Sulfanilamide, Sulfapyridine, and Allied Compounds (New York: MacMillan, 1939);

¹⁵⁸ TTC Minutes 8, (7 February 1938), MRC File 1523/15.

¹⁵⁹ W. R. Snodgrass, “Sulphanilamide in Chemotherapy” British Medical Journal (1939): 297.

¹⁶⁰ T.T.C. Minutes 10, (28 March 1939), MRC File 1523/15.

toxicity certainly needs to be carefully studied. It is a little difficult in our cases as so many of them have had a certain amount of sulphanilamide before admission".¹⁶¹

Reference was made to BDH and their compressing of tablets:

“The longer we maintain our strictly conservative attitude, the more difficult it becomes to establish the product of the firm and in view of the research work done in the Institute of the Foundation it is only reasonable that BW & Co should reap the fullest commercial reward”.¹⁶²

BDH had a sulphonamide available in 1937.¹⁶³ Meanwhile, Burroughs Wellcome prepared a series of sulphonamide derivatives, including a new heterocyclic sulphonamide,¹⁶⁴ and Buttle and Trevan worked on a diacetyldiaminodiphenylsulphone derivative, which was sent to Prof. Garrod at St. Bartholomew's,¹⁶⁵ while clinical trials of sulphonamide glucoside and also a diadipyl derivative were proposed, if laboratory tests were promising. In short, the excitement created by Prontosil and the lack of patent protection of the original base stimulated Burroughs Wellcome and other British firms to produce a series of sulphonamides for testing.¹⁶⁶ C. J. Hewlett and Sons, May & Baker, Evans Sons, E. R. Squibb and Burroughs Wellcome patented various sulphonamides in 1937, and Trevan arranged clinical trials of Sulphonamide P in 1938. The TTC found that Solu-salvarsan was less effective, and was more toxic than neoarsphenamine. There had been eight cases of arsenical dermatitis, including one with jaundice, out of only 20 cases treated. It “lacked the advantages claimed and gave general toxic symptoms or local pain only” In this case the TTC decided that the results would not be published unless the company withdrew the

¹⁶¹ L. Colebrook to F. H. K. Green, (11 May 1939), T. R. Elliott Files, WI GC/42, TTC 1935-42.

¹⁶² STC Meeting, (24 May 1937), WF: STC S/G/50.

¹⁶³ “Sulphonamide BDH”, Pharmaceutical Journal (13 February 1937): 187
Sulphonamide compounds: a Summary of Recent Reports, Pharmaceutical Journal (25 June 1938): 665-66.

¹⁶⁴ STC Meeting, (31 January 1939), WF: STC S/G/50.

¹⁶⁵ J. H. Gaddum, “John William Trevan” Biographical Memoirs of Fellows of the Royal Society 3 (1957): 275.

¹⁶⁶ C. L. Oakley, “Note on ‘Prontosil’ - Poisoning in Mice” Biochemical Journal 31 (1937): 729 – 730; “An Outline of Chemotherapy-Sulphonamides” Pharmaceutical Journal 142 (29 April 1939): 443-44.

product and they decided to “advise to withdraw application to the Ministry of Health”.¹⁶⁷ At the 1939 British Pharmaceutical Conference, chairman J. Rutherford Hill called for “clinical experience tests prior to definite authoritative recognition”.¹⁶⁸ His concern was that Britain was still fighting a battle against patent medicines and careless manufacturers recalling that this had been ongoing since the early efforts of Prof A. J. Clark and that the 1914 Select Committee had warned:

“British law is powerless to prevent any person from procuring any drug, or making any mixture, whether potent or without therapeutic activity whatever (as long as it does not contain a scheduled poison), advertising it in any decent term as a cure for any disease or ailment, recommending it by bogus testimonials and the unwanted opinions and facsimile signatures of fictitious physicians, and sending it under any name he chooses, on the payment of a small stamp duty, for any price he can persuade a credulous public to pay”.¹⁶⁹

The Venereal Diseases Act of 1917 represented the only real progress that had been made against such remedies.

Because of the publicity generated by Prontosil, British firms found ready takers for their new sulphonamides and did not need to evaluate them through the TTC. This was an important milestone in the development and testing of the synthetic British pharmaceuticals. When physicians were convinced of the activity of insulin, synthetic oestrone and sulphonamides, they were keen to participate in clinical trials.

8.6 Clinical Trials of Other Antisypilitics – Increased Synthetic Activity.

Although Salvarsan had been available and had been studied extensively for 25 years, research was still being performed on organic arsenicals at Burroughs Wellcome and several other British firms in 1934-37. Ewins of May & Baker registered patents for

¹⁶⁷ T.T.C. Minutes 6, (28 February 1936) and T.T.C. Minutes 10 (28 March 1939), MRC File 1523/15.

¹⁶⁸ J. Rutherford Hill, “Public Health in Relation to Recognition, definition, standardisation and Controlled supply of Medicines” Pharmaceutical Journal (22 July 1939): 85.

¹⁶⁹ *Ibid.*

organic arsenicals in 1935-6.¹⁷⁰ However, despite the establishment of procedures for testing novel agents by the second Salvarsan Committee from 1918, Colonel Harrison commented on “the unsatisfactory state of the present arrangements for testing new antisyphilitic remedies on behalf of the TTC...(it was) unfair to the manufacturer to expect one man to assess a new remedy”.¹⁷¹ His comments refer back to Bayer’s Solu-salvarsan in July 1936, imported under the Therapeutic Substances Act, which Harrison examined at St. Thomas’ Hospital, but his studies dragged on for eighteen months and were still inconclusive.¹⁷²

Green asked Harrison to nominate a small ad hoc conference of venerologists to meet at the Ministry of Health to undertake clinical trials of any promising new antisyphilitics submitted to the TTC. Those invited to participate were T. Anwyl Davies, and V. E. Lloyd of Guys’ Hospital, G. L. M. McElligott, and Mrs. M. Rorke of the Royal Free Hospital¹⁷³ and Thomas Carnwath¹⁷⁴, a senior medical officer in the Ministry of Health.¹⁷⁵ Firstly they discussed ongoing trials of Eustab (Boots), Bismutrat (distributed by Wilcox, Jozeau & Co. on behalf of a Nordmark Werke of Hamburg), Solu-salvarsan (Bayer), and Mapharsan (Parke Davis). The unusual step was taken of inviting an overseas investigator, Prof. H. Haxthausen of Copenhagen to participate in tests of Eustab.¹⁷⁶ However, Boots eventually agreed not to market Eustab and in 1938 Bismutrat was also given the verdict of “unpromising”¹⁷⁷

After the patents of the two principal drugs for treating sleeping sickness (tryparsamide and Bayer 205 or Germanin), lapsed in November 1935, Burroughs Wellcome announced that Tryparsonone would be available on demand as a special, following

¹⁷⁰ D. M. Joliffe, “A History of the Use of Arsenicals in Man” *J. Royal Soc. Med.* 86 (May 1993): 287-89.

¹⁷¹ F. H. K. Green to H. H. Dale (9 January 1936): T. R. Elliott Files, WI GC/42. TTC 1935-42; Colonel L. W. Harrison, was a specialist in syphilology, who was involved in the International Standards committee MRC Minutes, (20 January 1922): 190.

¹⁷² F. H. K. Green to H. H. Dale, (9 January 1936); TTC. Minutes 5, (5 March 1934) MRC File 1523/15.

¹⁷³ TTC Minutes 6, (28 February 1936), MRC File 1523/15.

¹⁷⁴ L. Bryder in J. Austoker and L. Bryder (eds.), (1989): 69.

¹⁷⁵ TTC Minutes 6, (28 February 1936), MRC File 1523/15.

¹⁷⁶ T. R. Elliott to F. H. K. Green, (10 January 1936), T. R. Elliott Files, WI GC/42, TTC 1935-42.

the introduction of 'Neocryl'. Most of the STC members felt there would be considerable demand though Jowett felt sales would be 'unremarkable' at the price.¹⁷⁸ Burroughs Wellcome's Neocryl, ('Crylarsan') was tested in about 100 cases of neurosyphilis, but no clinicians treated more than a handful of cases and as a result none had sufficient cases for a publication.¹⁷⁹ The TTC were convinced that the drug was less active than Tryparsamide, and when they notified this to the Manufacturers Association, the Company decided not to market the product in Britain. Prof. Warrington Yorke at the Liverpool School of Tropical Medicine arranged for his colleague, Dr. Ian S. Acres to study Neocryl for African sleeping sickness in the Belgian Congo and it was active, but only in the first stage of disease.¹⁸⁰ Further confirmation came from another of Yorke's former colleagues, Dr. F. Murgatroyd in the Gambia.¹⁸¹ In view of the renewed interest in Neocryl and the competitive prices, the Burroughs Wellcome strategy was that it was only to be sold on demand.¹⁸² However, the decision was short-lived as in 1938 they decided not to do any further clinical work on Neocryl because of safety issues.¹⁸³ In comparison to the sulphonamide, the arsenicals were now a poor alternative.

8.7 Novel Compounds Put Forward for Testing by British Firms 1931-1939.

I have outlined how the TTC extended the interests of the MRC in organotherapy, an area in which they felt they could exert control over manufacturers by biological standardisation and briefly described their studies of vitamins and antibacterials. The aim of this section is to evaluate which firms utilised the services of the TTC and for which additional products. It gives an insight into the state of the British pharmaceutical industry

¹⁷⁷ TTC Minutes 8, (7 February 1938), MRC File 1523/15.

¹⁷⁸ STC Meetings, (19 May 1933), WF: STC S/G/49; (15 November 1935), (13 March 1936), WF: STC S/G/50.

¹⁷⁹ TTC Minutes 10, (28 March 1939), MRC File 1523/15.

¹⁸⁰ W. Yorke to F. H. K. Green, (15 June 1937), T. R. Elliott Files, WI GC/42, TTC 1935-42.

¹⁸¹ Dr. F. Murgatroyd had trained in Liverpool under Warrington Yorke and had received a grant from the MRC: MRC Minutes II, (11 November 1927): 190.

¹⁸² STC Meeting, (28 May 1936), WF: STC S/G/49.

¹⁸³ STC Meeting, (18 February 1938), WF: STC S/G/49.

from 1931 to 1939 and allows an assessment of how many products were synthetic, or otherwise novel drugs and how many were copies of drugs discovered elsewhere. The general growth of British pharmaceutical manufacturing between 1919 and 1931 was described in chapter 5.

In the 10 years that the TTC was in existence a total of 59 products were accepted for testing as noted in the formal minutes of their meetings. There were three occasions when two companies submitted identical drugs, making a total of 62 drugs tested. These were provided as follows; Boots 9, Burroughs Wellcome 8, British Drug Houses 7, CIBA (Switzerland) 4, May & Baker 3, E. Merck (Germany) 3, Organon (Netherlands) 3, Hoffmann la Roche (Switzerland) 3, Bayer (Germany) 3, Napp (UK) 2, Imperial Chemical Industries (UK) 2, Parke Davis (USA) 2, Wilcox Jozeau 1, ABCM 1, Eli Lilly (USA) 1, Beiersdorf (Germany) 1, Glaxo 1, Merck (USA: New Jersey) 1, Chase (France) 1, Cilag (Switzerland) 1, Boake Roberts (UK) 1, Schering (Germany) 1, Upster Smith (USA) 1, independent 1, Smith Kline French (USA) 1. The Edinburgh based companies did not use the TTC and their main interaction was with the Research laboratory of the Royal College of Physicians in Edinburgh.¹⁸⁴

The principal British companies involved with the TTC were as follows:

8.7.1 Boots Pure Drug Company.

The immediate post war developments at Boots were described in Chapter 5, up to the appointment of Pyman in 1927. I have already described how Boots propyl guaiacol antiseptic was rejected at the first meeting of the TTC,¹⁸⁵ though the Chemotherapy Committee then arranged trials of it as an amoebicide in Kuala Lumpur.¹⁸⁶ Jesse Boot died in July 1931, but his son bought a new site at Bulwell on the outskirts of Nottingham and returned Boots to British control again in 1933.¹⁸⁷ The firm had effectively been in American hands since 1920 when Jesse Boot accepted an offer of £2.25 million to sell the

¹⁸⁴ "Edinburgh Manufacturing Houses" Pharmaceutical Journal 141 (20 August 1938): 163-4.

¹⁸⁵ TTC Minutes 5, MRC File 1523/15, (5 March 1934).

¹⁸⁶ TTC Minutes 1, MRC File 1523/15, (8 July 1931).

¹⁸⁷ Christopher Weir, Jesse Boot of Nottingham. Founder of the Boots Company (Nottingham: The Boots Company, 1994): 60-1; R. P. T. Davenport Hines, J. Slinn. (1992): 97.

business to the United Drug Company.¹⁸⁸ Boots had boasted being the largest authorised manufacturers of insulin and had “an unrivalled analytical department” within a plant of 14 acres and more than a million feet of floor space.¹⁸⁹ The Boots Pure Drug Company had 8 drugs accepted by the TTC, though 4 of these were variants of Harmol, a salt of the alkaloid harmine, tested as a potential vasodilator for coronary disease and the alternative nonyl- Harmol. Harmol could be used to cut short heart attacks, to forestall individual attacks and to prevent attacks. It was tested in only one case at the Tropical Laboratories in London, and was then sent to the London Hospital, to Guy’s Hospital, the National Eye Hospital, London and Manchester, and although still only tested in a limited number of cases, described as of “little value” - yet it received much praise in the National press. Bramwell in Manchester investigated Harmol in 41 cases, but only 7 responded and the more active, but also more toxic propyl Harmol in 20 cases.¹⁹⁰ Some investigators found Harmol useful for angina, when given subcutaneously but it caused irritation and had little effect when given orally, and larger doses caused colic.¹⁹¹ This was the reason that Boots offered a more soluble version to Fraser and Ryle and subsequently to a wider range of investigators, while G. Carmichael Low and N. Hamilton Fairley evaluated nonyl Harmol as an amoebicide in the tropics. It was very active against *Entamoeba* “but unfortunately it did not survive the acid test of clinical trial”.¹⁹² The analogy is interesting as ‘the acid test’ presumably refers to the use of litmus paper to give a clear unambiguous result. Boots released a circulatory stimulant called Phrenazol onto the market in 1939 and also marketed preparations of Hog’s stomach for pernicious anaemia and Anthostat, a gonadotrophin hormone extract but they came late to hormonal extracts and concentrated from the start on synthetics including diethylstilboestrol.

¹⁸⁸ “Boots Drugs Business. Reasons for the American Amalgamation” The Times (5 July 1920): 25.

¹⁸⁹ Jonathan Liebenau, “The MRC and the Pharmaceutical Industry” in Joan Austoker and Linda Bryder (eds.), (1989): 179.

¹⁹⁰ TTC Minutes 3, (8 July 1932), MRC File 1523/15; J. C. Bramwell, J. M. H. Campbell, W. Evans, “Harmol HCl and o-n-Propylharmol Lactate in Angina Pectoris” Lancet (8 July 1933): 69; G. K. Elphick, J. A. Gunn, Quart. J. Pharmacology (1932): 37.

¹⁹¹ TTC Minutes 2, (15 January 1932), MRC File 1523/15.

¹⁹² H. King, “Frank Lee Pyman” Obituary Notices of Fellows of the Royal Society 4 (1944): 681-697.

Boots had an earlier intestinal and urinary antiseptic called hexylresorcinol¹⁹³ and amyl meta-cresol, a synthetic derivative was found by Pyman to be 280-fold more active than phenol on the basis of laboratory tests. It was put up for clinical trial in 1931-2 at St. Peter's Hospital and Queen Charlotte's Hospital in London, but was found to be ineffective and no publication was issued.¹⁹⁴ Further Boots antiseptics were studied at St Bart's, St Thomas' and Queen Charlotte's in London and The London Hospital, the National Heart Hospital and in Edinburgh, Cambridge and Manchester but without real success.¹⁹⁵ On the basis of the TTC findings, Boots felt that the lack of activity was due to poor solubility, hence the reason for preparing more soluble salts were prepared but eventually Boots agreed not to issue the substance.

Prof. J. B. Cohen in Leeds was a member of the MRC Committee on Research in Chemotherapy and the recipient of an MRC grant for biological work.¹⁹⁶ He prepared Quinadil, and had a long – term interest in topical antiseptics and had produced various chloramines with Dakin during the First World War. Boots had already sent Quinadil to the Chemotherapy Committee and both Boots and BDH submitted their versions of it to the TTC, and it was then promptly sent it back to Prof. Cohen for evaluation, but it had “no special advantages in surgery” and it was decided not to publish the results.¹⁹⁷ W. A. Broom and E. M. Bavin of Boots performed potency tests on their heparin preparation and collaborated with the NIMR, but it was not sent to the TTC.¹⁹⁸

In summary, Boots achieved few truly novel compounds in the 1920s and early 1930's, when they continued their wartime interest in antiseptics. They marketed a new form of Burnol acriflavine cream in 1934. They must have been disappointed that their interactions with the TTC as antiseptics and Harmol derivatives that they thought were useful were shown to have limited value in small studies. The problem for the MRC was that laboratory testing of antiseptics did not reflect their potential activity when given

¹⁹³ Chemist & Druggist 103.3 (12 December 1925) xi advert

¹⁹⁴ C. H. Hampshire in What Industry Owes to Chemical Science Richard B. Pilcher, F. Butler Jones, (eds.), (Cambridge: W. Heffer, 3rd edition, 1945): 68-74; TTC Minutes 3, (8 July 1932); TTC Minutes 4, (unknown, 1933), MRC File 1523/15; S. A. B. Kipping. Chemistry and Industry (25 February 1963): 304.

¹⁹⁵ TTC Minutes 1, (8 July 1931), MRC File 1523/15.

¹⁹⁶ MRC Minutes II (15 July 1927): 127.

¹⁹⁷ TTC Meeting 3, (8 July 1932); TTC Meeting 4, (undated), MRC File 1523/15.

¹⁹⁸ “The Biological Standardisation of Heparin”, Dale Archive 93 HD 38.16.3

systemically. Boots eventually gave up their efforts on antiseptics and they too prepared sulphonamide antibiotic derivatives after the discovery of Prontosil,¹⁹⁹ patenting a sulphonamide antibacterial with increased stability, P-sulphonoamidobenzamine, which was shown by the NIMR to be the first agent to cure mice infected with *Salmonella typhi*. Under Pyman's direction a series of glycerophosphates salts, histidine preparations, glyoxalines, isoquinolines, arsenic derivatives and a variety of amidines were synthesised and his team evaluated local anaesthetics, antiseptics, pressor drugs, antimalarials, hypoglycaemics, purgatives, acridines and organic salts of bismuth²⁰⁰ Pyman gave an insight into Boots research in his paper to the SCI on 13 May 1935. He explained the chemistry behind Harmol and the preparation of bismuth in oil and the improved drugs that were now available to replace Salvarsan, such as Stabilarsan, a more stable form.²⁰¹

8.7.2 May & Baker.

Ewins built up a small but strong chemical and manufacturing team. In addition to Newberry, they took on Capt. R. W. E. Stickings, a graduate of Kings College. Their work focused on arsenicals from Rhône Poulenc and then from 1925 they prepared tryparsamide under license from the Rockefeller Institute. Frank Paxon joined as a chemist, then moved to the works and was replaced by Dr. H. J. Barber from Kings College in 1927 so they had 4 chemists, 2 pharmacists and 6 assistants.²⁰² Following Bayer's demonstration of the potential of organic arsenicals, May & Baker began producing these chemicals by chemical modification from September 1926, achieving the synthesis of some compounds with moderate activity against trypanosomes. One of the synthetic series was tested in the laboratory by Warrington Yorke in Liverpool, but did not progress to trials. May & Baker's Halarsol was evaluated by the TTC and found to be useful for syphilis but had severe side-effects and was considered "unsuitable" though good results were obtained in treating yaws, a tropical disease, caused by a similar spirochete bacteria to that causing

¹⁹⁹ S. A. B. Kipping, (1963): 302 – 310. Boots produced patents on sulphonamide derivatives in 1940 and 1942, H. King, (1944): 681-697.

