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'Between public and private, between science and industry: the Medical Research Council and British pharmaceutical firms, 1920s-1960s'

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Introduction

The patenting of genes for breast cancer in the 1980s has been identified as a radical break with the Intellectual Property Rights doctrine and practices that had helped to regulate and structure the relationship between private firms and public research institutions until then. Such doctrine and practices had distinguished between upstream basic research, which was shielded from monopolistic appropriation, and the downstream, practical applications of this research, which were not. Coupled with a change in the universities, which 'with their new, profit-seeking goals' have become more entrepreneurial, this has been seen as a potential threat to the *Open Science* system,[1] perceived not only as being favourable to innovation, but also of benefit to public health and welfare.[2]

However, such analyses have tended to ignore the criticisms that have been meted out against the *Open Science* system and its institutions for their failure to make positive economic impact at various times, and the role that these criticisms and learning from mistakes has played in the transformation described above. A more detailed examination, particularly in relation to different national and/or institutional contexts, shows it to be a much more complex and lengthy process. The change in attitudes towards the commercialization of the life sciences and biomedical research in Britain is often traced back to the shock experienced at the announcement, in the late 1970s, that American scientists had patented a technology to produce monoclonal antibodies that had in fact been pioneered in Britain.[3] The perceived failure to file a patent on the hybridoma technology developed at the Medical Research Council's Laboratory of Molecular Biology in Cambridge in 1975 caused a scandal which, together with the Spinks Report on Biotechnology, is often credited for the creation of the first British biotechnology firm, Celltech, and the take-off of the 'new biotechnology' in the 1980s. The MRC was at the forefront of the entrepreneurial turn in British life sciences that followed these events, and by the mid-1980s was providing a model for technology transfer, while LMB scientists were instrumental in developing biotechnology in Britain.[4] Thus, in

[1] L. Orsenigo, G. Dosi and M. Mazzucato, 'The dynamics of knowledge accumulation, regulation, and appropriability in the pharma-biotech sector: policy issues', in M. Mazzucato and G. Dosi (eds.), *Knowledge Accumulation and Industry Evolution: The case of Pharma-Biotech* (Cambridge: Cambridge University Press, 2006), pp. 402-431 (p. 419). For more on the 'open science system', see for example P. David, 'Understanding the emergence of open science institutions: functionalist economics in historical context', *Industrial and Corporate Change*, 13 (2004): 571-589.

[2] M. Cassier and J.-P. Gaudillière, 'Le genome: bien privé ou bien commun?', *Biofutur,* 204 (2000): 26-30; F. Orsi, C. Sevilla, and B. Coriat, 'Upstream patents and public health: the case of genetic testing for breast cancer', in Mazzucato and Dosi, *Knowledge Accumulation and Industry Evolution*, pp. 327-345.

[3] E.M. Tansey and PP.P. Catterall (eds), 'Technology transfer in Britain: the case of monoclonal antibodies', in Tansey et al (eds), *Wellcome Witnesses to Twentieth-Century Medicine* (London: Wellcome Trust, 1997, vol. 1), pp. 3-34.

[4] S. de Chadarevian, 'The making of an entrepreneurial science: biotechnology in Britain, 1975–1995' (forthcoming in *Isis*).

Britain, the entrepreneurial turn in the life sciences coincided with the start of the new biotechnology, and the MRC, a civil science organization, played a key role in this transformation.

Although these events and their consequences are well known, what is less well appreciated is the process by which the transformation occurred. The entrepreneurial attitude that became established within the MRC and the wider biomedical community in 1980s Britain marked a step change compared to the preceding period. However, it was not the first time that such a change occurred. Indeed, Jim Gowans, who was MRC Secretary between 1977 and 1987, and who played an important part in the Council's change of attitude towards the commercialization of biomedical research, had witnessed a similar change take place twenty years earlier, in the Sir William Dunn School of Pathology at Oxford, where in the 1950s-1960s he worked on a project to study the life-cycle of the lymphocyte.[5] In the same period, in reaction to the failure to patent penicillin – for which the MRC had received at least part of the blame – E.P. Abraham and his colleagues at the Dunn School of Pathology developed the antibiotic cephalosporin and patented it, this time with encouragement from the MRC.[6] Incidentally, it was also there that Henry Harris and John Watkins devised the technique of cell fusion, which helped to lay the foundation for Milstein and Köhler's method for producing monoclonal antibodies.[7]

