

Wellcome Witnesses  
to Twentieth Century Medicine

**POST PENICILLIN ANTIBIOTICS:  
FROM ACCEPTANCE TO RESISTANCE?**

Volume 6 – January 2000

A Witness Seminar held at the  
Wellcome Institute for the History of Medicine,  
London, on 12 May 1998

**Witness Seminar Transcript edited  
by E M Tansey and L A Reynolds**

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#### Key

##### Front cover photographs, L to R from the top:

Dr Robert Bud (chair)  
Dr Leo Hepner  
Professor Harold Lambert, Dr Derek Bangham (1924–2008)  
Dr Peter Doyle (1921–2004)  
Dr Milton Wainwright, Professor Douglas Eveleigh  
Sir Christopher Booth, Dr Robert Bud (chair)  
Professor Gordon Stewart, Professor D A Mitchison

##### Back cover photographs, L to R from the top:

Dr Robert Bud (chair)  
Professor David Greenwood  
Dr Peter Doyle (1921–2004), Dr Martin Cole  
Dr Geoffrey Asherson (1929–2003), Dr Peter Doyle (1921–2004)  
Professor Naomi Data (1922–2008), Professor D A Mitchison  
Sir John Crofton (1912–2009), Miss Pamela Waterworth (1920–2004)  
Dr F R Batchelor, Dr Basil Bard (1914–2002))  
Dr Peter Doyle (1921–2004), Dr Martin Cole

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# INTRODUCTION

The introduction of penicillin during the Second World War led to a revolution in both drug development and therapeutics.<sup>1</sup> From the 1940s to the 1960s that revolution spread from laboratories, institutes and companies, as penicillin was succeeded by a host of antibiotics – some, like streptomycin, addressing specific organisms immune to penicillin, others, like tetracycline and the cephalosporins, with a broad spectrum of activity.<sup>2</sup> In the United States this work underpinned the enormous growth of the pharmaceutical industry. In the United Kingdom the development of cephalosporins and semisynthetic penicillins became matters of national pride as well as commercial and therapeutic significance. This Witness Seminar gathered together many of those who had been a part of that revolution, and encouraged them to reminisce and discuss and debate the events and issues they recalled.

Several important themes emerged during the course of the meeting – including details of the scientific research in pharmaceutical company laboratories; the mechanisms whereby the products of that research were manufactured, marketed and utilized in the clinical encounter; the clinical successes and subsequent problems as antibiotic resistance was increasingly recognized.

Almost as soon as the original penicillin was produced, chemists began, as they had with the sulphonamides in the 1930s, to examine and modify the basic molecule, in an attempt to produce products with different antibacterial spectra. Of particular importance was the towering figure of Sir Ernst Chain, one of the Nobel Prize winners for the original penicillin discovery, who, from laboratories in both Rome and London, advised the pharmaceutical company, Beecham, then beginning to undertake original scientific research. Several of the scientists from that Beecham Group took part in the seminar, providing tantalizing insights, not only into the development of the research process itself, but also into the newness of the research enterprise within a pharmaceutical company better known, up to that period, for cold cures and health drinks.<sup>3</sup> This was, of course, in the days before the Committee on the Safety of Drugs (later Safety of Medicines) was established, and several witnesses describe the rapidity with which new compounds could be introduced onto the market, methicillin, for example, taking less than 18 months to transfer from laboratory discovery in 1959 to clinical application, a procedure that would now take at least eight years to complete (see pages 31–32). The commercial implications of these new products, and strategies of the several rival companies all competing to produce and market antibiotics, is touched on by several participants. Important too, is the issue of patents. Part of the penicillin story, some would

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<sup>1</sup> The penicillin literature is immense. It includes both contemporary and historical, hagiographical and analytical, descriptions and interpretations of the discovery itself and of the related scientific and clinical work; biographical and autobiographical accounts. The Wellcome Library includes 259 items catalogued with the keyword ‘penicillin’, and can be accessed via telnet at [library.wellcome.ac.uk](http://library.wellcome.ac.uk)

<sup>2</sup> Some useful summaries of aspects of that revolution are included in the papers from a symposium held in 1979, *The History of Antibiotics*, edited by John Parascandola (American Institute of the History of Pharmacy, Madison, WI, 1980). Another useful general account is *Antibiotics in Historical Perspective*, edited by David L Cowen and Alvin B Segelman (Merck, Sharp & Dohme, 1981).