²⁰⁰ H. King, "Frank Lee Pyman" Obituary Notices of Fellows of the Royal Society 4 (1944): 681-697.

²⁰¹ F. L. Pyman, Pharmaceutical Journal (25 May 1935): 619.

²⁰² J. Slinn (1984): 100-1.

syphilis.²⁰³ The TTC arranged for centres in Cardiff and Glasgow to evaluate a more dilute solution of Halarsol.²⁰⁴ Parosan was rejected by the TTC, though no reason was recorded. Neither Halarsol nor Parosan were mentioned in Slinn's '*History of May & Baker,*' nor in the 1948 British Pharmacopoeia, indicating they were probably dropped though Pyman referred to Halarsol in 1935.²⁰⁵

May & Baker had only limited interaction with the TTC: of the 3 products that they put forward one was rejected and the others were of limited value. It is perhaps surprising that with Ewins in charge May & Baker made such little progress, but in the past Ewins had been part of an experienced team with physiologists, both at Burroughs Wellcome and the MRC. In the 36 years after leaving Dale he put his name to only 6 further publications. He was not one for innovative work, but quickly built upon the findings of others. However one of his colleagues, H. J. Barber at M&B explained that he had played a significant role in building their research capacity at M&B. Dr R. Wien, (who joined the firm as a result of their collaboration with the Pharmaceutical Society), J. G. Ever and Mr E. J. Baines were colleagues in the chemistry section.²⁰⁶ May & Baker felt they needed a clinician to help them to maximise the new opportunity offered by M&B693. This is the first case I have found of a British pharmaceutical firm recruiting a physician specifically to perform clinical trials. May & Baker put their request to the ABCM for a doctor aged 30 to 35 years:

“ who could put in a half to three-quarters of his time at the works of the firm, and the rest of the time doing hospital work. The latter would have to be done somewhere eastwards of London in order that the doctor would not have to spend too much time travelling. The work would be related to venereal disease treatment and it would be therefore be advantageous if the hospital work could similarly be so related”.²⁰⁷

Although nobody was immediately came to mind, Landsborough Thompson wrote to Pratt of the ABCM that:

“the fact that at least half the man's time will be taken up suggests that he is to do something more than advise on clinical questions and deal with

²⁰³ TTC Minutes 4, (date not recorded, 1933), File 1523/15.

²⁰⁴ TTC Minutes 2, (15 January 1932), File 1523/15.

²⁰⁵ J. Slinn, (1984).

²⁰⁶ H. J. Barber, “ Arthur J. Ewins, Obituary” Chemistry & Industry (22 February 1958).

²⁰⁷ May & Baker to ABCM, (18 September 1935), “ABCM” MRC File 1523.

professional inquiries, but if he is to take any greater part in the production or testing of therapeutic preparations, then special qualifications would be required".²⁰⁸

However, within four days a candidate called Robert Forgan was identified. He was a little different to the requirement as he was nearly 44 years old and had been "sowing his political wild oats" before returning to general practice. He had specialised in Venereal Diseases for many years. Furthermore he had experience of the commercial side "having acted for a time in an advisory capacity with BDH Ltd. He was described as "a man of energy and ideas, with a leaning towards work of an administrative kind".²⁰⁹

In their next round of communication with the ABCM, May & Baker indicated that their requirements were wider than first indicated:

1. A medical man to do full time work on literature etc. inside the office.
2. Connections with a medical man still in practice who could give us advice and assistance in launching new products, especially in matters of dosage etc.
3. One or two medical men who will act for us as an outside representatives.

In the case of the latter they wanted a young man otherwise they would "probably want too much remuneration or be no good".²¹⁰ The aim was clearly to make the most of their breakthrough product M&B 693 and the employment of Forgan together with the collaboration with Whitby pointed to a greater independence in clinical testing. It was relatively easy to arrange studies of M&B 693. A large study of 102 cases reported in December 1938 was "indebted to M&B for supplies of the drug and to Dr. Robert Forgan for advice and literature".²¹¹ Forgan helped to produce a pamphlet about the drug.²¹²

²⁰⁸ A. Landsborough Thompson to J. D. Pratt, (20 September 1935), "ABCM" MRC File 1523.

²⁰⁹ A. Landsborough Thompson to J. D. Pratt, (24 September 1935), "ABCM" MRC File 1523.

²¹⁰ J. D. Pratt to A. Landsborough Thompson, (27 September 1935) "ABCM" MRC File 1523.

²¹¹ R. C. L. Batchelor, R. Lees, M. Murrell (Edinburgh RI), G. J. H. Braine (Colonial Medical Service), British Medical Journal (3 December 1938): 1142-5.

²¹² "M&B693" British Medical Journal (12 November 1938): 1028.

Thereafter, the most significant contributions of M&B were a series of diamines, prepared from December 1937 (M&B720). Several were tested by the TTC and some found use in tropical diseases: M&B 736 or phenamine for bovine and canine babesiasis and M&B744 or stibamine for kala-azar, while M&B782 and M&B800 were used in trypanosomal infections. Probably the most useful was pentamidine.

8.7.3. Burroughs Wellcome.

George Pearson of Burroughs Wellcome had been one of the main driving forces requesting assistance from the MRC in setting up clinical studies. Frustrated by the difficulty of getting drugs tested in Britain, Pearson had asked Thomas Henry of the WPRL at the start of 1931 to discuss with the firm's German office, the possibility of performing clinical trials of ergotoxine in Germany, as it had never been the subject of a thorough clinical trial on the continent.²¹³

The Burroughs Wellcome STC recommended that a clinical trial of ergotoxine should be made both in England and in Germany, and Dale was contacted informally to establish whether the 'Chemotherapy Committee' would raise any difficulty about doing a trial with the TTC if one had already started in Germany. Dale's reply, in line with the proposed guidelines was that a trial of ergotoxine should be performed, but that the TTC were only prepared to do this work if no trials were done in Germany.²¹⁴ In view of the establishment of the TTC, the STC reviewed all of their products since neo-avenyl in 1925 to decide which to submit for trials.²¹⁵

²¹³ Communicated from H. A. D. Jowett to G. Pearson, (25 February 1931) and G. Pearson to C. M. Wenyon, (25 March 1931), WF: STC S/G/49.

²¹⁴ STC Meeting, (21 October 1925), WF: STC S/G/49.

²¹⁵ The drugs considered for submission to the T.T.C. were Ascaridole (chenopodium oil), glutathione, ergotoxine, ovarian hormone, hirudin, adenosine, Kharophen, carotene, ventriculin, vitamin B, (neo) infundin, harmine, bulbocarpine, d-hyoscyamine, diginitin, and Collip's placental extract, bismuth cacodylate in combination with Stovarsol, reduced glutathione, digitalis glucosides, ouabain (extracted from seeds from Nigeria), thyroxine, and soloid iron alum, liver extract, irradiated ergosterol, quinoxyl, hypnocampus oil, quinine/urethane, and Carofax. STC Meeting, (27 March 1931), WF: STC S/G/49.

All of the three cardiovascular products that Burroughs Wellcome submitted to the first TTC meeting were accepted for trials. In addition to ergotoxine ethanesulphate,²¹⁶ these were digoxin and digitalinum verum (diginutin), discovered in August 1929.²¹⁷ There were new derivatives of *Digitalis*, which had been used as an extract for centuries.²¹⁸ However, with improved control of its activity, first by biological standardisation and then by purification of the active glycosides, digitoxin and digitalin that were described in 1928-9, many companies were developing new formulations. In 1930 Dr. Sydney Smith at the WPRL isolated digoxin from foxgloves (*Digitalis lanata*) and the TTC proposed to contact Prof. Lewis at University College to evaluate the new purified glycoside for treating heart pains (angina).²¹⁹ The TTC was “very satisfied” with the study performed and suggested a publication by Edward J. Wayne of UCH (later Professor of Medicine in Glasgow)²²⁰ in *Clinical Science* (previously *Heart*), the *British Medical Journal* and *Nature*.²²¹

Similar gradual advances had taken place in understanding the roles of the various active ingredients of ergot. Joshua Burn at the Pharmaceutical Society examined ergotoxine for Burroughs Wellcome and found that their preparation Ernutin was better than other biological and calorimetric standards. However, only ergotoxine was assayed and they now recognised the need to report the amount of ergotamine present. Burroughs Wellcome had patented their ergotoxine preparation and if ergotamine also turned out to be valuable they planned to apply for a subsidiary patent. The similarity between ergotoxine and ergotamine led clinicians to question, which was best. Meanwhile the WCRL examined Stoll’s new ergot alkaloid ergocristine, to evaluate whether that further confused the situation.²²²

²¹⁶ This preparation had the advantage of stability over previous versions; J. Chassar Moir, “Clinical Comparison of Ergotoxine and Ergotamine: report to the TTC of the MRC” British Medical Journal (4 June 1932) 1022-4; TTC Minutes 3, (8 July 1932), MRC File 1523/15.

²¹⁷ E. J. Wayne, “Clinical Observation of Two Pure Glucosides of *Digitalis*: Digoxin and Digitalinum verum” Clinical Science 1 (1933): 63.

²¹⁸ Walter Sneader, (1985): 136-38.

²¹⁹ STC Meeting, (23 January 1931), WF: STC S/G/49.

²²⁰ Lancet (13 October 1930): 932.

²²¹ TTC Minutes 3, (8 July 1932), MRC File 1523/15; STC Meeting, (19 May 1933), WF: STC S/G/49.

²²² STC Meeting, (2 April 1938), WF: STC S/G/49; Walter Sneader, (1985): 107.

The TTC invited F. J. Browne of UCH to compare the drugs clinically and one of his assistants, John Chassar Moir, devised a sensitive method of detecting their effects by inserting a balloon into the uterus of patients undergoing pelvic examination, a week after giving birth. Using the balloon to measure uterine pressure changes, Moir showed that neither of the recognised alkaloids, ergotoxine and ergometrine had an effect on the uterus but that the liquid extract previously thought to contain little ergot gave unprecedented activity, and Dudley later identified this in 1935 to be due to ergometrine.²²³ Within 3 weeks Wenyon arranged preparation of commercial supplies of ergometrine at Burroughs Wellcome.²²⁴ A favourable report led to cautious reference in the company literature.²²⁵ Both Allen & Hanbury's and BDH soon followed.²²⁶ Chassar Moir performed further clinical tests on ergometrine and confirmed its activity.²²⁷ Some years later Moir recalled his research:

“as a recent-comer to the hospital I had sensed the need for caution in conducting research. I knew that I had the support of my chief and other members of staff, but in some quarters there was undoubtedly an atmosphere of suspicion which sometimes even approached hostility”.²²⁸

The next drug that Burroughs Wellcome approached the TTC with was Prostigmine. Thomas Fraser in Edinburgh had extracted the active ingredient, physostigmine from

²²³ C. Moir, H. H. Dale, “The Action of Ergot Preparations on the Puerperal Uterus: a Clinical Investigation with Special Reference to an Active Constituent of Ergot as yet Unidentified” British Medical Journal (18 June 1932): 1119; H. Dudley, J. C. Moir, “The Substance Responsible for the Traditional Clinical Effect of Ergot” British Medical Journal (16 March 1935): 520-23, 532-33; J. C. Moir “Intrinsic Dysmenorrhoea” Proceedings of the Royal Society of Medicine 29 (1936): 950; P. M. Dunn, “John Chassar Moir (1900 – 1977) and the Discovery of Ergometrine” Arch. Dis. Child (Fetal Neonatal Edition) 87.2 (2002): F152—4; In 1935 Moir moved to the Hammersmith hospital and in 1937 became the first Nuffield Professor of Obstetrics and Gynaecology in Oxford and a member of the MRC Committee.

²²⁴ STC Minutes, (12 July 1935), WF: STC S/G/49; “Ergometrine” British Medical Journal (4 May 1935): 929.

²²⁵ STC Minutes, (7 October 1936), WF: STC S/G/49; Walter Sneader: (1985): 108-110.

²²⁶ “Ergometrine” British Medical Journal (25 May 1935): 1075.

²²⁷ C. Moir, “Clinical experiences with the new alkaloid ergometrine” British Medical Journal (24 October 1936): 799-801; E. M. Tansey, “Ergot to ergometrine: an obstetric renaissance?” Clio Med. 61 (2001): 195-215.

²²⁸ J. C. Moir, “The Obstetrician bids, and the uterus contracts” British Medical Journal (1964) ii: 1025-9, quoted in P. M. Dunn, “John Chassar Moir (1900-1977) and the discovery of ergometrine” Arch. Dis. Child Fetal Neonatal Ed (September 2002): F152-54.

Calabar beans, and it could prevent blindness caused by glaucoma, but physostigmine was readily broken down in the body by hydrolysis. The former Burroughs Wellcome researchers Edgar Stedman and George Barger, in Edinburgh discovered the structure of physostigmine in 1925 and produced stable analogues including miotine, which was tested in the clinic in 1931. Several pharmaceutical firms prepared further stable forms and the TTC was already testing Prostigmine for Hoffmann la Roche, which was found to be “of value” by Fraser, Carmichael and Wilkie. A series of factors led Burroughs Wellcome to evaluate Prostigmine and other urethanes at the WPRL. In 1932 Stedman showed that these analogues blocked the cholinesterase enzyme, which destroys acetylcholine in the body, thereby stopping nerve transmissions.²²⁹ Urethanes had been examined previously in Germany, by the pharmacologist, Schmiedeberg and Bayer had evaluated a compound called Hedonal in 1899, but found some minor toxicity issues and their patents expired in 1913.²³⁰ In 1934 a British clinician noted the similarities between the symptoms of the rare paralytic disorder myasthenia gravis and the poisoning by curare, for which physostigmine was an antidote, so she tried it on a patient with the disease and achieved excellent results.²³¹ Although the Burroughs Wellcome version was initially reported by Trevan to be unsatisfactory in the laboratory, it was beneficial in myasthenia gravis.²³² Ryle²³³ in Cambridge agreed, but thought there was little advantage over pituitary extract (pituintrin).²³⁴ Francis Fraser, at St. Bartholomew’s and E. Arnold Carmichael²³⁵ at the National Hospital in Queen Street, London reported a multicentre study that showed Prostigmine was helpful for post-operative atony of the intestine, causing contractions, without the cardiovascular effects caused by physostigmine. Prostigmine was also evaluated in asthma, bronchial asthma, myasthenia gravis and enuresis, and for raising

²²⁹ Walter Sneader, (1985): 116-17.

²³⁰ STC Meetings, (5 April 1935) and (12 July 1935), WF: STC S/G/49; Walter Sneader, (1985), 27, 337-338.

²³¹ Walter Sneader (1985), 118.

²³² STC Meeting, (7 October 1936), WF: STC S/G/49.

²³³ D. Porter, “Changing Disciplines: John Ryle and the Making of Social Medicine in Britain in the 1940s”, *Hist. Sci.* 30 (1992): 137-64; He was in charge of the lab set up under the EPHLS, the emergency Public health service: Geoffrey Tweedale, *At the Sign of the Plough: 275 Years of Allen & Hanbury’s and the British Pharmaceutical Industry 1715 - 1990* (London: Murray, 1990): 36.

²³⁴ J. Ryle to F. H. K. Green, (30 May, 1933), MRC File 1523/21.

²³⁵ E. A. Carmichael had received an M.R.C. grant in 1926 for research on cerebral glioma, M.R.C. Minutes II, (22 October 1926): 16, 181.

blood pressure following anaesthesia.²³⁶ In fact, overall the studies on Prostigmine were probably among the most successful by the TTC in terms of generating data and publications.²³⁷

Burroughs Wellcome also sent preparations of Indian ephedrine and pseudoephedrine to the TTC for evaluation. G. W. Bray and L. J. Witts, Nuffield Professor of Medicine in Oxford²³⁸ treated 52 courses in 18 patients with ephedrine and 49 courses in 20 control patients.²³⁹ Wilkie reported that in general, pseudoephedrine was not as good as ephedrine in raising blood pressure in anaesthetic shock. These agents were also evaluated in asthma clinics at Guy's Hospital and at Great Ormond Street,²⁴⁰ and in the relief of post-operative distension and paralytic ileus.²⁴¹ In this case the TTC were able to take advantage of emerging pharmacology and fully evaluate the Burroughs Wellcome and Roche preparations.

Burroughs Wellcome was always on the look out for other potential new drugs in the medical literature, such as an extract from *Potentilla anserma*, and an extract of larvae of *Lucilia cericorta*.²⁴² When ferrous iron preparations for anaemia were described in

²³⁶ E. H. Carmichael, S. R. Fraser, D. McKelvey, D. P. D. Wilkie, Lancet (5 March 1934): 342.

²³⁷ J. E. Monro, "Ephedrine and Pseudoephedrine in Spinal Anaesthesia" Quarterly Journal of Pharmacy and Pharmacology 7 (1934): 32; G. Barger, "From Physostigmine to Prostigmin" Pharmaceutical Journal 141 (29 October 1938): 437-38.

²³⁸ J. Austoker and L. Bryder (eds.), (1989): 214, 220, 223-4, 236. Ryle noted Witts when he was a young clinician at Guy's hospital. In 1934 he received MRC support for his research on splenic anaemia. He became the first Nuffield Professor in Oxford and later edited one of the earliest books on clinical trials, L. J. Witts (ed.), Medical Surveys and Clinical Trials: Some Methods and Applications of Group Research in Medicine (London: Oxford University Press, 1959).

²³⁹ TTC Minutes 2, (15 January 1932), TTC Minutes 3, (8 July 1932), MRC File 1523/15; G. W. Bray, L. J. Witts, "Pseudoephedrine in Asthma" Lancet (14 April 1934): 788-790.

²⁴⁰ TTC Minutes 2, (15 January 1932), MRC File 1523/15.