Also not quite so well appreciated is the fact that the author of the Spinks Report,[8] Alfred Spinks, had spent his career from 1940 until 1979 at Imperial Chemical Industries (ICI), during which time he saw the group develop a close relationship with the MRC for the production of penicillin and synthetic anti-malarials, and later as part of collaborative schemes to develop non-volatile anaesthetics and interferon, as well as venture into biotechnology, one of the first companies to do so in Britain.[9]

So why did it take yet another 'failure' – the failure to patent monoclonal antibodies, in a different institutional context (Cambridge instead of Oxford) – for the change in the MRC's attitude towards the commercialization of biomedical research to be complete? This paper describes the lengthy transformation by which the MRC, a civil scientific organization created to enhance the health of Britain and her Empire, but later blamed for failing to allow British science to profit from the fruits of her labours, came to play a key role in the entrepreneurial turn in British biomedical research in the last quarter of the 20th century. Focusing on the history of cephalosporin, this paper argues that – after the 'crucial moment' and 'constitutive

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[5] I thank Soraya de Chadarevian for pointing this out to me.

[6] V. Quirke, 'Developing penicillin, patenting cephalosporin, and transforming medical research in Britain: the Sir William Dunn School of Pathology at Oxford, 1930s-1970s', in J.P. Gaudillière, D.J. Kevles, and H.-J. Rheinberger (eds), *Living Properties: making knowledge and controlling ownership in the history of biology* (Max Planck Institute for the History of Science, Preprint 382, 2009), pp. 65-73.

[7] H. Harris, *Cell Fusion* (Oxford: Clarendon Press, 1970). See also Harris's autobiography: H. Harris, *The Balance of Improbabilities: a scientific life* (Oxford OUP, 1987). On the School of Pathology: http://www.path.ox.ac.uk/contact/history2, accessed 22/08/2010.

[8] [Spinks Report] *Biotechnology: report of a Joint Working Party of the Advisory Council for Applied Research and Development and Advisory Board for the Research Councils and the Royal Society,* (London: HMSO, 1980).

[9] V. Quirke, *Collaboration in the Pharmaceutical Industry: changing relationships in Britain and France, 1935-1965* (London/New York: Routledge, 2008), Chs. 4, 6; idem, 'From chemistry to pharmaceuticals, and from pharmaceuticals to biotechnology: the many transformations of ICI in the twentieth century', in I. Malaquias, E, Hombrurg and M.E. Callapez (eds), *Chemistry, Technology and Society*, (Lisbon: Sociedade Portuguesa de Quìmica, 2006); also accessible online at: http://5ichc-portugal.ulusofona.pt/; R. Bud, 'From applied microbiology to biotechnology: science, and industrial renewal', *Notes and Records of the Royal Society* , 64 (2010): S17-S29; first published online on 14/07/10, accessed on 13/08/10.

event' that was penicillin - [10] the novel antibiotic was more than just another 'episode' in the long march towards the commercialization of biomedical research,[11] but rather a first step in this entrepreneurial turn. It emphasises the importance of local, direct, and un-mediated experience in the process of learning and change, and addresses the issue of the limits of interchangeability between in-house and external expertise.

The paper is in four sections, which were also phases in the MRC's relationship with British pharmaceutical firms, for this relationship was a contributory factor to, rather than an outcome of, the Council's entrepreneurial turn: 1) The origins of the MRC and producing biological and chemical remedies for the war effort in World War One; 2) Reconstructing the MRC, developing standards and regulating drug companies in the inter-war period; 3) Collaborating and developing penicillin in World War Two; 4) Cephalosporin as a first step in the 'entrepreneurial turn' in British biomedical research.