<sup>3</sup> These were marketed under trade names such as Beecham’s Powders, Veno’s Cough Cure, Lucozade etc.

say the penicillin myth, is that British rights to penicillin were carelessly disregarded, allowing American enterprise to patent what had been a British discovery. Partially as a consequence of that experience the National Research and Development Corporation (NRDC) was created when the Labour Government passed the Development and Inventions Act 1948, to safeguard and commercialize patentable ideas emerging from publicly funded scientific research.<sup>4</sup> An early triumph of the NRDC was their role in the development of cephalosporins by Glaxo, and their 'penicillin in reverse' licensing agreements with the American firm of Eli Lilly, here recounted by Dr Basil Bard, a former Managing Director of the NRDC (pages 39–40).

These new wonder drugs raised enormous clinical expectations. Their astonishing impact is recalled by several clinicians, as are the problems that arose very quickly as the phenomenon of antibiotic resistance was recognized. Especial mention was made by several participants of Dr Mary Barber at the Hammersmith Hospital in London, and her introduction as early as 1957 of a hospital-wide policy to reduce the use of antibiotics (pages 36–38).

These are just a selection of the issues that are covered here by our witnesses, to whom we are grateful for the time they gave us not only in planning and holding this meeting, but also during the editorial process, which is described below.

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<sup>4</sup> The role of the NRDC has emerged in another witness seminar 'Technology transfer in Britain: The case of monoclonal antibodies', Tansey E M, Catterall P P. (eds) (1997) in Tansey E M, Catterall P P, Christie D A, Willhoft S V, Reynolds L A. (eds) *Wellcome Witnesses to Twentieth Century Medicine*, vol. 1. London: The Wellcome Trust, 1–34.

## WITNESS SEMINARS: MEETINGS AND PUBLICATIONS<sup>5</sup>

In 1990 the Wellcome Trust created the History of Twentieth Century Medicine Group to bring together clinicians, scientists, historians and others interested in contemporary medical history. Amongst a number of other initiatives, the format of Witness Seminars – used by the Institute of Contemporary British History to address issues of recent political history – was adopted, to promote interaction between these different groups, to emphasize the potentials of working jointly, and to encourage the creation and deposit of archival sources for present and future use.

The Witness Seminar is a particularly specialized form of oral history where several people associated with a particular set of circumstances or events are invited to meet together to discuss, debate, and agree or disagree about their memories.<sup>6</sup> To date, the History of Twentieth Century Medicine Group has held over 20 such meetings, most of which have been published, as listed in the Table below.

Subjects for such meetings are usually proposed by, or through, members of the Steering Committee of the Group, and once an appropriate topic has been agreed, suitable participants are identified and invited. These inevitably lead to further contacts, and more suggestions of people to invite. As the organization of the meeting progresses, a flexible outline plan for the meeting is devised, usually with assistance from the meeting's chairman, and some participants are invited to 'set the ball rolling' on particular themes, by speaking for a short period of time to initiate and stimulate further discussion.

Each meeting is fully recorded, the tapes are transcribed and the unedited transcript is immediately sent to every participant. Each is asked to check their own contributions and to provide brief biographical details. The editors turn the transcript into readable text, and participants' minor corrections and comments are incorporated into that text, while biographical and bibliographical details are added as footnotes, as are more substantial comments and additional material provided by participants. The final scripts are then sent to every contributor, accompanied by copyright assignment forms. As with all our meetings, we hope that even if the precise details of some of the technical sections are not clear to the non-specialist, the sense and significance of the events are understandable. Our aim is for the volumes that emerge from these meetings to inform those with a general interest in the history of modern medicine and medical science, to provide for historians new insights, fresh material for study, and prompt fresh themes for research, and to emphasize to the participants that events of the recent past, of their own working lives, are of proper and necessary concern to historians.