²⁴¹ T. R. Elliott to F. H. K. Green, (9 February 1934) and F. H. K. Green to T. R. Elliott, (21 February 1934), T. R. Elliott Files, WI GC/42 TTC 1933-34; J. B. Christophersen, M. Broadbent, "Ephedrine and Pseudoephedrine in Asthma, Bronchial Asthma and Enuresis", British Medical Journal (2 June 1934): 978-79; S. B. Dimson, "The Pressor Actions of Ephedrine and Pseudoephedrine in Man" Quarterly Journal of Pharmacy and Pharmacology 7 (1934): 23; J. E. Monro, "Ephedrine and Pseudoephedrine in Spinal Anaesthesia, Quart J. Pharm. 7 (1934): 32.

²⁴² STC Meeting, (1 October 1936), WF: STC S/G/50.

Lancet and *British Medical Journal* articles, Burroughs Wellcome prepared propaganda on Bland's pills, which they already sold, as a stable ferrous preparation, which in the presence of gastric juice produced ferric chloride.²⁴³ Even before Trevan arranged clinical trials on histidine hydrochloride for the treatment of duodenal ulcers it was suggested to release it on the basis of publications elsewhere.²⁴⁴ On a similar basis they marketed aryl esters of hydnicarpus oil acid, and Carbasone. The latter had no UK patent nor had a trade name registered.²⁴⁵ They felt there was sufficient evidence for tannic acid jelly to justify placing it on the market in Canada. These products were not sent to the TTC as they were prepared in response to a perceived clinical need, and could be sold on the basis of general publications.

On 19 May 1933 the ABCM wrote to Burroughs Wellcome again asking about the possibility of collaboration with the DSIR.²⁴⁶ Burroughs Wellcome felt that: "while progress in development of biological drugs (hormones, vitamins and plant constituents) is satisfactory, the discovery of new synthetic drugs still lags behind the achievements of foreign countries and is almost wholly dependent upon foreign initiative...the Committee are of the opinion that if Chemotherapy in this country is to hold its own in competition with foreign development, a more definite organisation than that indicated in the ABCM letter is required." This question should be considered from the point of view of

1. The possibility of co-operation among individual firms and if possible, the nature of this cooperation and its relationship to the DSIR.
2. The part to be taken by Government Departments and
3. The kind of research to be undertaken.²⁴⁷

The DSIR outlined their ongoing research and these points were discussed at the STC meeting on 14 July 1933. One of the main areas of collaborative work proposed was

²⁴³ "The Assimilation of Iron" *Lancet* (4 September 1937): 588; "The Action of Iron" *British Medical Journal* (13 November 1937): 970-971; *Proc. Roy. Soc. Med.* (March 1933): 607; STC Meetings, (19 May 1933) and (1 October 1936), WF: STC S/G/49-50.

²⁴⁴ STC Meetings, (5 April 1935), (12 July 1935) and (1 October 1936), WF: STC S/G/49-50.

²⁴⁵ STC Meetings, (19 March 1933), (24 May 1934), STC Meeting, (1 October 1936), WF: STC S/G/49-50.

²⁴⁶ 14 July 1933, WF: STC S/G/49.

²⁴⁷ 14 July 1933, WF: STC S/G/49.

in the field of malaria and the proposed collaboration took the form of both research and clinical cooperation. However, it is clear that Burroughs Wellcome was not focused on synthetic drugs.

Two sad effects hit the firm in 1936. The most lasting was the death of Henry as it altered the status of the firm to the charitable Wellcome Foundation. In his last will of 1932 Henry Wellcome had arranged for “all money made out of the company’s operations in the relief of suffering and disease shall be used further to further the relief of suffering and disease”.²⁴⁸ Then the STC of 7 October 1936 reported the sudden death of Jowett:

“the members of the Committee desire to place on record their sense of the great loss the Committee have sustained by the death of their esteemed colleague Dr Jowett whose ripe experience and sound judgement were always of the greatest value in their deliberations”.²⁴⁹

In the WCRL report of January 1937, Wenyon described extensive research on virus diseases, the development of parasites, general pathology, bacteriology and parasitology, antileprotic oils, antimalarials, streptococcal and mercury compounds. The discovery of sulphonamides had re-stimulated interest in the therapy of all infectious diseases.

Avenyl cream was a mercurial preparation, which had been used in leprosy for years.²⁵⁰ Earlier in 1931, Burroughs Wellcome sent it to leprologists in Sudan, Korea, Cape Province, South Africa, and China and received full reports. Henry, Smith and Trevan summarised its properties and the supporting data including stability at tropical temperatures.²⁵¹ Avenyl was then submitted to the TTC after evaluation at the WPRL as a possible antisyphilitic.²⁵² After a considerable delay, the TTC agreed to arrange studies of Avenyl, and supplies were made at Burroughs Wellcome.²⁵³ At the STC meeting of 25 May 1934 it was stated that results “cannot be expected for some time yet”. By 28 September 1934, “Dr Henry was dissatisfied with the manner in which this has been

²⁴⁸ G. MacDonald, *In Pursuit of Excellence: One Hundred Years Wellcome 1880 – 1980*. (London: Wellcome Foundation Ltd., 1980): 35; “Sir Henry Wellcome’s Will”, *Lancet* (30 January 1937): 275.

²⁴⁹ STC Meeting, (7 October 1936), WF: STC S/G/49.

²⁵⁰ STC Meeting, (14 February 1934), WF: STC S/G/49.

²⁵¹ STC Meeting, (13 March 1936), WF: STC S/G/49.

²⁵² STC Meeting, (24 November 1933), WF: STC S/G/49.

²⁵³ STC Meeting, (9 Feb 1934) and (19 May 1934), WF: STC S/G/49.

handled by the TTC, and finally in December the STC on 14 Dec 1934 the TTC report on Avenyl was discussed".²⁵⁴ The TTC questioned whether mercurials of this type were even necessary as British medical men preferred bismuth and arsenical preparations so no progress had been made. As a result, Burroughs Wellcome decided to proceed with a further trial of Avenyl with a doctor in Salford who had previously done trials for them on bismuth oxychloride.²⁵⁵ They provided him with the two conflicting pre-clinical reports from Calcutta and from the TTC. In the former study the Wassermann reaction tests for syphilis became negative in 10 cases after 15 doses of 0.025 grammes, whereas the TTC report showed no effect on the Wassermann reaction after bi-weekly doses for 6 months. The STC decided to await the outcome of the Salford study before proceeding with further trials with a Dr Leonard in the USA.²⁵⁶

Snodgrass eventually performed the TTC study in Glasgow and showed that Avenyl was better than calomel but he did not to publish the data, and as a result Burroughs Wellcome decided not to advertise it for uncomplicated syphilis.²⁵⁷ Their Tuckahoe site prepared and patented a series of novel organic mercuriated aromatic amines coupled to polyphenols, as novel germicides. However, only one compound had an unassailable patent position and 'mercurochrome' was considered unlikely to raise sufficient demand to justify manufacturing.²⁵⁸

In addition to reviewing patents for any opportunities arising in the medical literature, Burroughs Wellcome looked for the expiry of other firm's patents, but they found that some drugs that they wished to market were still protected. From 1933 they decided to do no further investigations on patented compounds, but to take the opportunity of producing their own line if any should come out of patent.²⁵⁹ They appointed three junior chemical assistants, two at the experimental department at Dartford and one at the WCRL who helped to search the chemical and patent literature, freeing the chemists to

²⁵⁴ STC Meeting, (14 December 1934), WF: STC S/G/49.

²⁵⁵ STC Meeting, (25 May 1934) and (28 September 1934) and (14 December 1934), WF: STC S/G/49.

²⁵⁶ STC Meeting, (5 April 1935), WF: STC S/G/49.

²⁵⁷ TTC Minutes 5, (5 March 1934); TTC Minutes 6, (28 February 1936), MRC File 1523/15.

²⁵⁸ STC Meeting, (25 May 1934), WF: STC S/G/49.

²⁵⁹ STC Meeting, (19 May 1933), WF: STC S/G/49.

concentrate on research.²⁶⁰ If competitor compounds were already patented the firm could try to negotiate a sales license.²⁶¹

In 1936 Benzedrine and other ephedrine derivatives were evaluated as analeptics (stimulants).²⁶² Smith, Kline & French had marketed these in an inhaler in 1932 for use as nasal decongestants, and Trevan summarised their effect in shortening the awakening time of anaesthetised mice.²⁶³ Burroughs Wellcome prepared modified versions, including methyl and dimethyl Benzedrine, nor- ephedrine, nor- pseudoephedrine, ephedrine, pseudoephedrine, methyl ephedrine and methyl pseudoephedrine. For each compound, one of the isomers was more active than the other, so the most active isomer was prepared. Dextro optical isomers were the most active of the benzedrines and laevo forms were the most active ephedrines. Overall, the most active and least toxic of these amphetamine-like substances was methyl isomyn (methyl Benzedrine),²⁶⁴ so this was submitted to Green of the TTC,²⁶⁵ who, in turn submitted it to the Maudsley Hospital, where its properties were confirmed, in comparison with isomyn (Benzedrine)²⁶⁶, which had been evaluated by Barger and Dale in 1910. Several firms examined these sympathomimetic amines in the early 1930's.²⁶⁷

Overall it seems that Burroughs Wellcome benefited from their interaction with the TTC, getting 8 products evaluated. They got useful feedback on their cardiac products and though Avenyl was a disappointment, they got a quick and clear decision about it, and the many publications on Prostigmine helped their marketing of the drug. Despite their successful collaboration with the TTC, Burroughs Wellcome continued to arrange some of their own studies. They performed their own evaluation of insulin combined with

²⁶⁰ STC Meeting, (14 December 1934), WF: STC S/G/49.

²⁶¹ STC Meeting, (25 February 1926), WF: STC S/G/49.

²⁶² STC Meeting, (7 October 1936), report (January 1937) "WCRL", WF: STC S/G/50.

²⁶³ STC Meeting, (7 May 1937), WF: STC S/G/50.

²⁶⁴ STC Meeting, (7 May 1937), WF: STC S/G/50.

²⁶⁵ STC Meetings, (19 November 1937); (18 February 1938), WF: STC S/G/50.

²⁶⁶ STC Meetings, (24 March 1939); (29 September 1939), WF: STC S/G/50.

²⁶⁷ TTC Minute 8, (7 February 1938), TTC Minute 9, (14 July 1938), MRC File 1523/15; "The Action of Benzedrine" Pharmaceutical Journal 141 (5 November 1938): 469.

antiseptics after moulds were found growing in preparations.²⁶⁸ Trevan prepared crystalline insulin and sent a note on this to *Nature* and the *Pharmaceutical Journal*.²⁶⁹ Samples were sent to Harrington, presumably for him to try to solve the structure of insulin and synthesise it as he had with thyroxine.²⁷⁰ They developed further insulin formulations, having ‘Local’ insulin tested at Glasgow Royal Infirmary.²⁷¹ Every batch of protamine insulin produced was tested in rabbits at the WPRL, but not having success in making the insoluble derivative of Protamine insulinate, it was suggested this could be licensed from another firm.²⁷²

8.7.4. Glaxo.

In the Post-war chapter I described how Glaxo evolved from Nathan’s by incorporating scientific concepts into their food business. After 1931 Glaxo continued to evaluate vitamins to add to their milk products. Calciferol was isolated in pure crystalline form in 1932, allowing Glaxo to produce ever more concentrated forms of Ostelin, that could be more readily standardised and which were more stable. Vitamin A was found in milk fat and Glaxo developed a series of products rich in vitamin A including the Adexolin lines, Ostomalt and Maltoline. They also produced vitamin - enhanced foodstuffs including Farex in 1932. Bacharach and Jephcott found they needed to educate ‘ignorant’ doctors as they tried to market products through ‘ethical’ channels.²⁷³ However, when their intramuscular combination formulation of vitamins A and D was submitted to the TTC in June 1933, it was initially rejected, as Glaxo gave no clear indication that it would be better than the oral form.²⁷⁴ An M.D. thesis provided by Glaxo was said by Edward Mellanby to be “absolute rubbish”.²⁷⁵ Dawson stated: “the concentrate of vitamins A and D for intramuscular use does not impress me much”,²⁷⁶ and T. Watts Eden was also

²⁶⁸ STC Meeting, (27 March 1931): G. E. Pearson to C. M. Wenyon, (8 June 1931), WF: STC S/G/49.

²⁶⁹ STC Meeting, (19 May 1933), WF: STC S/G/49.

²⁷⁰ STC Meeting, (8 May 1929), WF: STC S/G/49.

²⁷¹ STC Meeting, (18 February 1938), WF: STC S/G/50.

²⁷² STC Meeting, (29 May 1936), WF: STC S/G/50.

²⁷³ R. P. T. Davenport-Hines, J. Slinn, (1992): 80-83.

²⁷⁴ F. H. K. Green to Glaxo, (28 June 1933), TTC File 1523/22.

²⁷⁵ E. Mellanby to F. H. K. Green (12 June 1933), TTC File 1523/22.

²⁷⁶ TTC 1523/21 (10 June 1933).

“doubtful”.²⁷⁷ Further clinicians in London, Glasgow, and Edinburgh were invited to test vitamins A and D and Mellanby, T Watts Eden and Prof. Wilkie discussed the combination compound. The main problem was that the committee could not think of a way in which it could be tested except, perhaps in rickets, which would only evaluate the vitamin D component.²⁷⁸ Another possible reason for the rejection was that the MRC Patent sub-committee, which ran from 1929, disapproved of the Steenbock patents taken out by Glaxo.²⁷⁹ They felt that Steenbock, based in Wisconsin was profiting from a wide patent in a state of uncertain knowledge based on earlier British work. Frank Robinson joined the research team as a chemist in 1933.²⁸⁰

Glaxo remained primarily a nutritional producer until the establishment of Glaxo Laboratories in March 1935, when work began on a new site for 250 staff in Greenford, Middlesex.²⁸¹ By this time Jeffcott was Managing Director and Farmer was progressing to senior management. Glaxo established laboratories for bacteriology and for analytical work, biochemistry and organic chemistry, which were completed in September 1936 and occupied the upper floor.²⁸² They also had an ampoule unit and their own unique glass-blowing facilities. Among the fast-selling inorganic products they prepared were Fersolate tablets of ferrous sulphate, and Examen, the previously described injection of liver extract for pernicious anaemia, like that prepared at Burroughs Wellcome, but no synthetic products were produced in the interwar period. The TTC was clearly not influential in the development of Glaxo, as they submitted only one vitamin combination product and that was rejected.

It is interesting to note therefore that Glaxo went down the same path as May & Baker and appointed their own physician to take charge of external interactions and arranging clinical studies. Hector Walker was a young practising physician in Harrow

²⁷⁷ TTC 1523/22, (4 June 1933).

²⁷⁸ T Watts-Eden, TTC File 1523/22, (4 June 1933).

²⁷⁹ R. P. T. Davenport-Hines (ed.), History, Bagmen and Markets: Studies in the History of Marketing and British Industrial Performance 1830-1939 (Aldershot: Gower, 1986): 78-79; 93 HD 47.9.1; MRC Patents Sub-committee 1929-45, MRC Minutes II, (29 November 1929): 205.

²⁸⁰ R. P. T. Davenport-Hines, J. Slinn, (1992): 136.

²⁸¹ C. Turner (ed.), (1985): 32-42.

²⁸² C. Turner (ed.), (1985): 35-37.

when his patient Harry Jephcott, by now the Managing Director began asking his opinion about medical products and seeking his guidance on writing for doctors from 1935 when he was employed. Much of their external research was done in collaboration with the Lister Institute and NIMR. In 1937-8 they created a “consultative committee of external scientific advisors directed towards problems upon which we are working” but also had “substantial and useful co-operation from the principal universities in the country”.²⁸³ Research was being performed on the synthesis of vitamin A and a series of iodine compounds, a new acridine compound and the isolation of bacterial antigens and pituitary hormones and liver extracts. Glaxo already sold a liver extract, which they licensed from a Norwegian company in 1936, and in the latter part of the decade pharmaceuticals were contributing greater profits from a much smaller turnover than the food products.²⁸⁴ The Glaxo staff at Greenford rose to 600 by 1939, and the firm were spending £5,000 p.a. on research in 1938.²⁸⁵ The addition of scientific products such as vitamins to their milk stuffs range helped to extend their product lines, leading to an increase in manufacturing capacity, and bringing J. F. Nathan (Glaxo) into pharmaceuticals, although over 50% of sales were from just one product Glucodin (glucose and vitamin D). At the outbreak of the war Dr. Joseph Ungar, a Czech refugee joined the bacteriology department and became involved in studies on antibiotics.²⁸⁶

8.7.5. British Drug Houses.

As described in earlier chapters, British Drug Houses were probably the most progressive British firm immediately following the Great War, after chairman Charles Hill secured the chemical engineer Francis Carr and his colleagues, and they successfully manufactured thyroxin and insulin.

Over the period 1931 – 1939, BDH submitted 7 compounds to the TTC. One of the first agents was Perparine, the latest in a long line of anti-cholinergic drugs similar to atropine. German firms, particularly Merck had improved upon the original natural product,

²⁸³ R. P. T. Davenport-Hines, J Slinn, (1992): 86.

²⁸⁴ R. P. T. Davenport-Hines, J Slinn, (1992): 86; C. Turner (ed.), (1985): 63.

²⁸⁵ C. Turner (ed.), (1985): 38, 106; R. P. T. Davenport- Hines (ed.), (1986): 62.

²⁸⁶ R. P. T. Davenport-Hines, J Slinn, (1992): 136.

first splitting it into two optical isomers and then recognising activity could be maintained by giving only the tropeine part. Further synthetic modification improved the therapeutic margin, the difference between the doses giving activity against those giving side effects. A Hungarian firm had already prepared Perparine in 1930, before BDH made its own preparation.²⁸⁷ One concern that the TTC had was in persuading British doctors to use perparine, as papaverine had almost been abandoned in favour of atropine and morphine.²⁸⁸ Despite this John Bell & Co. put forward papaverine for clinical trials.²⁸⁹ Further studies of Perparine were delayed for 6 months, pending results from continental workers and it was never actually tested in Britain. Among the other agents submitted for testing just before the Second World War was Eupaverin,²⁹⁰ a synthetic papaverine derivative from Merck, claimed to be less toxic. Merck had first discovered this alkaloid from opium plants in 1848 after morphine and codeine had been removed.²⁹¹ Although as Green wrote to Elliott:

“I hardly imagine that the Committee will feel able to accept this, as you will remember that they recently declined an application I respect of a similar product from a British firm.” He added, “I understand from Trevan, of the Wellcome labs that BW are likely to submit a new application before the 7th. (The date of the next TTC) There is also in the offing an application from Parke Davis & Co.”²⁹²

Both Eupaverin and Perparine went on to be widely used as antispasmodics in the 1930's.

BDH produced analogues of cocaine including Boracaine, a local anaesthetic in several salt forms. They also prepared Caprorol (hexyl resorcinol), Intamine, (di-ortho-di-amino-thio-benzene), and Contamine (diethyl ammonium diethyl dithiocarbamate).²⁹³

²⁸⁷ Walter Sneader, (1985): 120-6.

²⁸⁸ TTC Minutes 4 (undated, 1933), MRC File 1523/15.