1) The origins of the MRC and producing biological and chemical remedies for the war effort in World War One:

A significant outcome of the National Insurance Act, by which the British government set up a scheme for basic health cover in 1911, was the creation of the Medical Research Committee (reconstituted in 1920 as the Medical Research Council), with the purpose of funding medical research in Britain. This innovation, which required 1d per contributor to the National Insurance Scheme to be set aside for medical research, was attributable to the Prime Minister Lloyd George himself.[12] Although welfare policies are always to some extent underpinned by economic interests (to maintain the health of the working population for example), the MRC was not subjected to the British government's economic objectives, and was given the right to define its research agenda as well as its research approach, and to modify them in response to advances in medical knowledge. Nevertheless, in the early phase in the history of the MRC, top priority was given to the study of tuberculosis, which had been the main impetus behind the government's decision to support medical research. It represented 44 out of the 104 grants awarded under the new National Insurance Scheme, totalling £8,875. Then came the study of rickets, in the field of nutrition research, which would soon become the most important area of the Council's general programme. As to its research approach, it was three-fold: 1) preventive medicine, 2) curative medicine, 3) basic science.

The advent of the First World War created a need for cooperation between civil science organizations – such as the Royal Society, the newly created Department for Scientific and Industrial Research (DSIR), and the MRC – government departments, and industry, as well as for coordinated research efforts. Thus, it was as member of the Chemical Sub-Committee (subsequently Drugs Sub-Committee) formed by the Royal Society in 1914 for the manufacture and testing of remedies required for the war effort, more especially synthetic drugs, such as the anti-syphilitic drug salvarsan and the local anaesthetic novocaine until then imported from Germany, that the MRC first became involved in drug development. This brought the Council into early contact with the pharmaceutical firms of Burroughs

[10] On 'crucial moment and 'constitutive events' within the longer time-frame of social and cultural change, see L. Hunt, 'Introduction: history, culture, and text', in L. Hunt (ed.), *The New Cultural History* (Berkeley: University of California Press, 1989), pp. 6-27; M. Vovelle, *Ideologies and Mentalities* (Paris: F. Maspero, 1982), pp. 228-31.

[11] R. Bud, 'Upheaval in the moral economy of science? Patenting, teamwork and the World War II experience of penicillin', *History and Technology*, 2 (2008): 173-190; de Chadarevian, 'The making of an entrepreneurial science'.

[12] For histories of the MRC see A. Landsborough Thomson, *Half a Century of Medical Research*, (London: HMSO, 1973), vols.1 and 2; J. Austoker and L. Bryder (eds), *Historical Perspectives on the Role of the MRC* (Oxford: OUP, 1989).

Wellcome and May & Baker, and led to A.J. Ewins's move from the Wellcome Physiological Research Laboratories to the MRC in 1916 (Ewins later moved back into industry, when he was appointed director of research by May & Baker).

2) Reconstructing the MRC, developing standards and regulating drug companies in the inter-war period;

The Council's role as coordinator of research, acquired in collaboration with the Royal Society and the DSIR during World War One, and built upon in the inter-war years, brought it into early contact with pharmaceutical firms. This contact became particularly close with Britain's first science-based drug company, Burroughs Wellcome, whose staff were frequently 'poached' for their expertise in biology and chemistry by the MRC, as well as by other firms.[13] However, although it continued after the war, the relationship between the Council and drug companies changed in nature, and the strict controls that had been imposed upon the industry in wartime were replaced by looser, 'moral control'.[14] This looser form of control not only consisted in encouraging the development of in-house research, but also providing firms with a scientific role model, and with instructions, standards and norms for the development of new drugs, such as the pancreatic hormone insulin.[15] Nevertheless, in this way a network of 'reputable' science-based companies was formed, to which the MRC and other government agencies would turn time and time again in order to develop novel drugs.

Between the wars, the MRC also encouraged clinical research – albeit not without resistance from some members of the medical profession – by awarding grants, creating clinical research units, as well as organizing and coordinating clinical trials by means of therapeutic committees, for instance the Therapeutic Trials Committee created in 1931 with the support of the Association of British Chemical Manufacturers (ABCM, representing the pharmaceutical industry before the creation of the Association of British Pharmaceutical Industries, ABPI).[16] In the same period, together with the British Medical Association, the MRC put pressure on government to improve drug safety legislation, which led to the 1925 Therapeutic Substances Act.

However, the extent to which this early contact with British pharmaceutical firms shaped the structures, strategies and practices of the Council on the one hand, and the industry on the other, is debatable. Indeed, the history of penicillin, which was not patented, and in this way was 'lost' to the American drug industry, for which the MRC received at least part of the blame, became emblematic of Britain's inability to develop the fruit of its discoveries, and of the Council's outmoded attitude to research.