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<sup>5</sup> Much of the following text is also published in the 'Introduction' to vol. 5 of *Wellcome Witnesses to Twentieth Century Medicine*. London: The Wellcome Trust, 2000.

<sup>6</sup> It is the *interactive* nature of Witness Seminars that distinguishes them from routine oral history interviews and reminiscences, such as those published in Moberg C L, Cohn Z A. (1990) (eds) *Launching the Antibiotic Era: Personal accounts of the discovery and use of the first antibiotics*, New York, NY: Rockefeller University Press, 97.

- 1993 Monoclonal antibodies<sup>7</sup>**  
Organizers: Dr E M Tansey and Dr Peter Catterall
- 1994 The early history of renal transplantation**  
Organizer: Dr Stephen Lock
- Pneumoconiosis of coal workers<sup>8</sup>**  
Organizer: Dr E M Tansey
- 1995 Self and non-self: a history of autoimmunity<sup>7</sup>**  
Organizers: Sir Christopher Booth and Dr E M Tansey
- Ashes to ashes: the history of smoking and health<sup>9</sup>**  
Organizers: Dr Stephen Lock and Dr E M Tansey
- Oral contraceptives**  
Organizers: Dr Lara Marks and Dr E M Tansey
- Endogenous opiates<sup>7</sup>**  
Organizer: Dr E M Tansey
- 1996 Committee on Safety of Drugs<sup>7</sup>**  
Organizers: Dr Stephen Lock and Dr E M Tansey
- Making the body more transparent: the impact of nuclear magnetic resonance and magnetic resonance imaging<sup>10</sup>**  
Organizer: Sir Christopher Booth
- 1997 Research in General Practice<sup>10</sup>**  
Organizers: Dr Ian Tait and Dr E M Tansey
- Drugs in psychiatric practice<sup>10</sup>**  
Organizers: Dr E M Tansey and Dr David Healy

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<sup>7</sup> Published in Tansey E M, Catterall P P, Christie D A, Willhoft S V, Reynolds L A. (eds) (1997) *Wellcome Witnesses to Twentieth Century Medicine*, vol. 1. London: The Wellcome Trust, 135pp.

<sup>8</sup> P D'Arcy Hart, edited and annotated by E M Tansey. (1998) Chronic pulmonary disease in South Wales coalmines: An eye-witness account of the MRC surveys (1937–1942). *Social History of Medicine* 11: 459–468.

<sup>9</sup> Lock S P, Reynolds L A, Tansey E M. (eds) (1998) *Ashes to Ashes: The history of smoking and health*. London: The Wellcome Trust, 228pp.

<sup>10</sup> Published in Tansey E M, Christie D A, Reynolds L A. (eds) (1998) *Wellcome Witnesses to Twentieth Century Medicine*, vol. 2. London: The Wellcome Trust, 282 pp.



**The MRC Common Cold Unit<sup>10</sup>**

Organizers: Dr David Tyrrell and Dr E M Tansey

**The first heart transplant in the UK<sup>11</sup>**

Organizer: Professor Tom Treasure

**1998 Haemophilia: recent history of clinical management<sup>12</sup>**

Organizers: Dr E M Tansey and Professor Christine Lee

**Obstetric ultrasound: historical perspectives<sup>13</sup>**

Organizers: Dr Malcolm Nicolson, Mr John Fleming and Dr E M Tansey

**Post penicillin antibiotics<sup>14</sup>**

Organizers: Dr Robert Bud and Dr E M Tansey

**Clinical research in Britain, 1950–1980**

Organizers: Dr David Gordon and Dr E M Tansey

**1999 Intestinal absorption**

Organizers: Sir Christopher Booth and Dr E M Tansey

**The MRC Epidemiology Unit (South Wales)**

Organizers: Dr Andy Ness and Dr E M Tansey

**Neonatal intensive care**

Organizers: Professor Osmund Reynolds, Dr David Gordon and Dr E M Tansey

**British contribution to medicine in Africa after the Second World War**

Organizers: Dr Mary Dobson, Dr Maureen Malowany, Dr Gordon Cook and Dr E M Tansey