²⁸⁹ John Bell & Croydon were a direct descendent of the firm of John Bell & Co. founded in 1798. They made surgical instruments, travel medicines and imported and exported drugs. They still trade under the same name today but would be considered as retailers rather than pharmaceutical manufacturers: MRC File 1523/15; T. A. Henry, (1939): 181-2, 185-91.

²⁹⁰ Walter Sneader, (1985): 125-6.

²⁹¹ T. A. Henry, (1939): 185

²⁹² F. H. K. Green to T. R. Elliott (1 February 1938), T. R. Elliott Files, WI GC/42 TTC 1935-42.

²⁹³ British Chemicals: Their Manufacturers and Their Uses (London: ABCM, 1927)

British Drug Houses made more synthetic drugs than other firms, probably reflecting the influence of Francis Carr, and they were also one of the first firms to produce steroid hormones from dehydroepiandrosterone, obtained from cholesterol by irradiation of sterols²⁹⁴ After the discovery of calciferol and its preparation by Glaxo, BDH sent their version, Radiostol to the TTC for testing in Sheffield, London, and Newcastle in studies controlled by X-rays. Mellanby found it “satisfactory” but wondered how it compared with American irradiated ergosterol.²⁹⁵ BDH also added concentrated vitamins to their malt products such as ‘Radiomalt’, which included standardised vitamins A, B1, B2, and D. Carr developed the technique of molecular distillation in 1932, making it possible to separate out the vitamins A, D and E from oils and prevent the destruction of vitamin A that occurred by heating with vacuum distillation.²⁹⁶ Another synthetic, acetyl – 6 – naphthoic acid (produced by BDH and ICI) was put to the TTC for testing as an analgesic in inoperable cancer. Studies were performed by Cuthbert Wallace at the Middlesex Hospital, Prof. T. R. Elliott and Sir Farquhar Buzzard, but the TTC were “unable to recommend it as it led to headaches and high blood pressure” and it was not issued.²⁹⁷

The results of the BDH interaction with the TTC are difficult to interpret. In one case BDH were late in copying a German drug and it was difficult to set up a study because British workers no longer used that type of drug, and in two cases they got clear feedback when products were either of limited value or led to side effects. The majority of the studies were simply inconclusive. It appears that the early successes with thyroxin and insulin were not built upon. A series of synthetic drugs were produced, but often only minor variations on existing products and with little obvious additional clinical benefit. It seems that the skills that Carr brought were in terms of large-scale manufacturing rather than innovation. However, the advances in manufacturing capacity allowed BDH to capitalise on external advances as they had with insulin and their preparation of steroids at in the 1930’s. The BDH annual meeting in 1935 reported that nearly £35,000 had been spent on a new factory building to produce fine chemicals and a new biology laboratory and

²⁹⁴ V. Petrow, Sir F. Hartley, *The Rise and Fall of the British Drug Houses*, *Steroids*, 61: 476- 482.

²⁹⁵ TTC Meeting 2 (13 January 1932) and 4 (undated 1933) 1523/15.

²⁹⁶ F. H. Carr, “Molecular Distillation” *Pharmaceutical Journal* 141 (12 November 1938): 498.

²⁹⁷ TTC Meeting 2, (13 January 1932); TTC Meeting 3, (8 July 1932), MRC File 1523/15.

sports ground had been developed.²⁹⁸ These foundations helped BDH become the leading producer of steroids in the next decades.²⁹⁹

8.7.6 Allen & Hanbury's.

Allen & Hanbury's prepared innovative products such as a Haliborange, which masked the taste of halibut liver oil and incorporated vitamins A, C, and D. In the early 1930s their growth-controlling hormone of the parathyroid gland was tested at the Royal College of Surgeons and at the Kings College for limiting the spread of cancer and an adrenal cortical extract, Eucortone was prepared for the treatment of Addison's disease.

In reviewing the state of the industry in 1935, Gamble described the strategy within Allen & Hanbury's, with new scientific products were being prepared alongside the centuries old remedies:

“When we survey the progress that has occurred in this period, we see that it is due to the introduction of new types of pharmaceutical products, which have required improvements of methods and plants. These have grown up alongside old products, which have continued to be manufactured by the old methods, though often improved in detail”.³⁰⁰

One of the surprises of my analysis is that after the involvement of Gamble in campaigning for the TTC, Allen & Hanbury's did not put forward a single drug to them for testing. They had developed their own reputation through the work on insulin and with the increase of products and clinical trial activity, Allen & Hanbury's took on a lady doctor to arrange clinics with nurses and mothers and “a specially qualified medical man was (also) hired to bring the merits of the infant foods to paediatricians and other specialists”.³⁰¹

8.7.7 Imperial Chemical Industries and Other British Firms.

Imperial Chemical Industries (ICI) was founded in 1926 as the British conglomerate to compete with IG Farben in chemicals and dyes. The company traced its roots to the earlier formation of British Dyestuffs Corporation with units in Blackley under A. G. Green

²⁹⁸ “British Drug Houses”, Pharmaceutical Journal (20 April 1935): 471.

²⁹⁹ W. Sneader, (1985): 203.

³⁰⁰ F. W. Gamble, N. Evers, “Advances in the Manufacture of Pharmaceutical Products, 1910-1935” Pharmaceutical Journal 134 (1935): 541-543.

³⁰¹ Geoffrey Tweedale, (1990): 151.

and in Huddersfield under Robert Robinson. A dyestuffs research consultative group was established in 1929, and after the discovery of sulphonamide antibiotics in the period from 1935, and the realisation that they were structurally related to dyestuffs, that a medicinal chemistry section was established and ICI embarked on pharmaceutical research, initially on a limited basis, still directed by Robinson.³⁰² One of the seven founding chemists³⁰³ Francis Leslie Rose, who had trained under Kipping in Nottingham, joined Blackley in 1932, after training at University College, Nottingham, including a PhD part sponsored by ICI.³⁰⁴ The research manager at ICI was Marmaduke Barrowcliff, also a Nottingham graduate who visited frequently along with his Academic Relations Officer. We encountered Barrowcliff earlier at Burroughs Wellcome and Boots; he had also spent some time in Malaya in research on rubber.³⁰⁵ Although ICI dyestuffs put in requests to the TTC for testing acetyl- 6 – oxynaphthoic acid and quinadil, previously referred to as submitted jointly with BDH, they also put forward their own quindoline methochloride as an antiseptic, but decided after discussions with the TTC to withdraw the application.³⁰⁶ The TTC had previously shown that often antiseptics that showed promise in the laboratory did not fulfil that promise in patients and they showed that quinadil had inadequate activity. In 1937 ICI began to appoint PhD pharmacologists including C. M. Scott, W. Lees, A. R. Martin, A. L. Walpole and J. R. Raventos but they also worked with externals such as Gunn in Oxford, Warrington-Yorke in Liverpool for tropical diseases and Clarke in Edinburgh.³⁰⁷ In 1938 Lord MacGowan, the chairman confirmed that ICI were “working on specialised pharmaceutical and medical products, which were expected to become an important part of the dyestuffs group activities and were collaborating with the LSHTM in

³⁰² Robinson had moved from Manchester to take up the chair at University College in London. Lord Todd and J. W. Cornforth, “Robert Robinson” Biographical Memoirs of Fellows of the Royal Society 22 (1976) 415 – 527.

³⁰³ Pharmaceutical Research in ICI 1936-57 (Macclesfield: Imperial Chemical Industries Ltd., 1957): 1-2. The others were F. H. S. Curd, W. R. Boon, J. C. Lumsden, D. J. Branscombe and H. C. Carrington and Sam Ellingworth led the team.

³⁰⁴ Obituary, Frank L. Rose, The Times, (5 March 1988); C. W. Suckling, “Francis Leslie Rose 27 June 1917-3 March 1988” Biographical Memoirs of Fellows of the Royal Society 36 (1990): 491-524.

³⁰⁵ The librarians at AstraZeneca assisted me in identifying the patents taken out by Barrowcliff. His first had been on trypan arsinites in 1908 and his first for ICI was in 1934 (UK patent 408258).

³⁰⁶ TTC Minutes 7, (11 February 1937), MRC File 1523/15.

³⁰⁷ C. W. Suckling, B. W. Langley, “Francis Leslie Rose 27 June 1909-3 March 1988” Biographical Memoirs of Fellows of the Royal Society 36 (1990): 490-524.

a basic study of immunisation” The company had established a research council and research committees were in touch with the leading scientists in the country, including chemists such as Robert Robinson, Ian Heilbron and Jocelyn Thorpe.³⁰⁸ The first sulphonamide antibiotic made by ICI chemists, Sulphathiazole was too late to claim patent priority. Another derivative, sulphadiazine was made in America, but ICI developed an easier to make derivative, sulphamezaphine, which became the first drug manufactured by ICI. at the start of the Second World War. This work led them to evaluate German antimalarials in preparation for World War Two. ICI did not establish a formal pharmaceutical department until 1954, and opened a new research site at Alderley Park, Cheshire in 1957.³⁰⁹

One of the fastest growing proprietary medicine manufacturers in the 1930’s was Beecham’s who reported sales of £500,000 in 1936 but they did not produce ethical products of interest to the TTC with sales of that magnitude they did not need to.³¹⁰ A. Boake Roberts & Co. of London³¹¹ submitted just one product to the TTC, an amyl salicylate (Abracide), which was a new phenol derivative, evaluated by Wilkie’s group in Edinburgh, who showed “it seemed to relieve pain at once” and decreased sepsis in burns patients and he prepared a paper for the *British Journal of Surgery*.³¹² The Committee did not seem to mind that Wilkie’s report gave “rather a puff to the proprietary antiseptic” as the company deserved it for it was the only antiseptic which blended well with amyl salicylate.³¹³ The actual results were secondary to what the Committee thought of the compound and in this case a letter to the *British Medical Journal* was suggested.

³⁰⁸ “Commercial Firms and Research”, *Pharmaceutical Journal* 140 (30 April 1938): 460.

³⁰⁹ *Pharmaceutical Research in I.C.I. 1936-57* (1957).

³¹⁰ Michael Robson, “The Pharmaceutical Industry in Britain and France 1919-1939”. (London: PhD, June 1989): 38; R. P. T. Davenport-Hines, J Slinn, (1992): 86.

³¹¹ Founded in 1869 they produced brewing chemicals, flavouring essences and essential oils. They merged with other small London firms Stafford Allen & Sons and W.J. Bush & Co. to become Bush, Boake Allen Ltd. in 1966 and this firm was acquired by International Flavors and Fragrances Inc. to become the world’s largest flavours and fragrance company. www.IFF.co.us

³¹² TTC Minute 2, (15 January 1932); TTC Minute 6, (28 February 1936), MRC File 1523/15.

³¹³ F. H. K. Green to T. R. Elliott, (16 November 1936): T. R. Elliott Files, WI GC/42 TTC 1935-42.

A request by Napp of Cambridge to have Hepamult (liver extract) and Profundol (Progesterin) tested was declined, but the former was still marketed as a dry calf liver extract.³¹⁴ Napp also produced sanocrysin, which had been tested earlier by the MRC.³¹⁵ Nevertheless, their collaboration with the TTC was fruitful and led to further significant interactions from 1942-48.³¹⁶

Evans, Lescher & Webb continued to produce vaccines and antitoxins but had no interactions the TTC regarding new drugs. By the mid-1930s they were operating a trading profit of £45,111.³¹⁷ They operated quite independently, most of their interactions being with the Evans Biological Institute at Runcorn. In 1935 they published papers showing that they had worked upon the storage of ergot and the standardisation of thyroid extracts.³¹⁸ Considerable extensions were made to the Evans Biological Institute in 1937 as the company produced vaccines for cholera, plague and smallpox, but also tuberculins, heparin and hyaluronidase and the synthetic Streptocide sulphonamide.

During this period British firms attempted for the first time to produce novel drugs, but did so by following several parallel strategies, each firm playing to their own particular strengths. Burroughs Wellcome continued to favour physiology and alkaloidal extracts, many firms purified and standardised hormones and took a similar path with vitamins. Although they basically produced the same products, hormone and vitamin therapy was an area where Britain was ahead of Germany. Some firms, and particularly Boots from 1927, May & Baker and most of all British Drug Houses emphasised synthetic drugs.

However it must be recognised that the number of novel chemicals synthesised was far below German efforts and the main emphasis was on marginal improvements- preparation of synthetic hormones, thyroxine and diethylstilboestrol, or optical isomers with enhanced activity or better tolerated or more soluble, even longer-lasting salts of available therapies. These led to marginal improvements but a frustration for the firms was that it was difficult to arrange studies with the TTC to show these benefits, or perhaps they

³¹⁴ TTC Minutes 5, (5 March 1934), MRC File 1523/15; "Preparations & Appliances" British Medical Journal (5 May 1934): 950.

³¹⁵ "Gold Preparation – Sanochrysin", British Medical Journal (4 May 1935): 927.

³¹⁶ The two main collaborations concerned Parpanit, MRC File 1523/71 and Irgamid, MRC File 1523/66.

³¹⁷ "Evans Sons, Lescher & Webb", Pharmaceutical Journal 134 (9 March 1935): 282.

were just insufficient. As a result companies continued to develop drugs for the tropical market and began to employ their own physicians as Glaxo, Allen & Hanbury's and May & Baker did.

An important conclusion also is that the processes developed for large-scale manufacture, for crystallisations, enhancing purity, developing better salts and for molecular manipulation were the skills that benefited British industry when sulphonamide antibacterials were discovered and many British firms were rapidly able to develop better alternatives to Prontosil. Whenever there was a step change in activity as with insulin and Prontosil there was a ready stream of physicians willing to test them.

8.7.8. Foreign Firms.

As well as the ever - present threat of the German firms, the interwar period was marked by the establishment of US firms in Britain, though initially their interactions with the TTC were limited. They acted primarily as sales units for products developed in America. Khellavis was a new drug said by Egyptian workers to assist in removing calculi.³¹⁹ Upster Smith & Co. were based in Minneapolis and their version of Khellavis was sent to Wilkie in Edinburgh in 1933, who treated 3 cases of ureteric calculi, one of whom passed a stone but the others had no benefit and suffered from severe flatulence.³²⁰ Another trialist asked to participate found no cases.³²¹ Eventually it was concluded that it was "no good".³²²

Smith, Kline, French tried to establish studies of pentanucleotide from 1933 through their U.K. subsidiary Menley James. The TTC sent the drug to 6 centres and Dawson treated 3 cases, showing it increased the leucocytes;³²³ Wilkie investigated its role in increasing leucocytes prior to surgery, in malignant neutropenia and other conditions associated with neutropenia.³²⁴ Garrod at St. Bartholomew's, Knott at Guy's, Wilkinson in Manchester and Witts in Oxford were involved and presented cases to the Royal Society of

³¹⁸ R. F. Corran, "Thyroid standardisation and Storage" and Evans Biological Institute, Runcorn" *Pharmaceutical Journal* (29 June 1935) 781-83.

³¹⁹ TTC Minutes 6, (28 February 1936), MRC File 1523/15.

³²⁰ TTC Minute 4, (undated 1933), MRC File 1523/15

³²¹ TTC Minutes 5, (5 March 1934), MRC File 1523/15.

³²² TTC Minutes 7, (11 February 1937), MRC File 1523/15.

³²³ TTC Minute 4, (undated 1933); TTC Minute 5, (5 March 1934), MRC File 1523/15.

Medicine.³²⁵ By TTC standards this drug was successful and the company benefited from the publicity generated.

Towards the end of the period under review an increasing number of foreign firms drugs were evaluated by the TTC, and many were described under the section on organotherapy. A request from E. Merck for testing of Epivarin tested was declined.³²⁶ Adovern from Roche and Tussipect from Beiersdorf were also turned down with no reason recorded and Helborsid from Roche was considered, but the committee decided to wait for 6 months for results from elsewhere, presumably overseas.³²⁷

CIBA offered compound 2834/35, the hydrochloride of quinoline-8-oxyacet-n-dibutyl amidine, which was meant to have ergotamine – like properties. The TTC were only interested if Chassar Moir examined it, and it was dropped after he posted preliminary unsatisfactory results.³²⁸ A further CIBA compound, 3259 or benzyl-dihydro-imidazolin hydrochloride, was sent to W. R. Trotter at UCH and although he showed a vasodilator effect on the conjunctiva, the compound had negligible effects on blood pressure and it also had unpleasant effects, and therefore was not developed.³²⁹

Bayer submitted a vitamin D3/calciferol (vitamin D2) combination prepared by synthesis of irradiated 7-dehydrocholesterol, and said to be identical to the natural vitamin D of cod liver oil. Unlike calciferol it was effective in chickens. The initial TTC appraisal was that “it was very doubtful whether certain German claims that it was more active than calciferol in human rickets could be substantiated”.³³⁰ Prof. Noah Morris of Glasgow and J. C. Spence of Newcastle compared the two forms, treating four cases on each treatment with little difference between them. This was the nearest that the TTC got to a controlled

³²⁴ TTC Minute 6, (28 February 1936), MRC File 1523/15; G. Stewart Smith, “A Case of Agranulocytosis Treated with Pentanucleotide” *Lancet* (16 March 1935): 607.

³²⁵ L. J. Witts “Agranulocytosis” *Proc. Royal Society of Medicine* 29 (1936): 671.

³²⁶ TTC Minutes 5, (5 March 1934) File 1523/15.

³²⁷ TTC Minutes 7, (11 February 1937) File 1523/15.

³²⁸ TTC Minute 9, (14 July 1938), MRC File 1523/15.

³²⁹ TTC Minutes 8, (7 February 1938); TTC Minutes 9, (14 July 1938), MRC File 1523/15.

³³⁰ TTC Minutes 8, (7 February 1938), MRC File 1523/15.

trial³³¹ Bayer was based at St. Dunstan's Hill in London and they employed George H. Morrison: "a medical advisor"³³²

Hoffmann la Roche put forward their Syntropan or amprotropine, introduced in 1933. The chemical structure was provided along with details of preliminary laboratory and overseas clinical studies.³³³ This was the first of several atropine- like molecules where an attempt had been made to separate out the beneficial pharmacological effects of the drug from its side effects, such as causing a dry mouth.³³⁴ The references provided by the firm were highly eulogistic, such as the "brilliant" results of this antispasmodic in 15 cases.³³⁵

The TTC studies found Syntropan to be similar to, but weaker than atropine in its spasmolytic activity on the gut. It was "of value, particularly in cases of bladder pain and acute cystitis with dysuria" and found it to be free of the unpleasant side effects of atropine.³³⁶ The use of Syntropan in seasickness was reported in the *Lancet* of 21 January 1936. It showed "great promise" as a better anti-spasmodic than atropine and with a weaker mydriatic effect, lessening the problem of dry eyes.³³⁷ Burroughs Wellcome considered preparation of Syntropan, but their staff traced its patent so this was not pursued.³³⁸ Mr. Ian Lawson Dick of the pathology laboratories in Edinburgh first showed that Syntropan was pharmacologically less active than atropine: "my clinical observations are not extensive enough – it works in mild colic only," but Prof. Alfred Joseph Clark,³³⁹ Professor of Materia Medica and Pharmacology in Edinburgh, thought there was a case for

³³¹ TTC Minutes 9, (14 July 1938), MRC File 1523/15.