3) Collaborating and developing penicillin in World War Two;

During World War Two, once again mobilization for the war effort created a need for coordination and cooperation in research. For the main purpose of developing penicillin, the MRC collaborated with a consortium of science-based pharmaceutical firms: the Therapeutic Research Corporation (TRC), formed in 1940, and later joined

[13] R. Church and E.M. Tansey, *Knowledge, Trust, and Profit: a history of Burroughs Wellcome & Co. and the transformation of the British Pharmaceutical Industry* (Lancaster: Carnegie Publishing, 2007).
[14] J. Liebenau, 'The MRC and the pharmaceutical industry: the model of insulin', in J. Austoker and L. Bryder (eds), *Historical Perspectives on the Role of the MRC* (Oxford: OUP, 1989), pp. 163-80 (169-70).
[15] C. Sinding, 'Making the unit of insulin: standards, clinical work, and industry, 1920-1925', *Bulletin of the History of Medicine,* 76 (2002): 231-70.
[16] C. Booth, 'Clinical research', in J. Austoker and L. Bryder (eds), *Historical Perspectives on the Role of the MRC* (Oxford: OUP, 1989), pp. 205-21.

by companies like ICI, whose capabilities in large-scale chemical processes complemented those of the TRC.[17] Penicillin had been developed at the School of Pathology at Oxford, partly with support from the MRC. As it was also there that cephalosporin would be developed after the war, having learnt the lessons of penicillin, I will say a little more about it here.

The first occupant of the chair of pathology at Oxford, created in 1907, was Georges Dreyer, who moved from the physiology department to the Sir William Dunn School of Pathology after its completion in 1927. However, in the inter-war period central funding for research was particularly weak, and when Howard Florey succeeded Dreyer to the post in 1935, with a brief to rejuvenate a department that had become moribund under his predecessor, he had to make the rounds of the 'money dispensers': the Nuffield Foundation, the MRC, the British Empire Cancer Campaign, and the Rockefeller Foundation.[18] The multi-disciplinary research projects he devised, beginning with a study of lysozyme, which was later extended to other antibacterial substances, including penicillin, were therefore well adapted to the fragmented nature of his funding.[19] They also reveal the intricate link between the pure and applied aspects of the projects, described in grant applications as having the aim of 'investigating the relationship between bacteriolytic substances and natural immunity',[20] so that 'upstream' and 'downstream' research are quite difficult to distinguish from each other.

Although there were other topics under study, in particular cancer, after the outbreak of war the School's research activity was dominated by the penicillin project. For this, Florey adopted a three-pronged approach, to work on the 'production', 'chemistry', and 'biology' of the antibiotic substance.[21] Each aspect was assigned to different members of the team, although there was some overlap between their roles, particularly between Norman Heatley, who dealt with production, and Ernst Chain, who was responsible for the chemical studies. The Oxford team produced two key papers, published in 1940 and 1941 in the *Lancet*.[22] While the first described the biological experiments, also known as the 'mouse-protection experiments', the second gave more detailed technical information, most notably about the assay method and counter-current apparatus devised by Heatley, as well as reporting on the first tests in man. The School of Pathology therefore succeeded in producing the drug on a small scale, and in transferring the scientific knowledge and practical skills associated with it to other research centres and drug companies, not only in Britain, but also in the USA, where as part a major Allied collaborative programme mass production techniques were developed and patented.[23] This meant that after the conflict was over, British firms were expected to pay royalties to American firms, and as Robert Bud has noted, this became a 'cause célèbre' of the post-war era, although in the end what was paid for seems to have been access to know-how in deep-fermentation methods.[24] Nevertheless, the School's important contribution to the development of penicillin led to greater professional stability and financial security for at least three of its junior members and key players in the