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<sup>11</sup> Tansey E M, Reynolds L A. (eds) (1999) Early heart transplant surgery in the UK. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 3. London: The Wellcome Trust, 72 pp.

<sup>12</sup> Tansey E M, Christie D A. (eds) (1999) Haemophilia: Recent history of clinical management. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 4. London: The Wellcome Trust, 90pp.

<sup>13</sup> Tansey E M, Christie D A. (eds) (2000) Looking at the unborn: Historical aspects of obstetric ultrasound *Wellcome Witnesses to Twentieth Century Medicine*, vol. 5. London: The Wellcome Trust, 80pp

<sup>14</sup> Tansey E M, Reynolds, L A. (eds) (2000) Post penicillin antibiotics: From acceptance to resistance? *Wellcome Witnesses to Twentieth Century Medicine*, this volume, 72pp.

## ACKNOWLEDGEMENTS

'Post Penicillin Antibiotics' was suggested as a suitable topic for a Witness Seminar by Dr Robert Bud of the Science Museum, London, and a member of the Steering Committee of the Wellcome Trust's History of Twentieth Century Medicine Group. Dr Bud also provided the names of many of the individuals to be invited, assisted us in planning the meeting and deciding the topics to be discussed, and presented a far-ranging and useful introduction to the meeting as a whole. We are very grateful to him for his input. We are equally grateful to Sir Christopher Booth for his excellent chairing of the occasion. Our particular thanks go to Professor David Greenwood of the University of Nottingham who has helped at almost every stage, and has been particularly generous in answering our numerous queries during the editorial phase. Similarly Dr Lisé Wilkinson has painstakingly read through earlier drafts of the transcript, and offered us helpful comments and advice, for which we are grateful.

As with all our meetings, we depend a great deal on our colleagues at the Wellcome Trust to ensure their smooth running: the Audiovisual Department, the Medical Photographic Library, and the Publishing Department, especially Julie Wood who has supervised the design and production of this volume. Mrs Jaqui Carter is our transcriber, and Mrs Wendy Kutner and Dr Daphne Christie assist us in running the meetings. Finally we thank the Wellcome Trust for supporting this programme.

Tilli Tansey

Wellcome Institute for the History of Medicine

# **POST PENICILLIN ANTIBIOTICS: FROM ACCEPTANCE TO RESISTANCE?**

The transcript of a Witness Seminar held at the  
Wellcome Institute for the History of Medicine,  
London, on 12 May 1998

**Edited by L A Reynolds and E M Tansey**

**PARTICIPANTS**

|                               |                           |
|-------------------------------|---------------------------|
| Dr Geoffrey Asherson          | Professor David Greenwood |
| Professor Graham Ayliffe      | Dr Leo Hepner             |
| Dr Derek Bangham              | Professor Harold Lambert  |
| Dr Basil Bard                 | Professor D A Mitchison   |
| Dr Ralph Batchelor            | Dr Keith Rogers           |
| Sir Christopher Booth (Chair) | Dr Geoffrey Scott         |
| Dr Robert Bud                 | Professor Gordon Stewart  |
| Dr Martin Cole                | Dr Tilli Tansey           |
| Sir John Crofton              | Dr David Tyrrell          |
| Professor Naomi Datta         | Dr Milton Wainwright      |
| Dr Peter Doyle                | Miss Pamela Waterworth    |
| Professor Douglas Eveleigh    | Dr Alan Yoshioka          |
| Professor Alan Glynn          |                           |