³³² Letter from George H. Morrison to TTC (21 September 1931) regarding their liver preparation, Campoloon, MRC File 1523/15.

³³³ Summary on Syntropan, (dated 18 January 1934), T. R. Elliott Files, WI: GC/42 1933-43.

³³⁴ Walter Sneader, (1985): 123.

³³⁵ F. H. K. Green to T. R. Elliott, (10 June 1936), T. R. Elliott Files, WI GC/42 TTC 1935-42; K. Fromherz, "The Mode of Action of Syntropan in Animal Experiments" *Quarterly J. Pharm and Pharmacology* IX (1936) 1-6.

³³⁶ TTC Minutes 5, (5 March 1934); TTC Minutes 6, (28 February 1936); TTC Minutes 7, (11 February 1937), MRC File 1523/15.

³³⁷ STC Meeting, (28 May 1936), WF: STC S/G/50.

³³⁸ STC Meeting, (7 October 1936), WF: STC S/G/50.

³³⁹ E. B. Verney, "Alfred Joseph Clark" *Obituary Notices of Fellows of the Royal Society* 3 (1941): 969- 984.

further studies.³⁴⁰ Sir David Wilkie and Major McKelvey were invited to perform further tests on Syntropan. The urologist C. J. Bond had already performed some studies in dysuria. F. J. Barrington, another urology surgeon, examined the drug in tubercular cystitis, as did R. Ogier Ward, Geoffrey Parker, James Carver and Victor Dix.³⁴¹

In 1938 Parke Davis wanted their sodium thioethyl tested and submitted it first to the anaesthetics committee, who in accordance with policy passed it on to the TTC. However, only limited data was provided and the compound was returned to the anaesthetics committees for testing, and eventually C. Langton Hewar, anaesthetist at St Bartholomew's and the Brompton published the data.³⁴² Merck and May & Baker both provided Trichloroethanol but this was also passed to the Anaesthetics committee for evaluation.

Dr. G. H.A. Clowes at Lilly in Indianapolis, who had arranged insulin studies, provided a surgical antiseptic, Merthiolate. It had been praised in the 1933-4 MRC report for its benefits in tuberculosis by Capt. D. P. Lambert in India, who also published data in the *Lancet*, but when Prof. S. L. Cummins in Cardiff further tested it, he found it to be of "no value" in tuberculosis.³⁴³

Merck submitted an application for Doryl, an extremely stable carbamic acid ester of choline, which was sent to Chassar Moir at the British Postgraduate Medical School, who found it useful for (urinary) retention. It was also evaluated in Wilkie's department in

³⁴⁰ F. H. K. Green to T. R. Elliott, (26 February 1936), V. Dix to F. H. K. Green, (8 January 1936), and F. H. K. Green to T. R. Elliott (14 March 1936), T. R. Elliott Files, WI GC/42 TTC 1935-42.

³⁴¹ C. J. Bond, "On the Influence of Antiseptics on the Activities of Leucocytes" British Medical Journal (1916): 777-82; British Medical Journal (1917): 164; C. J. Bond, Consultant Surgeon at Leicester Royal Infirmary, joined the MRC on 10th April 1920: 510-11; F. H. K. Green to T. R. Elliott, (26 February 1936), T. R. Elliott Files, WI GC/42 TTC 1935-42.

³⁴² TTC Minutes 8, (7 February 1938), MRC File 1523/15; C. Langton-Hewer, "Sodium thioethyl" British Medical Journal (21 January 1939): 109.

³⁴³ F. H. K. Green to T. R. Elliott, (18 December 1937), T. R. Elliott Files, WI GC/42 TTC 1935-42; TTC Minutes 7, (11 February 1937), MRC File 1523/15; Merthiolate is still in use as thiomersol, (sodium ethyl mercurithiosalicylate), a preservative in vaccines despite controversy over its safety. www.Ansme.com

Edinburgh. This was a stimulant with the same action as acetylcholine and it was marketed in May 1935.³⁴⁴ Burroughs Wellcome produced a version of Doryl in November 1939.³⁴⁵

It is clear that apart from their interest in hormonal extracts, foreign drugs received limited support from the TTC, until the discovery of Prontosil opened the way for more German and Swiss drugs, though several were turned down. Ironically, the development of several further sulphonamides stimulated firms to hire their own medical staff to establish clinical trials and this new policy led to physicians being taken on by Allen & Hanbury's, Glaxo and May & Baker, to arrange their own clinical trials.

However lack of clinical trials did not always stop foreign companies from releasing their products here, especially if they fell into the category of vitamins or organotherapies when there was sufficient data available. For example Merck marketed a liver extract Oroheptal in 1937 and Hoffmann la Roche marketed a histidine preparation Lorostidin for ulcers.

8.8 MRC Studies of Antisera: Large Co-operative Trials and Statistics.

While the previous account regarding novel drugs shows that the TTC seemed to be satisfied with testing a few patients, they also performed studies with antisera, which until 1935 the TTC believed offered better hopes of combating infections. Two examples are given here to show the scope of the studies. Dr. Murray Lyon in Edinburgh, Prof. Davidson in Aberdeen and R. Cruickshank and Cowan in Glasgow, performed a trial of specific sera for pneumonia between 1929 and 1934, which Lilienfeld ascribed as the first collaborative study.³⁴⁶

³⁴⁴ TTC Minutes 6, (28 February 1936) 1523/15; J. Chassar Moir, "The Use of Doryl in Post –Operative and Post – Partum Retention of Urine" Lancet (30 January 1937): 261-63; J. S. Maxwell, "The Treatment of Post – Operative Retention of Urine with Doryl" Lancet (30 January 1937): 263-64; "Doryl (Merck)" British Medical Journal (11 May 1935): 980; R. Ogier Ward, "Acute Retention of Urine" British Medical Journal (21 January 1939): 121-23; "Surgical Procedure in General Practice: Chronic Retention of Urine" British Medical Journal (28 January 1939): 177-78.

³⁴⁵ STC Meeting, (29 November 1939), WF: STC S/G/50.

³⁴⁶ MRC 1487, TTC; "The Serum Treatment of Lobar Pneumonia" British Medical Journal (10 February 1934): 241-5. "The Serum Treatment of Lobar Pneumonia. A Report of the TTC of the Medical Research Council" Lancet (10 February 1934): 290-95; A. M. Lilienfeld, "Ceteris Paribus; the Evolution of the Clinical Trials" Bulletin of the History of Medicine 56 (1982): 1-18; G. F. Petrie, and R. A. O'Brien. (two letters) "Treatment of Lobar Pneumonia in Adults" British Medical Journal (28 March, 1931): 557-8.

However, for their own larger serum studies, the MRC adopted a different approach to that of the TTC, and included input from the medical statisticians, Major Greenwood³⁴⁷ and Austin Bradford Hill.³⁴⁸ Greenwood was Director of the MRC Statistical Unit and chairman of the Nutrition Advisory Committee. Bradford Hill eventually took over as Director of the statistical unit when Greenwood retired in 1945. In the pneumococcal serum study the MRC established several centres, including Fraser, Ellis, and R. Cruickshank and Cowan from Glasgow together with Cecil and Prof. Dochez from America who shared their experience, with Ryle of St. Bartholomew's chairing their initial meeting.³⁴⁹

The one other occasion when the TTC established a large trial program was again for serum therapy, when Burroughs Wellcome and the Lister Institute submitted staphylococcus antitoxin for testing in 1934. It underwent vigorous tests in 15 London centres.³⁵⁰ The criteria for entry of patients into the study were spelt out clearly. The antitoxin could only be used in acute osteomyelitis, staphylococcal septicaemia and pyaemia, chronic skin infections including boils and sycosis, all with proven bacteriology, but excluding ringworm. The blood was to be measured pre and post-treatment for the development of anti-haemolysin for rabbit corpuscles. When a conference was arranged to discuss the findings Dr. Petrie of the Lister Institute, Dr. O'Brien of Burroughs Wellcome and Dr. Percival Hartley of the National Institute were invited to attend. The meeting was chaired by Dr. S. C. Dyke, secretary of the Association of Clinical Pathologists, who had collaborated with the MRC in arranging studies on pernicious anaemia studies at Wilkinson's centre, and by Edward Mellanby as head of the toxoid committee.³⁵¹

³⁴⁷ M. Greenwood, "Epidemiology and its Lessons" *Lancet* (27 January 1934): 201. Greenwood was an officer of the Ministry of Health from 1920, MRC Minutes II, (7 July 1920): 111.

³⁴⁸ Bradford Hill was only appointed to the TTC at meeting 9 on (14 July 1938), MRC File 1523/15; P. Armitage, "Bradford Hill and the Randomized Controlled Trial, *Pharmaceutical Medicine* 6 (1992): 23-37; R. Doll, "Sir Austin Bradford Hill and the Progress of Medical Science" *British Medical Journal* 305 (19-26 December 1992): 1521-6.

³⁴⁹ The conference to be held on 27 July 1932 was reported in TTC Minutes 3, (8 July 1932), MRC File 1523/15.

³⁵⁰ TTC Minutes 5, (5 March 1934), MRC File 1523/15.

³⁵¹ TTC Minutes 5, (5 March 1934), MRC File 1523/15.

O'Brien independently arranged for Dr Richard Armstrong, a bacteriologist at Charing Cross Hospital³⁵² to test staphylococcus toxoid in cases of breast abscess, causing confusion when Armstrong sent his data on increased antibody levels to the MRC and asked for a small grant.³⁵³ In doing this O'Brien upset the MRC rules on sole testing rights.

Following the second conference on staphylococcal toxoid at the end of July 1935, a report was prepared by Dr. D. S. Murray of Richmond and was circulated to TTC members and to Dale and Hartley.³⁵⁴ Because of conflicting results in the independent studies further discussions between the groups were suggested;³⁵⁵ a conference concluded: "the staphylococcal toxoids at present available in Great Britain may be useful for the treatment of boils and sties but have little, if any value for the treatment of sycosis" (follicular pustules, due to infection by staphylococcus).³⁵⁶ There was a difference of opinion between pathologists and dermatologists, regarding furunculosis (a more deep seated infection of the hair follicle).³⁵⁷ The overall conclusion was that the toxoid helped in treating superficial skin lesions, but was of limited value for more deep-seated infections, which were prone to relapse. As a result, different reports were requested for carbuncles where it was "promising" and for toxæmia,³⁵⁸ whereas a group of six surgeons found it "not encouraging".³⁵⁹ These apparently discrepant findings were discussed, and then

³⁵² "Richard Robins Armstrong 1885-1975, Obituary" British Medical Journal (5 April 1975): 44.

³⁵³ TTC Minutes 5, (5 March 1934), MRC File 1523/15.

³⁵⁴ TTC Minutes 6, (28 February 1936); D. S. Murray, "Staphylococcal Toxoid, a Clinical Trial" Lancet (9 February 1935); L. Forman, "On the Treatment of Sycosis with Staphylococcal Toxoid" Proc. IXth Int. Cong Dermatology, Budapest (1935).

³⁵⁵ F. H. K. Green to T. R. Elliott, (12 May 1935), T. R. Elliott Files, WI GC/42, TTC 1935-42.

³⁵⁶ TTC Minutes 6, (28 February 1936), MRC File 1523/15.

³⁵⁷ L. E. H. Whitby, "The Treatment of Staphylococcal Skin Lesions with Toxoid" Lancet (27 June 1936): 1454-56; R. Klaber, "Specific and Non-specific Treatment of Boils, with Special Reference to the Results of Treatment by Staphylococcal Toxoid" Lancet (3 October 1936) 784-86; R. S. Wale, K. Maddis, "Staphylococcal Toxoid in the Treatment of Diabetes" British Journal of Comparative Pathology 17 (1936): 279.

³⁵⁸ Wilkie was a member of the committee of the MRC. In 1938 a Unit for Clinical Research was established in Edinburgh; TTC Minutes 6, (28 February 1936), MRC File 1523/15.

³⁵⁹ TTC Minutes 6, (28 February 1936), MRC File 1523/15; F. H. K. Green to T. R. Elliott, (28 December 1934), T. R. Elliott Files, WI GC/42, TTC 1933-34.

relayed to O'Brien of Burroughs Wellcome so that they could define which patients were most likely to benefit. Lionel Whitby of the Middlesex Hospital published a further study in staphylococcal skin lesions in which he tested two intramuscular preparations from Burroughs Wellcome and one from the Lister Institute. He evaluated almost 200 cases and achieved good outcomes in boils, sties and cataracts with 65-88% responding but only one of 8 cases of sycosis responded, and that one later relapsed.³⁶⁰

Following a recommendation from Dale and with the backing of both the Chemotherapy and Anaesthetics Committees it was decided to test Merck's basal hypnotic, trichloroethanol.³⁶¹ This had been found to be dangerously toxic in a study performed at St. Georges and at the Prince of Wales Hospital in Tottenham.³⁶² Dr. C. Langton Hewer, anaesthetist at St. George's, London had studied Parke Davis' Sodium thioethanyl showing it was almost identical to Pentothal.

The TTC did not follow up on the claims of a company called Causyth Ltd. from Italy that their substance Causyth was "definitely superior" to the sulphanilamide antibiotics. They simply did not believe it.³⁶³

Chase Laboratories of Newark, New Jersey applied to have clinical tests performed of a French neuroleptic, Cyclamide (morpholine nicotinamide), but they provided very little pharmacology data so it was sent to Prof. Clark in Edinburgh for pharmacological tests and he found that instead of having the same activity as Coramine with less toxicity as was claimed, it had one fifth of the activity. He showed that although its action on the C.N.S. was low it had no toxic effects. Clark concluded: "I suppose from the point of view of the TTC the absence of toxicity is the most important feature". However it was dropped.³⁶⁴ It was suggested that William Evans at the London Hospital could perform clinical work, as he had recently done independent work on Coramine and other cardiac or respiratory

³⁶⁰ L. E. H. Whitby, "The Treatment of Staphylococcal Skin Lesions with Toxoid, Lancet (27 June 1936): 1454-56.

³⁶¹ "Sodium Thiethamyl" British Medical Journal (21 January 1939): 109.

³⁶² C. Langton-Hewer, Douglas Belfrage, "Trichloroethanol on Trial" Lancet (3 December 1938) 1290-1.

³⁶³ F. H. K. Green to T. R. Elliott, (18 March 1938), T. R. Elliott Files, WI GC/42 TTC 1935-42. This substance, prophenazone is still produced by Causyth and used as an anti-inflammatory and analgesic (Biam; accessed April 2003).

³⁶⁴ TTC Minute 9, (14 July 1938), MRC File 1523/15.

stimulants.³⁶⁵ Others suggested were Fraser, Gunn and L. J. Witts.³⁶⁶ Elliott replied: “I suppose that for international reasons we should seek to support the French Cyclamide as against Coramine. But I am not eager to do much for these continental firms unless they have very promising substances to offer”.³⁶⁷

The meeting of the TTC in March 1939 was the tenth and last meeting of the Committee before the war. Sir David Wilkie of Edinburgh had just died so a replacement surgeon was required, while Prof. (Sir) John W. McNee was attending for the first time. McNee had been the first to demonstrate the infective nature of trench fever back in 1915. He worked under Elliott at UCH before becoming Professor of Medicine in Glasgow.³⁶⁸

The Committee discussed compounds from Organon, Parke Davis, Merck, Burroughs Wellcome, BDH and Boots, May and Baker and Cilag)

8.9 Conclusions Regarding the Therapeutic Trials Committee.

The TTC was established against a background of increasing government intervention in drug production and a wave of protectionism brought about by the harsh economic climate. By the end of 1939 the TTC had performed studies on over 60 drugs. I have attempted to give a flavour of the overall studies and although I recognise that this is inevitably incomplete, the important point is to get an overall impression of the type and scope of studies performed. The studies should be judged on the merits of the research at the time, not according to which drugs gave the lasting benefits: insulin, sulphonamides and steroids. It was a complex process to unravel the testing of all of the drugs and further supportive data could be found, but the work done so far gave me an insight into the research and strategies of British pharmaceutical manufacturers in the interwar period.

³⁶⁵ Coramine, or nicethiamide is a stimulant still produced in Germany for the treatment of cardiac insufficiency. www.ansme.com

³⁶⁶ F. H. K. Green to T. R. Elliott, (25 June 1938), T. R. Elliott Files, WI GC/42 TTC 1935-42

³⁶⁷ T. R. Elliott to F. H. K. Green (29 June 1938): T. R. Elliott files WI GC/42, TTC 1935-42.

³⁶⁸ The committee at the end of 1939 was Prof. Elliott, Col. Harrison, Dr. Carnwath, Dr. Bradford Hill, Prof. Clark, Prof. J.W. McNee, Sir Henry Dale, Sir Edward Mellanby, Lord Dawson, Prof. John Ryle, Regius Professor of Physic at University of Cambridge. Dr. Watts Eden, Dr. Herald (acting secretary), Prof. Fraser, Prof. Gunn; John McNee - J. Austoker and L. Bryder (eds.), (1989): 66, 212.

Certain overall trends are discernable. Firstly, several British firms had a backlog of compounds ready to be assessed in 1931 when the TTC was established. The TTC clearly set out their stall not to evaluate German drugs and to assist British manufacturers wherever possible, and the majority of drugs tested up to 1935 were British until Prontosil changed the whole approach. On the other hand, organotherapies from both Switzerland and Holland were evaluated in the hope of bringing some order to the very varied preparations on sale. But on several occasions when organotherapies were available from foreign manufacturers, the TTC still went ahead to test and encourage the release of a British version. The MRC performed clinical trials, primarily in those centres where they had already funded research. This meant that a large proportion of studies were performed at UCH, St. Bart's and Guy's in London, but also in Edinburgh, Glasgow, Manchester, Sheffield and Oxford, with the same trialists names appearing several times.

The former secretary of the TTC, F.H.K. Green nicely summarised the requirements and the achievements of the TTC in two papers. In one paper he confirmed the difficulties faced by British manufacturers “owing to a certain reluctance of many British doctors to carry out clinical trials at the direct request of commercial firms, and especially to allow their names to be quoted as the authors of such tests” and this “placed British manufacturers at a disadvantage compared with some of their European competitors”.³⁶⁹

Certain trends also appear in the types of drug assessed, with a prolonged focus on organotherapy. The needs of the TTC and the companies were complementary, because of the close involvement of the MRC in biological standardisation. As a result, the weaker biologicals were weeded out, and the more concentrated versions allowed MRC staff and university chemists to elaborate the structures and to synthesise the active ingredients, which could in turn be standardised. A consequence with long-lasting consequences for the pharmaceutical industry is that many companies simultaneously jumped onto the bandwagon and prepared synthetic derivatives of each ‘new’ drug. Nowhere was this clearer than in the example given of organotherapy, when there were several preparations of Oestrin and Progestin and suprarenal cortical extract. In 1935, just five years later the same situation arose when sulphonamides were discovered in Germany, but French workers showed that the patents were invalid, as the active ingredient had been identified

several years earlier. Again this allowed a wide range of companies to simultaneously prepare synthetic derivatives of the sulphanilamide base. This process was repeated over and over, and multiple firms prepared insulin and vitamins, and the various organotherapies; this more than anything, kept the pharmaceutical industry as a diverse, poorly concentrated industry.