[17] J. Liebenau, 'The British success with penicillin', *Social Studies of Science*, 17 (1987): 69-86; also Quirke, *Collaboration in the Pharmaceutical Industry,* Ch. 3.
[18] Bodleian Library (hereafter BOD) PT 17/1-2; L. Bickel, *Rise up to Life: a biography of Howard Florey who made penicillin and gave it to the world* (London: Angus ad Robertson, 1976), p. 48; T.I. Williams, *Howard Florey: penicillin and after* (Oxford: Oxford University Press, 1984), pp. 45-6; J.B. Morrell, *Science at Oxford, 1914-1939: transforming an arts university* (Oxford: Clarendon Press, 1996), p. 204.
[19] Quirke, *Collaboration in the Pharmaceutical Industry,* pp. 102-105.
[20] Contemporary Medical Archives Centre (hereafter CMAC) Ernst Chain papers (hereafter PP/EBC): 9 B16 (Nov. 1939).
[21] Royal Society Sir Howard Florey papers (hereafter RS 98 HF): laboratory notebooks.
[22] E.B. Chain *et al*, 'Penicillin as a chemotherapeutic agent', 2 (1940), 226-228; E.P. Abraham *et al*, 'Further observations on penicillin', 2 (1941), *Lancet*, 177-189.
[23] G.L. Hobby, *Penicillin: meeting the challenge* (Yale: Yale University Press, 1985).
[24] Bud, 'Penicillin and the new Elizabethans'; idem, 'Upheaval in the moral economy of science?'.

penicillin story, Edward Abraham, Norman Heatley, and Gordon Sanders, who received fellowships endowed by the Nuffield Foundation to Lincoln College (but not Chain, who left for Rome).[25] This would ensure the continuity of knowledge and skills associated with penicillin inside the School, and play an important part in the development of cephalosporin.

After the war, Florey's group at the School of Pathology pursued the question of the rise of resistance to antibiotics. However, from 1955 onwards his own research interests shifted, and he left antibiotics research to his junior colleagues, in particular Edward Abraham, whilst he returned to some of his earlier interests, atherosclerosis and gastric secretions, more clearly within the remit of 'classical' pathology, a trend continued under his successor, Henry Harris, who took up the Professorship of the School of Pathology in 1962 when Florey retired to become Provost of the Queen's College in Oxford.

As to the MRC, the experience of wartime collaborative projects, particularly of developing penicillin and subsequently losing it to American firms who patented the deep-fermentation process for manufacturing the antibiotic, contributed to a change in attitude towards the patenting of drugs and other medical discoveries. Hence, in the aftermath of the conflict, the Council turned its attention towards patents, putting its full weight behind the creation of a national trustee, the National Research and Development Corporation (NRDC, formed in 1948), as well as the new 1949 Patents Act, which were both intended to stimulate innovation in the biomedical field. At the same time, the MRC began to play a more pro-active role as instigator of collaborative research programmes, from antibiotics, to anaesthetics, and anticancer drugs, thus placing itself at the centre of Britain's burgeoning biomedical complex, whilst helping to satisfy the post-war government's requirement for a strong and innovative pharmaceutical sector. Combined with the drive to rationalize the allocation and use of resources under the National Health Service, this led to a re-configuration of Britain's post-war biomedical landscape, in which the MRC continued to play a key role between the state, the medical profession and the pharmaceutical industry, but more as an equal partner of other government agencies, such as the NRDC, of research institutions, and of drug companies.

4) Cephalosporin and the 'entrepreneurial turn' in British biomedical research:

In Britain, the new 1949 Patent Act coincided with the creation of the NRDC, an agency modelled on the American Office for Scientific Research and Development (OSRD), and set up to hold in trust the patents resulting from university research, including medical research.[26] The idea for it pre-dated the war and penicillin, but the experience of developing penicillin in wartime, and the sense of having lost the drug to the Americans because of the decision not to patent penicillin because it was a drug, and also (although it never was clearly articulated as such) because it was a natural product, helped to make it a reality.[27] The MRC, and especially its then Secretary, Edward Mellanby, who was blamed for the failure to patent penicillin, was a major driving force behind the creation of the NRDC and the new Patent Act. An important reason for this change of heart was the contribution of several of its members to the field of chemotherapy, which had expanded with the discovery of the sulphonamides and the synthetic anti-malarials, and in which Council found patenting less objectionable than in the field of biological remedies (such as vitamins

[25] Williams, *Howard Florey*, pp. 348-349; Clark, *The Life of Ernst Chain*.
[26] On the NRDC, see S.T. Keith, 'Inventions, patents, and commercial development form governmentally financed research in Great Britain: the origins of the National Research and Development Corporation', Minerva, 19 (1981), 92-122.
[27] Quirke, *Collaboration in the Pharmaceutical Industry*, pp. 208-211.