**Others attending the meeting:** Dr Donald Gillies, Sir Gordon Wolstenholme

**Apologies:** Sir Edward Abraham,\* Mr Derek Anthony, Sir Austin Bide, Dr Robert Blowers, Professor T L Blundell, Dr Barry Cookson, Professor Roger Finch, Professor Gary French, Professor A Geddes, Dr J Lightbown, Professor Malcolm Lilly,<sup>†</sup> Professor E Lowbury, Professor J M T Hamilton-Miller, Dr Bob Howells, Professor Francis O'Grady, Professor Ian Phillips, Sir Mark Richmond, Dr David Roberts, Dr George Rolinson, Dr Harold T Swan, Professor John Williams.

\* Deceased 8 May 1999

<sup>†</sup> Deceased 18 May 1998

Sir Christopher Booth:<sup>1</sup> I think the History of Twentieth Century Medicine Group has held some very intriguing meetings over the past few years, and one of the things that interests me is that within a historical environment people feel freer to speak the truth about life in science than they would in a scientific meeting. I can well remember Max Perutz coming here for a meeting on haemoglobin – and Max is the most modest and unassuming of men – but some of the things that he told us at that meeting were something we could never have learnt any other way than through a historical meeting at the Wellcome Trust.<sup>2</sup> We chose the subject of post-penicillin antibiotics because Robert Bud and his group at the Science Museum had a very successful meeting on penicillin (two years ago) with some of the people in Oxford and in industry who had been involved, and I think it was his suggestion that we should have a meeting here on the post-penicillin era of antibiotics.

We thought we would try and divide this afternoon up into four sections. Between now and tea we would like firstly to deal with streptomycin and we have some experts in the field of tuberculosis (TB) treatment here. Secondly, we will deal with the semisynthetic antibiotics. Then after tea the cephalosporins and finally the very important contemporary question of resistance and immunity and bacteria.

Dr Robert Bud:<sup>3</sup> What an intimidating responsibility to tell people who are so distinguished in the area, about their own work. But just to set a framework for this meeting. We could not have known, of course, when we started organizing it that it would follow so closely upon the enormously widely reported House of Lords report on antibiotic resistance which gives an urgent timeliness to our discussion today.<sup>4</sup> Of course, the penicillin story itself has been told numerous times, particularly by the participants, one might say. There's the famous film, made in 1944 originally, by ICI,

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<sup>1</sup> Sir Christopher Booth Kt FRCP (b. 1924) trained as a gastroenterologist and was the first Convenor of the Wellcome Trust's History of Twentieth Century Medicine Group, from 1990 to 1996, and Harveian Librarian at the Royal College of Physicians from 1989 to 1997. He was Professor of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London, from 1966 to 1977 and Director of the Medical Research Council's Clinical Research Centre, Northwick Park Hospital, Harrow, from 1978 to 1988.

<sup>2</sup> The History of Twentieth Century Group held a Summer School on the History of Haemoglobin, 14–16 July 1993, at the Wellcome Building, London. Invited speakers were Professor Larry Holmes, Dr John Edsall, Dr Harmke Kamminga, Dr Max Perutz, Professor Irving London, Professor V H Ingram, Professor Franklin Bunn, Professor Sir David Weatherall, Professor Lucio Luzzatto, Professor Morris Goodman, Dr John Clegg and Professor John West. The proceedings have not been published.

<sup>3</sup> Dr Robert Bud (b. 1952) joined the Science Museum in 1978 and has been Head of Life and Communications Technologies group since 1994.