By 1934 collaborations were increasingly common but the relationship of scientists and doctors to commerce was problematical. Dale, in his Royal Society role received a letter from Elliott discussing a Prof. (Kapitza) who asked “to receive fees for secret work with business firms”. Elliott raised the possibility of deflection to short-term aims and asked Dale the theoretical question:

“Would you allow Laidlaw to take comfortable fees from Wellcome for advice on preparation of distemper virus? Why not have Mellanby have given his advice and even his powerful name to Glaxo Ltd. in the preparation of their patent covered vitamine D and been suitably recompensated”.³⁷⁰

Elliott referred to the A list of Royal Society men and expressed concern at the impartial position of the Society in its increasing role with industry.³⁷¹ According to Green the TTC were meant to evaluate only entirely new remedies, minor modifications and improvements of known remedies being excluded and mixtures were also excluded. They had to be submitted to the Committee before they were placed on the market, “so that the manufacturer might be saved embarrassment if the results of the tests were unfavourable”.³⁷² The MRC legitimised drugs – not doctors or individual scientists. The advantage of the arrangement was primarily that the view of the MRC was seen as independent.

Regarding the testing of new drugs, an editorial in 1935 stated that: “the use of any new compound is not justified until extensive laboratory investigation has revealed its type and mode of action, its probable toxicity and its superiority over other drugs having the

³⁶⁹ F. H. K. Green, *Brit. Med. Bull* (1944) 2: 58 –60.

³⁷⁰ T. R. Elliott to H. H. Dale, (19 February 1934) Dale Archives, HD 36.4.4.

³⁷¹ H. H. Dale letters to/from T. R. Elliott; T. R. Elliot to H. H. Dale, (19 February 1934) in Dale Archives, HD 36.4.6.

³⁷² F. H. K. Green, *Brit. Med. Bull* (1944) 2: 58 –60.

same or similar action.³⁷³ Not all companies went to the same lengths to evaluate their drugs and it was suggested that a central laboratory would be useful: “Few laboratories are equipped adequately for the proper pharmacological evaluation of new drugs and although arrangements can be made by commercial houses for the clinical trial of new drugs through the TTC of the MRC, there is an obvious need for a central laboratory, such as that carried on by the (Pharmaceutical) Society, where the pharmacological testing of drugs can be undertaken. Many of the synthetic chemicals employed as chemotherapeutic agents are tributes to the enterprise of our large pharmaceutical manufacturers, who take considerable financial risk in the development of new remedies. Often, however enthusiasm has been allowed to override caution, and many compounds have been placed on the market with insufficient preliminary laboratory and clinical testing”.³⁷⁴ The reason for insisting that the MRC were the sole agents performing studies was ostensibly “to prevent the appearance of conflicting and confusing reports upon the product, due to the premature publication by independent workers of reports on its trial in inadequate series of cases, before the official investigation”.³⁷⁵ They recognised that this effectively excluded any product already on the market in Britain or abroad. Green listed the most important agents launched by the committee as calciferol, digoxin, Prontosil, stilboestrol and Sulphanilamide.³⁷⁶

The MRC were to get around the problem for doctors by publishing studies as a ‘report to the TTC of the MRC,’ thus exonerating clinicians, keeping them free from commerce. According to Green “over 40 compounds were tested” and in his words “some of the investigations have been on a statistical basis, and these have been planned and assessed with the advice from the statistics staff of the Council”.³⁷⁷ In a separate account he wrote that: “it was early realised that the medical statistician is a valuable member of the planning team, even when the nature of the investigation is not such as to require large

³⁷³ “The Investigation of New Drugs”, Pharmaceutical Journal (1 June 1935): 653.

³⁷⁴ “A Central Laboratory”, Pharmaceutical Journal (1 June 1935): 653.

³⁷⁵ F.H. K. Green, “Clinical Evaluation of Remedies in Britain”, Brit. Med. Bull. 2 (1944): 58-60.

³⁷⁶ F. H. K. Green, “The Clinical Evaluation of Remedies” The Lancet (27 November 1954): 1085 - 1091. F. H. K. Green, Brit. Med. Bull (1944) 2: 58 –60; L. Colebrook, A.W. Purdie, Lancet (1937): 1237, 1291; W. R. Snodgrass, T. Anderson, British Medical Journal (11 December 1937) II: 1156.

³⁷⁷ F.H. K. Green, “Clinical Evaluation of Remedies in Britain”, Brit. Med. Bull. 2 (1944): 58-60.

numbers of subjects”.³⁷⁸ He refers to the notorious difficulty of securing controlled data and how this was overcome by the organisation of blinded tests and the use of inert substances. Unfortunately there is no data in the files or publications to support such statements. The studies arranged by the TTC, generally employed several centres, but recruited relatively few patients. The design of the studies allowed them to readily identify overtly toxic drugs or drugs that simply did not work or were poorly tolerated. Where they struggled was with the many drugs being produced by different firms that were variants or marginal improvements on a theme – those that were better extracts or synthetic versions or improved salts. This was particularly problematic when the drug was tested in an unusual and rare disease such as myasthenia gravis. Despite the claims of the role of statisticians, I found no evidence and the numbers required were not planned, rather the TTC arranged for as many patients to be treated as could be mustered.

The impression is given that the evaluation of medicines was based on a combination of the ‘scientific rationale’, the data presented from animal studies, the purity of the drugs and freedom from other contaminants and finally the clinical efficacy and tolerance in clinical trials. In addition factors such as the availability of a British version and to some extent costs were also taken into consideration.

What about from the manufacturers point of view. Aside from the disappointment of the slow progress of some studies, firms were frustrated by the lack of control over their products destiny, and their lack of access to clinicians but as Rutherford Hill pointed out there was nothing to stop them placing products on the market. At the end of 1937 J. W. Trevan gave an outspoken Presidential address on this subject to the Section of Therapeutics and Pharmacology of the Royal Society of Medicine. He recalled how the spate of synthetic drugs had begun in the 1880’s. He announced that some responses had been less dramatic than hoped for. He reasoned that:

“If a physician is prepared to take the risk of administering a new product to a series of patients he should be prepared to take the risk of withholding the

³⁷⁸ F. H. K. Green “The Clinical Evaluation of Remedies” Lancet (27 November 1954): 1088.

remedy in the case of some patients until a certain probability was established, greater than say ten to one, that the material was active”.³⁷⁹

He gave examples such as the use of vitamin A for infections and vitamin B for constipation based on little evidence. He referred to the fact that due to “the happy hunting ground of the synthetic chemist, chemotherapy was now one of the chief growing points of therapeutics and medical men might look forward to a considerably enlarged daily post”. He complained about the reprehensible practice of making statements, which were demonstrably untrue, although made with apparent scientific assurance and he thought the rubbish outweighed the good and he was pessimistic about heading towards a therapeutic dark age. The money spent was enormous, so clearly the advertisements had some effect. Trevan had reviewed 43 recent cases and found that even by lenient standards only 27 claimed foundation in the laboratory or clinic and that 13 were misleading or “simply silly”. He felt that one solution would be to have an independent laboratory at the London School of Hygiene and Tropical Medicine or at the Pharmaceutical Society. One of the problems of competition was the multiplication of similar products by competing manufacturers and this could not be avoided as long as production was in private hands.

He did comment of the TTC that they were: “doing extremely valuable work and of which he wished the manufacturers would make more use. Could it be hoped that no new remedy would be introduced until it had been passed by such a committee”.³⁸⁰

At the end of the period under review and with the outbreak of War, a further series of more specialised committees, including one on penicillin, and another on antimalarials were established allowing manufacturers to maintain closer conduct with the clinicians making the tests than has hitherto been permitted in peacetime in line with a desire to see faster reporting of results.³⁸¹

Cox-Maksimov, in her evaluation of clinical trials methodologies covered the same period that I do, but from quite a different perspective. She recognised the TTC as assessing therapeutic authority. Her main thesis contrasted the interactions between mainstream medical researchers led by Fletcher at the MRC with the fraudsters and charlatans that peddled their patent medicines, and challenged the medical establishment. In

³⁷⁹ J. W. Trevan, Pharmaceutical Journal 140 (1 January 1938): 3.

³⁸⁰ *Ibid.*

dramatic style she wrote that: “What was at stake was the very future of the nation”. This was a contest between the pursuit of secret remedies with unfounded claims against the ‘rigorously’ tested, scientifically validated methods of the establishment involving disclosure, integrity and character together with standards, fairness and statistics. “But it was just as much about maintaining the social order of Britain”.³⁸²

One should be careful of generalisations here. Cox-Maksimov focussed on the TTC study of concentrated pneumococcal serum at the Royal Infirmary, Edinburgh and UCH: but this was not at all representative of the main work of the TTC, nor its stated objectives. It was not a British preparation, it was certainly not from industry and its study had already been planned in 1929, two years ahead of the TTC. It was an expensive preparation that Panel doctors could not afford and it was initially imported from America.³⁸³ Cox-Maksimov went on to examine the multicentre study of patulin for the common cold.³⁸⁴ Patulin was a natural extract derived a fungus that grew on apples. This latter study was the brainchild of Phillip D’Arcy Hart, Director of tuberculosis work for the MRC, who was to be intimately involved in the 1946, randomised controlled study of streptomycin.³⁸⁵ Cox-Maksimov summarised her interpretation that the TTC became a “regular machine.”³⁸⁶ She focused on statistical methodology, arguing that the first recognised randomised controlled trial on streptomycin organised by Austin Bradford Hill, the MRC statistician in 1946-1948³⁸⁷ was based on a line of descent from the statistical concepts of randomisation evolved by Ronald Fisher in agriculture in 1935.³⁸⁸ Austoker and Bryder found no evidence

³⁸¹ Sir Arthur S. MacNalty, *History of the Second World War: Medical Research* F. H. K. Green. G. Covell eds. (London: HMSO, 1953).

³⁸² D. Cox-Maksimov, (1997): 185.

³⁸³ MRC Minutes III, (25 October 1929): 167; (16 May 1930): 84; (28 November 1930): 175; (23 October 1931): 127; (21 October 1932): 171.

³⁸⁴ H. Raistrick, “Patulin in the Common Cold: Collaborative Research on a Derivative of *Penicillium patulum* bainier” *Lancet* (20 November 1943): 625.

³⁸⁵ P. D’Arcy Hart, “A Change in Scientific Approach: from Alternation to Randomized Allocation in Clinical Trials in the 1940’s” *British Medical Journal* (28 August 1999): 319

³⁸⁶ D. Cox-Maksimov, “The Making of the Clinical Trial in Britain, 1910- 1945. Expertise, the State and the Public” (Cambridge: PhD thesis, September 1997): 185.

³⁸⁷ J. Fisher Box, “R. A. Fisher and the Design of Experiments, 1922-1926” *The American Statistician* 34 (February 1980): 1-7.

³⁸⁸ R. A. Fisher, *The Design of Experiments* (Edinburgh: Oliver and Boyd, 1935).

of Fisher interacting with the TTC and this “meant that his expertise was not utilised in order to translate his powerful ideas on experimental design into a clinical context.”³⁸⁹

Bradford Hill was certainly aware of Fisher’s work but the random scattering of seeds in fields was a different matter to physicians adopting the ‘null hypothesis’ and admitting to themselves and to their patients that they really did not know which of two treatments was best and that they could face the ethical issues of randomly assigning patients to one of two therapies.³⁹⁰ This contrasted with the physicians ‘art’, which was in carefully diagnosing an individual patient and carefully choosing the most appropriate therapy for that patient and the methods of clinical study that I have described in the remaining TTC studies in the 1930’s. Bradford Hill questioned the methods of allocation to treatment, criticising that greater effort should be taken “that the division of cases really did ensure a random selection”.³⁹¹ These concepts were embodied in a series of articles published in the *Lancet* at the start of 1937 and summarised in a book in the same year.³⁹² According to Bradford Hill and others, Fisher played no part in the design of clinical trials.

The interwar period shows an increasing sophistication of drugs and the means of assessing them. Liebenau agreed that:

“As drug companies required increasingly technically advanced people for research and development, and as medical scientists were increasingly available for industrial employment during the interwar period, the use of new science became the central element of competition”.³⁹³

The reluctance of the British medical profession to collaborate with industry in testing their new drugs stifled British research in synthetic drugs until the MRC assisted at the request of industry in establishing the Therapeutic Trials Committee in 1931. I have examined the success or otherwise of this venture. It was helpful in those areas in the MRC comfort zone where they could assist in getting a British version of a drug on the market. They had greater success in testing some but not all organotherapies and other drugs that could also be tested by biological standardisation or the success of which could be followed in the

³⁸⁹ J. Austoker and L. Bryder, in J. Austoker and L. Bryder (eds.), (1989): 47.

³⁹⁰ Personal correspondence by letter with Sir Austin Bradford Hill. (6 October 1988) and telephone discussion (1 January 1989).

³⁹¹ A. B. Hill, “Serum Treatment of Pneumonia” (22 December 1933), MRC File 1487.

³⁹² A. B. Hill, “Principles of Medical Statistics”- series of articles *The Lancet* (1937)

³⁹³ J. Liebenau, “Research and Development in Pharmaceutical Firms in the Early Twentieth Century” *Business History* 26 (1984): 329 -346.

laboratory. The synthetic drug studies were far less successful, partly because of the reluctances mentioned above, but also because individual doctors saw only limited cases. Apart from vaccine and toxoid studies, the TTC studies were generally small and often inconclusive, except where even a small study showed some safety problems. Synthetic drugs brought new issues, not least regarding patents but both Harry Jephcott of Glaxo and Prof. H. Hörlein of Bayer defended patenting as a means of protecting investments and allowing a return to invest in further research.³⁹⁴

Another reason for insulin not being a good model for clinical trials was that the firms had to interact with physicians through the MRC and were not allowed independent studies. It was only after the discovery of Prontosil, and the preparation of sulphonamides by many British firms that their synthetic drugs were in demand.

The TTC dealt with a backlog of drugs that had not been tested, giving clear priority to British drugs. It helped to establish a network of clinical research centres and contributed towards the standardisation of drugs. It also offered an independent body of opinion on novel drugs and methods of treatment, keeping doctors free of direct collaboration with industry. The TTC was most successful in dealing with biological drugs, largely because that was an area where the MRC were comfortable and had considerable expertise.

This thesis does not extend into and beyond the Second War. However it is clear that British firms came out even stronger having been involved in the development of both penicillin and the antimalarials. The former was again unpatented and offered further scope for chemical manipulation. Such were the benefits of antibiotics that the larger British firms did not see the need to collaborate with the TTC post-war although the smaller firm Napp did. Indeed ironically, given its initial *raison d'être* of the TTC it became a means for foreign companies especially from Holland and Switzerland to have their drugs tested. British firms instead began to establish their own studies. This trend had begun in 1936 when May & Baker appointed the physician Robert Forgan to establish clinical trials of M&B 693 and to answer medical queries. Glaxo had their own physician in Dr Hector

³⁹⁴ “Medical Patents” replies by H. Jephcott and by H. Hörlein, Pharmaceutical Journal 140 (15 January 1938): 50. This was in reply to an editorial in Pharmaceutical Journal 139 (4 December 1937): 589 and to similar points raised in America- Dr. Fishbein, Journal of American Medical Assoc. 109 (1937): 1539-43.

Walker and Allen & Hanbury's took on two female doctors to 'sell' their vitamin products and Bayer had a physician even earlier. Thus the major British firms began to establish their own Medical departments and took control of the process of clinical testing of drugs. Sir Eric Scowen was involved in studies with M&B and before the Second World War on the antiseptic, pentamidine and worked directly with ICI on sulphadimidine after 1936. M&B's compound was evaluated in Edinburgh in studies set up by a company man called Harry Thrower.³⁹⁵

³⁹⁵ Eric Scowen visited ICI in June 1990. Personal communication. He also evaluated Progestin in patients with chronic interstitial mastitis, TTC Minutes 7 (11 February 1937): 5.

CHAPTER 9: Concluding Comments.

This chapter aims to bring together a summary of the research performed, the broad trends discovered and some provisional conclusions. It also identifies areas where future researchers may profitably extend this study.

Following the introductory chapter in which I examined the historiography of the pharmaceutical industry and clinical trials, I demonstrated in Chapter 2, the extent of the reliance on Germany for synthetic drugs and chemical intermediates, and the small capacity of British pharmaceutical firms in comparison. British pharmaceutical firms faced a particular shortage of chemists with practical skills of chemical engineering and drug production. The government had failed to support the competitiveness of British industry in its patent laws, and with its high duty on alcohol, and focussed instead on the battle against ‘patent medicines’. In contrast to the esteem in which the German industry was held, that in Britain had a poor image, contributing to the difficulty in getting drugs tested in Britain in contrast to the close collaborations between industry and academia in Germany. The impression in Britain was that it was easy for German firms to get their new drugs tested.

In the remainder of the thesis I have addressed these points, firstly to explain how British firms were able to make synthetic drugs and then how they remained competitive. In Chapter 3, I demonstrated how Burroughs Wellcome became an innovative company, continually striving to produce differentiated drugs, taking ideas from other innovators such as Parke Davis and German firms. Burroughs Wellcome cut their ties with Wyeth to establish their own manufacturing facilities, and employed German engineers to build and run their chemical manufacturing site. Henry Wellcome established Chemical and Physiological Laboratories that collaborated closely. Their strategy was set out early, combining advanced American tableting technology with novel drugs from Germany and combining German-style patenting and trade names with American-style selling techniques employing sales representatives.

Henry Wellcome employed the most promising researchers of the era, through his contacts in Cambridge and London. The appointments of Barger, Dale and Glenny were inspired choices that have been well documented, but I have emphasised the importance of chemists such as Frederick Power, who had a unique combination of experience resulting from work in pharmacies, training at the Philadelphia College of Pharmacy, and research at important German and Swiss laboratories. I also emphasise the benefits of the close

collaboration with the alkaloid expert William Dunstan, at the Imperial Institute in London, which resulted in the recruitment of Jowett, Carr, Thompson and Reynolds.

The physiological research performed in the laboratories under animal licenses is well known thanks to Tansey, but I have shown that synthetic chemistry was a far more important and earlier feature than has previously been described, beginning soon after the arrival of Power and Jowett in 1896.

The Tabloid name at Burroughs Wellcome signified known purity and strength, achieved by employing expert botanists and chemists to define the species of plants, to standardise extracts, and to determine the chemical structures of purified alkaloids and glycosides, which were then assayed physiologically against pure synthesised chemical standards. Some active ingredients were chemically modified to evaluate the relationship of chemical structure to biological function. Potency was measured by the content of specific alkaloids, rather than total alkaloids, and this gave competitive advantages over firms without laboratories. Synthetic chemistry also contributed to the preparation of salts of natural products to make them more soluble or stable. Further differentiation was achieved by incorporating German synthetic drugs into Tabloids, and from 1906 by incorporating 'optical isomers' of some drugs, such as tropeines and hyoscyamine, increasing potency dramatically. Some natural molecules had chemical structures that existed in a mixture in two or more mirror image forms (one for each chiral¹ centre in their chemical structure); Jowett and his team discovered how to separate these, and how to prepare chemicals in only the biologically active form.