and hormones).[28] Although penicillin was an antibacterial substance derived from a mould, it and the other antibiotics that followed it became the mainstay of the chemotherapeutic approach to the treatment of infectious diseases, as suggested by the first article on it by the Oxford team, in which it was described as a new kind of 'chemotherapeutic agent'.[29] Moreover, in relation to research on the chemistry of penicillin, which aimed not only at unravelling its structure but also at finding a route to its synthesis, the MRC viewed the prospect of taking out patents far more favourably, and were prepared to defend the right to patent any discoveries at the expense of the right to publish results.[30] Another reason for the Council's change of heart, was biomedical researchers' increasingly common experience of collaborating with drug companies, which was enhanced by wartime projects, and brought them into close contact with an attitude to patenting that did not attach the same stigma to it as that which prevailed in the medical field.[31]

Reflecting this transformation, penicillin functioned as a precedent for cephalosporin in three ways: 1) the School's involvement in the development of penicillin in wartime meant that it was an obvious choice for investigations of the new antibiotic; 2) much of the knowledge and techniques associated with penicillin were directly applied to the cephalosporin project; 3) however, the 'lessons of penicillin' had been learnt, not least the need to patent any advances made in developing cephalosporin, despite this being, like penicillin, a product derived from nature and destined to be a drug.

Edward Abraham had done research on peptides in the Dyson Perrins Laboratory under the organic chemist Robert Robinson, before working on lysozyme in collaboration with Florey and Chain, and moving across to the School of Pathology in 1940 to take part in the penicillin project. In 1948, Florey received a paper and sample of a fungus that was reported to be active against Gram-negative bacteria (against which penicillin was ineffective) from Giuseppe Brotzu, professor of bacteriology in Sardinia.[32] A number of the School of Pathology's researchers began work on the fungus, including Heatley and Abraham. In 1950, Florey received a letter from the MRC urging them to patent any discoveries related to cephalosporin,[33] which they did as early as 1952, 'for improvements relating to the production of an antibiotic substance effective against gram negative and gram positive organisms', and would continue to do every two-to-three years on every major incremental step achieved in their research.[34] That patenting activity went hand in hand with research can be seen in the notebooks and other written material amassed by Abraham in the course of his work on cephalosporin.[35] It also raises the question of the extent to which patenting may have influenced the very course of this research, or even generated knowledge and skills that might not have been created otherwise.

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[28] See Bud, 'Upheaval in the moral economy of science?'. Bud has noted that as a biochemist working in the field of vitamins, Mellanby had become involved in the vitamin D patenting controversy, and this provided an important precedent for the MRC's attitude towards the patenting of penicillin.

[29] E.B. Chain *et al*, 'Penicillin as a chemotherapeutic agent'.

[30] National Archives MRC papers (hereafter NA FD1 series) 6833: Mellanby to Richards (n.d.); NA FD1 6834: TRC to Robinson (3 Nov. 1943); NA FD1 6838: Penicillin agreements with commercial firms vol. 11 (1944), (19 Jan. 1944). For more on this, see Quirke, *Collaboration in the Pharmaceutical Industry*, pp. 130-132.

[31] Ibid., Chs. 2, 3 and 6.

[32] E.P. Abraham, 'Penicillin and its successors: a personal view', *Bull. Amer. Acad. Arts and Sc.*, 39 (1985): 8-27; idem, 'Selective reminiscences of ß-lactam antibiotics: early research on penicillin and cephalosporins', in *Bioessays*, 12 (1990) 601-6.

[33] Abraham, 'Penicillin and its successors', p. 24.

[34] BOD EPA Bodleian Edward Abraham papers (hereafter BOD EPA), C.364: patent application no 745208 (31589/52).

[35] Some of the material at least appears to have been amassed to be able to answer the challenge by a former colleague of Abraham and Newton, H.S. Burton, who claimed that he had been unfairly excluded from the patents. BOD EPA C.364-74.