Power contributed to the Pharmacopoeia and Codex, and ensured that the highest possible standards were set, so that fewer firms could achieve those targets and therefore few could compete. Burroughs Wellcome sold a few synthetic drugs including the arsenical, Kharsin, some isoquinolines and synthetic Suprarenin, but these were minor compared to their thriving Tabloid alkaloid business. They did not even try to compete with Germany in preparing the popular salicylates or other synthetic drugs even when they were beyond the period of patent protection. The importance of synthetic chemistry at Burroughs Wellcome from 1896, and the parallel development of an understanding of chemical engineering principles at the Works, helps to explain how Burroughs Wellcome

¹ A chiral centre is a carbon in the chemical structure with different groups attached. They rotate light differently according to which group is on the right and which on the left. The important feature is that one form might be almost inactive and the other highly active.

were in a position to prepare complex German synthetic drugs within weeks of the outbreak of the First World War.²

Chapter 4 assessed the general impact of the First World War on the British Pharmaceutical Industry.³ Although the extent of the dependence on Germany was well recognised, the specific quantities of each drug and chemical intermediates required were very poorly understood at the outbreak of the war, as Board of Trade figures were not specific or detailed enough. The situation was complicated by the need for chemical intermediates and especially as the same intermediates were required for the production of dyes and explosives, so central coordination was essential, and a Ministry of Supplies was created.

I demonstrated how various committees were established to decide which drugs were essential; to assess which companies made or could make them, where the shortages were, and what was needed to prepare the German drugs. Further committees organised supplies of essential chemical intermediates. Pharmaceutical manufacturers were represented on all of these committees, including the individuals Howard, Tyrer, Hill, Morson, Lescher, Webb and Jowett.

Immediate legislation prevented the export of essential materials, while German patents of synthetic drugs were abrogated along with their Trade Marks to encourage manufacture in Britain. Several companies eventually produced the less complex synthetic drugs, but they sought assurances that their efforts would be rewarded by protection against German competition post-war, before they invested heavily in manufacturing facilities, which formed the basis of a stronger industry post-war.

Before the war, German Salvarsan had been standardised and tested for purity by Ehrlich in Frankfurt, so the MRC took over this role in Britain during the war. I have demonstrated by reference to the Salvarsan committee how the previous Burroughs Wellcome work on biological standardisation was influential. Dale and Ewins and a string of ex-Burroughs Wellcome staff supported their former colleagues, and later May & Baker, by demonstrating that British Salvarsan was as good and safe as the German version, by collating data from hospitals at home and in France. However, their external

² F. H. Carr. "Synthetic Organic Drugs; their Manufacture as Affected by the War" *Chemist & Druggist* 88.4 (29 July 1916): 778-9.

³ M. Robson, in *The Challenge of New Technology* J. Liebenau (ed.), (Aldershot: Gower, 1988): 82-105.

support for British drugs masked poorly recorded data that they had little control over. They failed to convince some British physicians, who had extensive first-hand experience of the various products. One in particular campaigned that British Salvarsan could not be as good as the German versions- an example of the lack of faith in British chemistry, and of the conservative nature of British physicians. As a result of ongoing concerns over jaundice and some rare deaths, a second Salvarsan committee was established in 1918, specifically to compare clinical data on the use of various Salvarsan derivatives. The Salvarsan work was important in establishing a central role of the MRC as an arbiter of biological standards and then of the clinical efficacy of new drugs. By the end of the period under review the MRC were coordinating International efforts on standards and this became a central feature of their work.⁴

During the winter of 1914-15, after Power left Burroughs Wellcome to return to America, Francis Carr led a further exodus of staff to join rivals Boots, where he established synthetic drug manufacture, extended their laboratories, and prepared salicylates, anaesthetics and antiseptics, but also absorbent materials for gas masks. The government encouraged the supply of chemical intermediates to companies in 1915 by establishing British Dyestuffs, and the merger of several firms to form Distillers provided plentiful alcohol. The establishment of the Department of Scientific and Industrial Research in 1915 provided further chemical intermediates and encouraged collaboration with industry. Carr and other pharmaceutical manufacturers took an active role in the establishment of the Association of British Manufacturers in 1916, which led to a better bargaining position for British Pharmaceutical manufacturers in the campaign for longer-term protection; he was a member of their fine chemical committee along with Hill and Howard.

I emphasised the growing importance of Francis Carr, who was rewarded with a CBE for his wartime drug manufacturing at Boots, and was chosen to represent his country, along with Ivan Levinstein, on ABCM visits to the German factories within the occupied territories. Francis Carr was then 'headhunted' to join Charles Hill at British Drug Houses in 1920, with the promise of major funding to create an extensive manufacturing business - and his loyal team followed him. I showed how at the end of the war Burroughs Wellcome lost several further experienced staff, including Frank Tutin and Harold King, who joined Dale at the MRC. Frank Pyman left for Manchester University,

⁴ P. Hartley, "International Biological Standards: Prospect and Retrospect" *Proc. Royal*

being replaced by Thomas Henry, who specialised in alkaloids. These staff losses may have influenced some of their policy decisions regarding whether to focus on synthetics or traditional drugs.

The period from 1919 to 1931 was dealt with in 3 parallel chapters (5-7), dealing with post-war markets, how each firm responded and new legislation on drugs, how the ABCM campaigned to the MRC for a system of clinical trials, and the strategies for product development, described by the Burroughs Wellcome Scientific and Technical Committee. Much of this related to the recognition that a strong industry was needed in Britain for strategic reasons and required nurturing and I demonstrated several ways in which protection for the British pharmaceutical industry was achieved. The Trading with the Enemy Act and tariffs on dye imports were extended to pharmaceuticals in February 1919. With export markets reopened, there was a 'honeymoon' period of trading, but the Sankey judgement in December 1919 led to a flooding of the market with German products. Together with German reparations, and a downturn in the economy, this led to overcapacity; once again the industry was under threat. Carr campaigned for further protection and research to protect the country against future attack, while Pearson of Burroughs Wellcome promised that a synthetic drug industry could be developed in Britain **if** firms were allowed a period of protection.

I demonstrated that in 1922 the ABCM, representing the pharmaceutical industry, approached the MRC for a system whereby novel drugs could be evaluated in clinical trials. Previous historical work, originating from Liebenau, suggests that the MRC imposed a 'method' of testing of new drugs. All British firms had difficulty arranging studies of novel products, and Burroughs Wellcome only had successful clinical trials with their tropical medicines, evaluated overseas. The Trials Committee did not materialise immediately, as the MRC became engrossed with insulin, collaborating with several British firms to prepare insulin on a large-scale, and to organise clinical studies of insulin. However, following exploratory studies by the MRC, it was Francis Carr at BDH who perfected the production of insulin, such that within a year BDH produced 95% of the material required for British use, thus making the clinical trials possible. Production of insulin was a highly technical large-scale operation that required significant modification of existing manufacturing plant. In 1924 Carr achieved similar success in the large-scale production of the previously prohibitively expensive hormone, thyroxine and Britain held

a leading position in production of the new hormones. In 1925 the Therapeutic Substances Act was passed, making it compulsory to have biologicals evaluated before sale, and formalising the MRC role in biological standardisation – a role it will be recalled that was initially developed within Burroughs Wellcome. As a result some foreign drugs were excluded from the British market. The ABCM approached the MRC again in 1926 for a system of clinical testing, but the MRC instead established a Chemotherapy Committee, which aimed to evaluate novel chemotherapeutic agents, based upon the success of a new German drug active against trypanosomal infections, Bayer 205. The DSIR were meant to develop novel chemotherapeutic agents, and were granted £30,000 to assist this process and they approached Burroughs Wellcome with an offer of collaboration; but the firms Scientific and Technical Committee (STC) dismissed the request, insisting that the main collaboration needed was in establishing clinical trials *of their new own drugs*.

Jowett set down guidelines for testing of novel products at Burroughs Wellcome, and the criteria for bringing them to market. He bemoaned the fact that Burroughs Wellcome had fallen behind both Boots and British Drug Houses, and he put the blame firmly on the shoulders of Francis Carr and his external political influence. Burroughs Wellcome was insular by contrast, and having lost so many staff, they rarely allowed employees to attend external meetings, for fear of more poaching. I demonstrated how Carr established himself as a driving force for chemical engineering, but he also was President of the Society of the Chemical Industry 1926-7, giving him the platform to describe his vision of the future synthetic pharmaceutical industry, and the *need for an organised system of clinical trials for drugs produced by industry*.

The MRC finally got the message and created the Therapeutic Trials Committee (TTC) in 1931, after a further push from the ABCM involving Hill, Carr, Pearson and Gamble. British doctors remained reluctant to collaborate with pharmaceutical firms despite their growing commitment to laboratory science, and the few who did work were not prepared to put their names to publications supporting new drugs. This placed British firms at a competitive disadvantage. Whereas doctors in Germany were used to testing novel drugs, this was not the case in Britain. Previous historical research on Salvarsan and insulin has not addressed this issue as these drugs were already recognised as significant advances following studies overseas, and doctors were keen to obtain supplies. The quite different challenge for British firms was to secure clinical testing of their own novel drugs, especially their early attempts at making synthetic drugs.

Although the TTC proposed restricting their service to novel drugs, they often took the opportunity to 'trial' an English version, even if there was already a foreign version of a drug on the market. They gave preference to British drugs and turned away several foreign drugs until one came along that was too good to ignore – Prontosil from Bayer. The TTC was most successful in their areas of special interest such as organotherapy, and I agree with the conclusion of Valier, who examined studies of liver therapy in pernicious anaemia, that the MRC were most comfortable following progress in the laboratory rather than at the bedside. Several of their studies were failures, not only because of poor results, but often simply due to poor recruitment of patients. The analysis of all of the studies left me with quite a different impression compared to the reflections of the TTC's Secretary, Frank Green, who summarised the major studies.⁵ He focused on the TTC successes, most of which occurred in the later years, and often as a result of improved formulations of extracts and the provision of synthetic hormones and vitamins.

I have examined the TTC from the perspective of the pharmaceutical firms as well as from the MRC side. The MRC repackaged the TTC as being their own creation and a focus for developing novel drugs, and yet I have shown that it was only established after repeated attempts by the ABCM in 1922, 1926 and 1930-1, and did not only examine novel drugs. The most frustrating aspect for British pharmaceutical firms was that firms were not allowed to contact clinicians directly. Valier described how the MRC frowned upon John Wilkinson of Manchester in the pernicious anaemia study, when he collaborated directly with Boots. I noted similar examples when O'Brien of Burroughs Wellcome established his own trials, and when Burroughs Wellcome was asked not to establish parallel trials of ergotoxine in Germany. I discovered that several firms got around this in the later 1930s by employing their own physicians to liaise with doctors, once they had established a successful product. Glaxo, Allen & Hanbury's and May & Baker all employed their own physicians to answer medical queries, but also to establish clinical trials. This trend continued into the post-war period, until in the mid 1950's there were enough physicians working in industry to create their own Association of Medical

⁵ F. H. K. Green, "Clinical Evaluation of Remedies in Britain." Brit. Med. Bulletin 2 (1944): 58-60; F. H. K. Green, "The Clinical Evaluation of Remedies" Lancet (27 November 1954): 1085-90.

Advisors in the Pharmaceutical Industry (AMAPI) in 1957.⁶ I interviewed many physicians involved in pharmaceutical trials in the early 1950's, but on account of the material I had already, I concluded this thesis at the outbreak of the Second World War. An extension of this work into the post-war period will follow.

We may note that Britain only gained an insight into the clinical trials operations of German firms after the Second World War, and a further visit to German factories, this time by the Combined Intelligence Objectives Subcommittee. It had been wrongly assumed that some sort of centralised clinical testing procedure existed. Representatives of the main companies including May & Baker, Burroughs Wellcome, Glaxo and ICI found that Bayer had a Scientific Director of Publicity in the period 1923-35, with a department split into two sections for arranging clinical trials and for sales propaganda. In the first section there were 5 physicians covering both general and tropical medicine. Firms had to organise their own tests and IG Farben were given 3-4 years before drugs were put on the market. Initial trials were first carried out by 1-4 clinicians, and then were broadened if the product looked promising. Less than 5% of drugs tested stayed the course and were issued commercially, following an application to the government. In the sales department at Bayer there were 70 doctors qualified in biology, pharmacology and chemistry and they were divided to cover the regions of Germany. "Therapeutische Berichte" (Therapeutic Reports) was sent out monthly to 70,000 doctors, and a physician's yearbook was also provided.⁷

Unlike several previous historians I chose not to focus on a single chosen example of a drug or a study, but I have tried to get under the skin of the problem by trying to understand some underlying fundamentals. In doing so I evaluated a wide range of the drugs produced by British Pharmaceutical Industry, covering the period up to 1931 in chapters 5 and from 1931-39 in chapter 8. Inevitably I have not done justice to any

⁶ This became the British Association of Pharmaceutical Physicians, and in 1976, The Society for Pharmaceutical Medicine to reflect the expansion of the role. A Faculty of Pharmaceutical Medicine, affiliated to the Royal Society of Medicine was established in October 1989; T. B. Binns, "What do Pharmaceutical Physicians Actually Do?" *Pharmaceutical Medicine* 1 (1986): 213-219; P. D. Stonier, *Discovering New Medicines: Careers in Pharmaceutical Research and Development* (Chichester: J. Wiley, 1994); D. M. Burley, T. B. Binns (eds.) with a foreword by Sir Abraham Goldberg, *Pharmaceutical Medicine* (London: Edward Arnold, 1995); F. J. Gabbay, A. J. Salter, "The Society of Pharmaceutical Medicine- Development of the Discipline, *J. Pharm. Med.* 1 (1991): 53-60.

⁷ "IG Farben: The Propaganda Department" *Pharmaceutical Journal* (2 March 1946): 137.

specific drug but that was not the intention. Instead I aimed to examine patterns of change and general trends and to try to understand why firms chose a particular strategic direction. My conclusions differ from Robson who wrote: “the pharmaceutical industry in reality had learnt little from the war- with few notable exceptions research and development were not a major feature of the industry during the interwar period”.⁸

My general conclusion is of gradual progress being made by British pharmaceutical firms. They had ended the First World War calling for protection so that they could establish a synthetic drug industry to compete with Germany. This was always going to take time, so they evaluated the many other opportunities that came their way, and were successful in producing enough insulin, thyroxin and various organotherapy preparations and vitamins, which satisfied the home market and also generated export sales. Whereas previous authors have taken insulin as a model for the development of clinical trials, little attention has been given to the complexities of manufacture. I have pointed out the scaling up of plant required, the new centrifugal filtration procedures, the refrigeration of the various processes and the need for careful control of acid concentration. There were similar problems in the production of other hormones and techniques had to be developed for continuous low temperature evaporations and for retrieving the vast quantities of alcohol used as a solvent.⁹ The same was true for vitamins and Francis Carr overcame many of these difficulties at BDH, including the complex sterile manufacture placing his firm in a good position for similar work on further hormones, vitamins, and ultimately antibacterials.¹⁰ Had it not been for these developments British firms would not have been able to react quickly to supply sulphonamide antibacterials. Carr recognised that: “once we understand the chemical nature of insulin it is not too much to expect that the history of adrenalin and thyroxine will be repeated, and insulin, like the two latter, will be

⁸ M. Robson “The British Pharmaceutical Industry in the First World War” in J. Liebenau (ed.), (1988): 82-105.

⁹ F. H. Carr, “The Commercial Production of Hormones”, *SCI, Chemist & Druggist* 105.1 (1926): 181.

¹⁰ F. H. Carr, “How insulin is isolated”, *Chemist & Druggist* 106.1 (26 February 1927): 263; F. H. Carr, “The Vitamins in their Relation to Medical Supplies” *Pharmaceutical Journal* 117 (1926) 729, 739. F. H. Carr, “Vitamins in their Relationship to Medical Supplies”, *Chemist & Druggist* 105.2 (18 December 1926): 897-99.

manufactured artificially.¹¹ In other words, the pattern he foresaw was a gradual switch from natural extracts to pure synthetic drugs.

Liebenau concluded that Allen & Hanbury's, Morson, Whiffen's, Howard's and May & Baker had "an aversion to innovate" and May & Baker had "no important products until 1937".¹² His assessment of British Drug Houses was that there was "also little emphasis on R & D. He wrote: "to produce insulin they hired Carr," whereas I clearly showed that BDH hired Carr in 1920, and were prepared to invest £250,000 before insulin was even discovered. Liebenau wrote that Boots had "analysts only," but this was not the case; it seems that he measured British firms only against the German model of a large laboratory staff, searching for many years for novel drugs such as Salvarsan or a Bayer 205. German firms such as Hoechst and Bayer could afford to 'indulge' this model as they had the infrastructure, including supplies of intermediates and profits from the dye business and also benefited from high sales of many of the early synthetic drugs such as phenacetin and aspirin. The British industry in contrast was 'opportunistic' in the interwar period, but it could be argued that this was an efficient use of the limited resources, tailoring their efforts to identify opportunities that had already come out of patent; modifying patented drugs and collaborating with external inventors, as Glaxo did with Steenbock.

Such historical judgements beg the question, what is research and development? Does research not also include finding better drugs, purer drugs, preparing those with greater solubility and lower side effects, and particularly was the work done by Burroughs Wellcome to identify and standardise the active ingredients of their drugs not research? It certainly led to the identification of novel active drugs. Development includes identifying methods to assess the safety of drugs in pre-clinical models and improving the production and reliability of the manufacturing, as Carr so often did. My argument is that by these standards of research and development the British industry was successful in the interwar period, and furthermore expanded the collaborations developed in the First War, to provide a better infrastructure for the biological and clinical testing of new drugs.

¹¹ F. H. Carr, "Insulin and its Manufacture" Pharmaceutical Journal (5 March 1927): 244-45. In fact this never happened as insulin turned out to be a complex protein, and human insulin has only recently been prepared by cloning the gene in bacteria.

¹² J. Liebenau "Patents and the Chemical Industry: Tools of Business Strategy" in J. Liebenau (ed.), (1988): 135-50.

The significant advances made in manufacturing during the interwar period were summarised by Frederick Gamble and Norman Evers. The extraction of hormones bore little resemblance to the earlier extraction of alkaloids. “Manufacture of these products required a delicacy of control beyond any which had previously been available: in fact it would have been impossible to make insulin on a large scale a few years before its discovery. The control of hydrogen ion concentrations was essential and huge amounts of alcohol and other solvents were needed and methods had to be developed to recover these. Evaporating plant was required to resist breakdown by the acids used and in this respect the replacement of copper vessels with stainless steel had been vital. Old methods of filtering were also inadequate and high-speed centrifugal devices had been installed. Sterilisation technology also had to be developed so that large volumes could be sterilised without the use of heat, and this was done using asbestos based Seitz filters, which allowed refrigeration. Special irradiation techniques had to be developed to prepare vitamin D and new techniques had been developed for preparing emulsions.¹³

Through the work on standardisation of drugs, British scientists such as Trevan, Gaddum and Burn made important statistical contributions to the understanding of biological variation, and British firms took advantage of this, and their strong links with physiologists and the expertise in alkaloids, to produce new standardised alkaloids, and help to identify the active constituents. Although the actual discoveries might be credited to an external academic such as Chassar Moir with ergometrine or Dodds and Robinson with the synthesis of stilboestrol, they collaborated with industry and their discoveries were only made possible by the provision of large manufactured quantities of organ extracts. However, when it was discovered that existing patents did not cover the active ingredient of Prontosil, British firms rapidly seized upon this opportunity and produced and patented their own chemically distinct sulphonamides. This involved the chemical synthesis of hundreds of derivatives and their evaluation in the laboratory and with external consultants. May & Baker worked closely with Lionel Whitby, a pathologist at the Middlesex Hospital and rapidly mastered the large-scale manufacturing.

Hill summarised the progress made by 1935: “the whole foundation of pharmaceutical manufacture has been undergoing a change, at first gradual but in the later years increasingly rapid”.

¹³ F. W. Gamble, N. Evers, “Advances in the Manufacture of Pharmaceutical Products, *Pharmaceutical Journal*, (4 May 1935): 541-3.

He continued:

“the manufacture of organo-therapeutic products has become a highly organised section of the fine chemical industry. It involves the synthesis of complex substances, and also the separation and purification of natural principles from animal sources- challenging the supremacy of synthetic organic chemicals which have held sway for several generations”.¹⁴

Although the production of drugs had increased significantly there were still concerns at the MRC that Britain was copying rather than discovering drugs and that this still placed the country at risk. The MRC report of 1936 had kicked off this controversy, hotly disputed by British pharmaceutical firms by writing: “the discovery and production of chemical compounds of value in chemotherapy has depended almost entirely on German science and industry and still so depends, a situation which in the event of war could be fraught with grave danger”. The ABCM countered: “during the last 20 years the British Chemical Industry, with the stimulus of the Key Industry duties has made such great strides that the position was vastly different from what it was in 1914. Most of the synthetic products which are essential to the health services of the Empire are now manufactured in this country in adequate quantities”. Patents protected a few but it was felt that they could be made under license. The MRC had invested £30,000 for new research in chemotherapy but most of the costs were taken up by spending on new buildings for the NIMR at Mill Hill.¹⁵

Thomas Edward Lescher of Evans, Lescher & Webb, chair of the British Pharmaceutical Congress 1936-37 recalled in July 1937 that: “the war experience gave British chemists their opportunity and the manufacture of fine chemicals and biologicals today is on a scale sufficient to meet the requirements of our trade, both at home and overseas”.¹⁶

Increased numbers of synthetic drugs, but also other forms of sophisticated medications had led to increased manufacturing capacity, which together with a better infrastructure of chemical intermediates and a system of testing drugs, led to Britain being in a strong position at the outbreak of the Second War. Charles Hill and others clearly felt that this was due to the Key Industry Acts. Not only were new synthetics prepared such as procaine, benzocaine, orthocaine and amylocaine, but also chemicals such as

¹⁴ C. A. Hill, “The Changing Foundations of Pharmaceutical Manufacturers, Pharmaceutical Journal (4 May 1935)

¹⁵ “Chemotherapy and the British Chemical Industry”, Pharmaceutical Journal 140 (26 March 1938): 353.

phenolphthalein were produced in such quantities that some could be exported. Hill wrote: “The new drugs included palatable fish oils as sources of vitamins, purified hormones such as thyroxin, insulin and oestrone and isolated alkaloids such as ergometrine. Vitamins B, C and D had been isolated in pure crystalline form and vitamin C had been synthesised”.¹⁷

Mr. David Adams, Labour M.P. for Consett, asked the President of the Board of Trade a question in Parliament on 20th May 1938 about how successful Britain had been in replacing German imports. The latest data (from 1935) showed that output of Salvarsan-like compounds in Britain was 7,900 lbs. (equivalent to £107,000). Adams had specifically asked about the level of imports of the key German anti-infective products Salvarsan, Neosalvarsan, Bayer 205, tryparsamide, Atebrin, Plasmogone, trypan blue and Trypaflavin. These were not separately recorded but in 1933 there were imports of only 69 lbs. of Salvarsan, neosalvarsan and organic-arsenicals. Britain had clearly overcome a reliance on Germany for this drug. The main problem with imports was not the £2.5m of the NHI drug bill but the UK spend of £20-28m on patent medicines and this explains the constant focus of the government and BMA on these secret remedies. Fred Gamble confirmed that the use of secret and proprietary medicines had increased and that “prior to 1932 this country was the dumping ground of the world and still is to some extent ... in spite of the fact that, with the rarest exceptions British pharmaceutical firms can manufacture all that is required”.¹⁸

A useful barometer of the changes that had occurred in the interwar period was an editorial written in April 1939, which referred back to what had been written in the same journal in May 1918, gave some prophetic warnings about the need for Britain to be self-reliant in medicines:

“It is not so much a question of protecting our own manufacturers, although within economic and certain limits that is essential enough, as the imperative necessity of setting up and perpetuating on a stable and enduring basis in this country fundamental industries, so that *absit omen* should the

¹⁶ “British Pharmaceutical Congress” Chemist & Druggist (31 July 1937): 118-19.

¹⁷ C. A. Hill, (4 May 1935)

¹⁸ F. W. Gamble, “Facing Realities”, Harrison Memorial Lecture to the Pharmaceutical Society, Pharmaceutical Journal 140 (12 March 1938): 267-69.

time ever return when the British Empire has to fight for its very existence, it would be provided with all the internal resources required for the occasion. Thanks in part to the removal of some unfair trading conditions, but chiefly to the enterprise of British Chemical manufacturers we are now in a far different position from that which obtained in 1914, and little difficulty should be experienced in meeting all demands, for all the military and civil need of our people”.¹⁹

In a similar recollection Herbert Levinstein recalled how unprepared Britain had been for war in 1914, even to the extent that no firm made T.N.T. here. There were “deficiencies of chemical plant and few well-trained engineers could be found”. In contrast in March 1937 he felt that: “should another war come this country will be prepared for it at least on the chemical side”.²⁰

In Britain between 1920 –38, the capital employed in the pharmaceutical industry trebled, and the number of research chemists and research spending increased 4-fold. The weight of fine chemicals produced, increased 11-fold and J. Davidson Pratt of the ABCM was able to describe a “comprehensive and progressive synthetic organic chemical industry”.²¹ In terms of balance of payments, the country owed a great debt to the pharmaceutical industry in the interwar period. Many hormone preparations were made, such that Britain did not rely on Lilly, Organon, Schering and CIBA, and the same was true of vitamin preparations. During this period great emphasis was placed on giving the correct diet and this led to a strong focus on vitamin supplementation.²² In 1938 the ABCM took on its own initiative, active steps to promote the manufacture of those medicinal chemicals then imported from Germany and likely to be essential in the event of war so there would be no shortages.²³

By 1939 all of the major British firms produced a wide range of vitamin products.²⁴ British firms had not increased dramatically in size, with only ICI approaching the size of the German giants. However firms such as Glaxo and Allen & Hanbury’s had become

¹⁹ “Drugs in War Time, Pharmaceutical Journal (22 April 1918): 403-04.

²⁰ Herbert Levinstein, “Progress of the British Chemical Industry”, Pharmaceutical Journal (13 March 1937): 264.

²¹ J. Davidson Pratt, “The Economics of the Fine Chemical Industry”, Chemistry and Industry (20 January 1951): 38

²² Celia Petty, “Primary Research and Public Health: the Prioritisation of Nutrition Research in Inter-war Britain” in J. Austoker and L. Bryder (1989): 83-108.

²³ ABCM Report on the Chemical Industry (London: ABCM, 1949).

leading producers of hormones and vitamins. Figures reported in 1939 (and therefore referring to 1938) showed that ICI made a profit of just over £7m. Boots, which was primarily a retail business made profits of £776,292, J. Nathan (the forerunner of Glaxo) made £90,647, BDH made £49,790 and Evans made £39,140.²⁵

Britain was well prepared for the Second World War in terms of drug supplies.²⁶ The ABCM had continued to catalogue essential drugs and their manufacturers. Burroughs Wellcome reviewed a list of 40 such German drugs at their STC meeting on 29 September 1939. Five were already being produced, and a dozen or so were considered not worth making, but plans were made to manufacture the remainder, as long as chemical intermediates could be obtained from ICI, and most were in hand by November. The merger of many dyestuffs and alkali firms to create ICI had resolved many of the problems of the provision of chemical intermediates for pharmaceutical manufacturers. It was recognised that the recent German drugs such as Atebrin and Plasmoquine would have to be replaced in the event of war and this was one of the reasons behind the granting of funds for research in chemotherapy.²⁷

The main challenge to Britain in the Second World War was to prepare synthetic versions of the antimalarials that Bayer had recently developed, and this was to be a collaborative challenge, with ICI playing a leading role during the war.²⁸ Burroughs Wellcome, as they had in the First World War dominated the supply of antitoxins and vaccines so both Glenny and Parish contributed to the wartime committees.

While it is not within the scope of this thesis to examine the Second World War, it is clear that the models developed in the First World War were built upon. Committees like those in the Great War were established in 1939-40, and many of the scientists that I

²⁴ "The Vitamins", Pharmaceutical Journal (21 January 1939): 54-59.

²⁵ Figures are quoted from Pharmaceutical Journal 143 (1939) as follows: ICI (25 March 1939): 322; Boots (3 June 1939): 884; J. Nathan (14 January 1939): 49; BDH (8 April 1939): 377 and Evans (11 March 1939): 269.

²⁶ Association of British Chemical Manufacturers Pharmaceutical Specialities: British Equivalents and Alternatives for Foreign Proprietary Products (London: ABCM, 2nd edition 1940)

²⁷ "Parliamentary News. Imports of Fine Chemical" Pharmaceutical Journal 140 (28 May 1938): 581; "The Patent Medicine Trade. Prof A. J. Clark's Indictment", Pharmaceutical Journal 140 (14 May 1938): 518.

²⁸ D. Greenwood, "Conflicts of Interest: the Genesis of Synthetic Antimalarial Agents in Peace and War. J. Antimicrobial Chemotherapy 36 (1995): 857-72; A. S. MacNalty, History of the Second World War – Medical Research – section edited by F. H. K. Green, G. Covell, (London: HMSO, 1953): 9, 155-59.

have described participated. A Ministry of Food was established and from 1941-3 Harry Jephcott was an advisor. A Therapeutic Research Corporation was established in 1941 involving Boots, Burroughs Wellcome, British Drug Houses, May & Baker and Glaxo, and later joined by ICI.²⁹ Collaborations between firms continued, with Dale taking a prominent central role as President of the Royal Society from 1942.

A Therapeutic Requirements Committee, chaired by Prof L. J. Witts of Oxford and including J. H. Burn was established, together with a series of specialised sub-committees and once again a Ministry of Supply was established, this time with a Chemical Factories Medical Sub-Committee, Chaired by Prof. Sir Joseph Barcroft and involving Prof. J. A. Ryle and Prof. C. G. Douglas.³⁰ Many of those who contributed to earlier examinations of medicines were invited to participate and these included E. A. Carmichael, Edward Mellanby, Austin Bradford Hill, C. Langton Hewar, Leonard Colebrook, E. C. Dodds, Lionel Whitby. In addition to Burn there, the former Burroughs Wellcome staff included were Prof. P.A. Buxton, Percival Hartley, Harold King, and J. H. Gaddum.³¹

Liebenau attempted to evaluate the success of firms in this period and refers to a survey carried out in 1942 and covering the period 1936-41, which coincides with the latter period covered by the TTC, in which he evaluated the number of patents and publications produced by each firm.³²

	British Patents	publications	graduates	doctorates
May & Baker	40	11	58	15
Burroughs Wellcome	6	220	66	24
Glaxo	13	345		8
BDH	7	32		5
Boots	10	12	270	24

²⁹ R. P. T. Davenport-Hines, Judy Slinn, *Glaxo: A History to 1962* (Cambridge: Cambridge University Press, 1992): 138-41.

³⁰ *Ibid*: 328—331.

³¹ A. S. MacNalty, (1953).

³² J. Liebenau “Patents and the Chemical Industry: Tools of Business Strategy” in J. Liebenau ed., (1988): 135-50.

It would be useful to gain some further insights into these figures as I believe the firms involved had quite different approaches to patenting and publishing and Liebenau himself cautions against this. Because the analysis above covers the period from 1936, I believe it must be strongly biased by the significant efforts that went into sulphonamide drug production from 1936.

Compared to 1914 when only one third of the 250 active principles were synthetic, by 1948 this had risen to more than half of 440. “The Second World War proved abundantly that the key industry duty has been instrumental in protecting the country against a recurrence of 1914”. By 1948 the ABCM included 90 firms with a capital of £68m.³³ In summary, I have provided a rationale for how Britain became independent in regard to ethical drug supplies. While this was not the route of major drug discoveries that others have sought, it does explain how and why Britain survived the two world wars. For those who detract from the achievements of the industry, no explanation has been offered as to how the industry did become successful in Britain as it certainly is.

Regarding clinical trials, the sulphonamides in particular, and synthetic hormones, were recognised as important by doctors, helping to overcome their reluctance to be involved in clinical testing so it was no longer difficult to find doctors willing to test these exciting new therapies. And here my work can be compared with that of other historians of ‘trials’. Alan Yoshioki concentrated his research on the first significant randomised controlled clinical trials, of streptomycin (another external discovery from America) organised between 1946 and 1948 by the MRC.³⁴ His research topic relates to another major drug bought from America post-war with precious dollars. Because not enough could be bought to treat everybody, it was acceptable to evaluate it in comparison with no active treatment in the first major successful randomised placebo-controlled trial. The subject is therefore more about methodology of a centrally controlled trial rather than the practicality of getting standard new drugs tested. Cox-Maksimov points to a separate

³³ J. Davidson Pratt, (1951): 38

³⁴ Alan Yoshioka. “Streptomycin, 1946: British Central Administration of Supplies of a New Drug of American Origin with Special Reference to Clinical Trials in Tuberculosis; Medical Research Council Streptomycin in Tuberculosis Trials Committee, (University of London: PhD Thesis, 1998); Alan Yoshioka “Streptomycin in Post-War Britain: a Cultural History of a Miracle Drug” in *Drugs on Trial*, *Clio Med.* (1999): 53 “Streptomycin Treatment for Pulmonary Tuberculosis: a Report of the Streptomycin in Tuberculosis Trials Committee” *British Medical Journal* (30 October 1948): 769-782.

evolutionary path of trials in the USA as described by Harry Marks,³⁵ although Bradford Hill, the MRC statistician for the streptomycin was highly influential in spreading this methodology to the USA through a series of lectures.³⁶ The streptomycin study stimulated further major collaborative studies in America, and Harry Marks examined the sociological and organisational aspects of collaborative studies by academic therapeutic reformers rather than pharmaceutical companies, but again he focused on the ‘major’ drugs.³⁷ Lara Marks³⁸ addressed gender issues in trials of the contraceptive pill, and David Cantor examined studies of cortisone, which a series of companies, including BDH and Boots worked on in the 1950’s. More recently it has been left to scientists to recall their own early efforts in the testing of new drugs.³⁹ Quirke, Slinn and Tweedale also offer some further insights into later developments.

Although Quirke and Cox-Maksimov argued for a progression from the TTC model through to the randomised controlled trials, I am more sceptical. I examined all of the TTC studies and saw hardly any evidence of statistical input, and the TTC committee were satisfied to evaluate the drugs in a small series of patients and proclaim a benefit or not. In parallel, the MRC were performing quite sophisticated epidemiological and vaccine studies, involving statisticians. As Valier argued, the MRC had less control over the bedside than the laboratory, but I believe that there was a major difference between offering a vaccine or not for a disease that might occur, as opposed to offering a drug or a placebo for an active disease that needed treating. The TTC was not formally reconstituted post war but a significant number of mostly foreign companies, especially

³⁵ Harry M. Marks. “Ideas as Reforms: Therapeutic Experiments and Medical Practice, 1900-1980” (Massachusetts Institute of Technology, Boston Mass: PhD Thesis, 1983).

³⁶ “Report of a Conference on the Place of Statistical Methods in Biological and Chemical Experimentation” (28-29 January 1949) Ann. New York Acad. Sci. 52 (1950): 789; D. Maitland, “The Clinical Trial, Some Difficulties and Suggestions” J. Chronic Diseases 11 (1960): 484-96.

³⁷ Harry M. Marks, (PhD. thesis, 1983); H. M. Marks, “Notes from the Underground. The Social Organisation of Therapeutic Research” in D. Long, R. Maulitz (eds.), Grand Rounds: 100 years of Internal Medicine, (Philadelphia: University of Pennsylvania, 1987); H. M. Marks, The Progress of Experiment. Science and Therapeutic Reform in The United States, 1900 – 1990 (Cambridge: Cambridge University Press, 1997).

³⁸ Lara Marks, Sexual Chemistry: A History of the Contraceptive Pill (Yale: Yale University Press, 2001).

³⁹ Carl Djerassi, This Mans Pill: Reflections on the 50th Birthday of the Pill (New York, Oxford University Press, 2001); J-F. Borel, H. Staehelin, “Cyclosporin A- The History and Significance of its Discovery” Sandorama II (Basel: Sandoz, 1983): 55-9.

CIBA, established further trials with the TTC as a coordinating body. The majority of British firms went on to make their own arrangements, except for smaller companies such as Napp of Cambridge. The clinical development process was internalised in Britain and companies built upon the success and demand for antibiotics by establishing their own studies.

My hope is that I have not only answered my own questions, but have also raised some further questions worthy of more detailed study. I would like to have pursued the career of Francis Carr to complete his 'biography,' and further study of his work at Boots and British Drug Houses would be of value. I only explored his campaigns for chemical engineering training to a limited degree, and did not divert into his committee work on war gases and on patents. Equally there was a great deal of detail on the career of Fred Power that I had to omit, and a more detailed account of the scope of chemistry performed at Burroughs Wellcome 1896- 1914 would be valuable. I am certain that a more detailed study of the complex themes of ensuring drug supplies during the World Wars is warranted, utilising sources at the PRO and the Royal Society.

This thesis has been wide ranging but there are some clear points to emerge:

- Synthetic chemistry became important far earlier in Britain than was previously recognised but it was initially used for checking the purity and standards of extracts.
- Burroughs Wellcome was an important source of manufacturing chemists for other companies Francis Carr was an important chemical engineer and played a central role in developing the synthetic drug industry in Britain.
- British firms campaigned for clinical testing of their drugs- this was not something imposed upon them. The MRC led studies of the TTC were not based on statistical principles or modeled on earlier insulin studies.

A series of factors contributed to the success of the British industry in the interwar period. It was not just tariff protection or the new Therapeutic Substances Act but also the emergence of new types of organotherapy and vitamins, which helped them to make profits while building their manufacturing capacity. The importance British supplies of chemical intermediates and solvents should not be underestimated.

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