However, the first antibiotic substance isolated by the group, which they named cepaholosporin N (and later identified as a penicillin, and re-named penicillin N), was sensitive to penicillinase, an enzyme responsible for penicillin resistance, which was becoming a problem at that time, and had been the main reason for Florey's interest in the substance. The majority of the School's researchers therefore lost interest, and by 1953 only Abraham and Guy Newton, a graduate student, were still studying it. An important reason for Abraham's continuing interest in cephalosporin was the relationship between its unusual chemical structure and biological activity against Gram-negative bacteria.[36] Together, Abraham and Newton therefore went on to isolate and identify a new substance (named cephalosprin C), which was not only effective against Gram-negative bacteria, but was also resistant against penicillinase.[37] However, huge amounts of the drug were needed to treat infections in man, and scaling up production was proving difficult, despite the discovery of a mutant strain by researchers the MRC's new Antibiotic Research Station in Somerset, and despite the best efforts of the fermentation experts of the British drug firm Glaxo, who had been persuaded to join the project in 1955, at finding a suitable large scale process for manufacturing the drug.[38] Then, in 1958 came the news that researchers at the Beecham Research Laboratories had isolated the penicillin nucleus, 6-aminopenicillinic acid (6-APA) and started synthesizing new molecules with different side-chains, which made them effective against penicillin-resistant bacteria.[39] Although this meant that cepahlosporin C could not longer be considered as potentially useful against penicillinase-producing staphylococci, it made increasing its activity against Gram-negative bacteria as well as achieving its large-scale manufacture much more likely. Hence, not only did the news spur Abraham and Newton's efforts at isolating the cephalosporin nucleus, 7-APA (7-aminocephalosporanic acid), followed by the elucidation of its structure,[40] but Glaxo changed their policy and started looking for chemical as well as fermentation processes for producing the drug.[41] At about the same time, the American firm Eli Lilly contacted the NRDC, which held in trust Abraham and Newton's patents, with the aim of obtaining the rights to manufacture cephalosporin, and like Glaxo began to search for biosynthetic means of producing the drug.[42] In 1964, the first semi-synthetic (that is to say part-chemical, part-fermentation) cephalosporins, cephalothin and cephaloridine, were marketed by Eli Lilly and Glaxo respectively.

As to Abraham, in 1958 he was elected Fellow of the Royal Society, becoming a consultant for the NRDC in the same year, and at the same time resigning the consultancy he had held for a short period with Imperial Chemical Industries (ICI).[43] He received funding from the MRC for his programme of research, which was on biosynthetic pathways and chemical structure-biological activity relationships in the beta-lactam family of antibiotics.[44] This was a hybrid

[36] Quirke, *Collaboration in the Pharmaceutical Industry*, pp. 228-233.
[37] E.P. Abraham and G.G.F. Newton, 'Isolation of cephalosporin C, a penicillin-like antibiotic containing D-α-aminoadipic acid', *Biochemical Journal*, 79 (1961): 651-8.
[38] Bodleian Edward Abraham papers (hereafter BOD EPA), especially MRC: C.287-357 (MRC's antibiotic station at Clevedon) 1949-87; C. 882-913: Glaxo Gr Ltd. (1957-85). NB: having outlived its usefulness ni the eyes of the MRC, the Antibiotic Research Station closed in 1960. For more on the industrial context, see R. Davenport-Hines and J. Slinn, *Glaxo: a history to 1962* (Cambridge: CUP, 1992); E. Jones, *The business of Medicine* (London: Profile Books, 2001).
[39] F.R. Batchelor *et al*, 'Synthesis of penicillin: 6-aminopenicillinic acid in penicillin fermentations', *Nature,* 183 (1959): 257. For more on the industrial context for the discovery, see H.G. Lazell, *From Pills to Penicillin: the Beecham story* (London: Heinemann, 1975).
[40] E.P. Abraham and G.G.F. Newton. 'The structure of cephalosporin C', *Biochemical Journal*, 79 (1961): 377-393.
[41] BOD EPA C.401: 'Cephalosporin C Aide-Mémoire'; ibid., C.376: Abraham to J.C. Cain (NRDC), 12 Sept. 1959; ibid., C.371: Bloxham to Abraham, 8 July 1959; C. 882-913: Glaxo Gr Ltd. (1957-85).
[42] BOD EPA C. 633-881: Eli Lilly (1954-94).
[43] BOD EPA C.358-406.
[44] BOD EPA C.287-357.

biological/chemical (rather than biochemical programme), which was paralleled in the activities of the NRDC, which funded research into the biosynthesis of natural products, in the research programmes of drug companies such as Beecham, ICI, Glaxo, and Eli Lilly, and would help to pave the way for the new biotechnology, of which it constitutes one of three 'legs' (i.e. fermentation technology, the other two being rDNA and monoclonal antibodies).[45] However, even though Abraham would continue to receive funding from the MRC until 1980, within the School of Pathology, his research would somehow remain marginal, and somewhat removed from the 'basic' pathology embodied in the MRC's Cellular Immunology Research Unit.

To sum up the continuities and discontinuities between penicillin and cephalosporin projects:

Continuities:

1) There was continuity of scientific and technical expertise;
2) Many of the same actors participated in the projects (both inside and outside the School);
3) There was an initial reluctance on the part of pharmaceutical companies (in Britain as elsewhere) to become involved;
4) Both were at once 'pure' (as in retrospect the principal actors often presented their work) and applied projects.[46]

Discontinuities:

1) In 1950 Abraham received a letter from the MRC urging him to patent any discovery and assign them to the NRDC;
2) Cephalosporin was more difficult to mass produce by fermentation methods, therefore required greater bio/chemical intervention;
3) From the beginning the production work was done outside the School of Pathology;
4) Cephalosporin was patented.

Concluding remarks: the entrepreneurial turn in British biomedical research, and the transition to biotechnology in Britain

The NRDC eventually made £150 M from cephalosporin, for many years its chief source of income. As to the researchers, after Oxford University had had to change its ruling so that they would not be penalised by their royalty income, they put the largest part of this income into trust funds, the Edward Penley Abraham Research and Edward Penley Abraham Cephalosporin Funds, which together with the Funds created by Guy Newton funded medical, biological and chemical research at the School of Pathology, at Lincoln College, as well Oxford University more generally. This, and the fact that Oxford University recently announced that it was launching a £1.25bn fundraising drive to put it 'on a level playing field with the leading universities in the United States',[47] suggests that an 'Upheaval in the moral economy of science' has indeed taken place as a result of the penicillin experience.[48] The history of cephalosporin suggests that the transformation of the life sciences and biomedical research, of which the MRC was instrumental, was the result of a process of

[45] On the 'three legs' of the new biotechnology, see R. Bud, *The Uses of Life: a history of biotechnology* (Cambridge: CUP, 1993); idem, 'Molecular biology and the long-term history of biotechnology', in A. Thackray (ed.), *Biotechnology and the Rise of the Molecular Sciences* (Philadelphia: University of Pennsylvania Press,1998), pp. 3-19.
[46] Quirke, *Collaboration in the Pharmaceutical Industry*, pp. 132-134, 232.
[47] See BBC NEWS Channel, http://news.bbc.co.uk/1/hi/education/7422192.stm, 28 May 2008.
[48] Bud, 'Upheaval in the moral economy of science?'.

acculturation, through contacts with chemists, and with pharmaceutical firms, for instance ICI and Glaxo. However, this transformation had limits.

Although it brought great benefit to the School, Abraham's research project remained somewhat marginal to its traditional and more basic research programme under Florey after 1955, and under Harris subsequently. Moreover, whilst acknowledging the long-term impact of 'test cases' (in the historical as well as legal sense), such as penicillin, one must also query them. The example of the monoclonal antibodies, which like penicillin were not patented and were 'lost' to the Americans, and became the source of yet another scandal to the embarrassment of all concerned, including the MRC and the NRDC, which had failed to see their commercial potential, suggests that it is sometimes difficult to transfer the lessons from one technological area or 'path to biotechnology' (in this case antibiotics) to another (monoclonal antibodies), or from one institution, directly concerned by those lessons (the School of Pathology at Oxford), to another (the Laboratory of Molecular Biology at Cambridge).

When Jim Gowans became MRC Secretary in 1977, and the monoclonal antibody scandal erupted in 1979, he must have had a feeling of 'déjà vu'. Within a year, the monoclonal antibody to interferon *was* patented in 1980 by Secher and Burke from Cambridge University, and the patent was passed on to Celltech, the 1st British biotech company, formed as a result of the Spinks Report on biotechnology.[49]

[49] E.M. Tansey and P.P. Catterall (eds), 'Technology transfer in Britain', pp. 3-34.