<sup>4</sup> House of Lords, Select Committee on Science and Technology. (1998) *Seventh Report: Resistance to Antibiotics and Other Antimicrobial Agents*. HL 81, 2 vols. London: HMSO.

providing a vivid opportunity for Fleming, Florey and Chain<sup>5</sup> to tell their stories, and after the war numerous books told the story of Fleming's fortunate encounter with penicillin and several, if fewer, recounted in detail the work of the Oxford group. The Americans, not to be outdone, also frequently told their side of the story. Of course, this was not the end of the matter. How much credit should go to each of the participants and this has been debated until recent days in the letter columns of the *New Scientist* and in apparently endless streams of historical documentaries. I think a new profession, 'expert for historical documentary', should be identified for the Census.

Naturally, the discovery of penicillin-G was an important event in itself. However, the continuing interest it has held goes beyond that single drug. For penicillin-G was, of course, the first of the fermentation-based antibiotics, the first antibiotic if one excludes the sulphonamides. These other drugs, however, have experienced much less historical attention, and it is really that hole that we wish to address today, at just that moment when resistant organisms remind us how very dependent we are on antibiotics, and people are indeed now talking about the end of the antibiotic age. Of course, the whole story is very complex and much has happened in the United States, the continent of Europe, and in Japan. I think of Watanabe's work.<sup>6</sup> So only one part can be told by bringing together a group in this country. Nevertheless, today we can recapture some of the issues, both those unique to this country and those experienced worldwide. The afternoon will encompass the treatment both of new drugs and of antibiotic resistance. I hope we will therefore capture and understand better the competition between the creativity of the chemists and of the bacteria, rather than the heroic story of the discovery of a new drug and competition between people and germs.

A few words, I hope, will link the history to the issues raised today. Very shortly after the announcement of penicillin, streptomycin was announced, and that entered the market in 1946. This development at the Rutgers University by Selman Waksman was keenly watched in this country. For the first time, tuberculosis could be attacked chemotherapeutically and we are fortunate that Douglas Eveleigh from the Waksman Institute<sup>7</sup> has been able to join us. Of course, whereas the discovery of streptomycin was an American development, major contributions to its evaluation and exploitation were made in this country by Sir John Crofton, whom we are fortunate to have here, and others. Penicillin itself was developed with the Americans, first the

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<sup>5</sup> Sir Alexander Fleming Kt FRCP FRS (1881–1955), Lord Florey OM Kt FRS (1898–1968) and Sir Ernst Chain Kt FRS (1906–1979) shared the Nobel Prize for Physiology or Medicine in 1945 for the discovery and development of penicillin. For further details on the making of the film, which is held by the Science Museum, see Bud R. (1998) Penicillin and the new Elizabethans. *British Journal for the History of Science* 31: 305–333.

<sup>6</sup> The original series of studies by T Watanabe and T Fukasawa appeared in Japanese in *Medicine and Biology [Tokyo]* in 1960–1961 on resistance factors in *Enterobacteriaceae*. For later studies, published in English, see Watanabe T, Fukasawa T. (1961) Episome-mediated transfer of drug resistance in *Enterobacteriaceae*. I. Transfer of resistance factors by conjugation. *Journal of Bacteriology* 81: 669–678; *idem* II. Elimination of resistance factors with acridine dyes. *ibid.* 81: 679–683; *idem* (1962) III: Transduction of resistance factors. *ibid.* 82: 202–209; *idem* (1962) IV. Interactions between resistance transfer factor and F factor in *Escherichia coli* K-12. *ibid.* 83: 727–735.

<sup>7</sup> Professor Eveleigh is at the New Jersey Agricultural Experiment Station of Rutgers, the State University of New Jersey. See discussion on pages 6–7.

more stable penicillin-V, which could be given by mouth. In the 1950s, however, a group at Beecham developed the first semisynthetic penicillins based on 6-APA (6-aminopenicillanic acid), and they had been working with Chain in Rome on para-aminobenzyl penicillin. How much was he their inspiration? Many of the key members are here today and can contribute. Perhaps we will learn more from them. Their work led to the new penicillins immune to penicillinase, such as methicillin, and this helped medicine cope with hospital-acquired infections with resistant staphylococci and one question we may ask is how urgently did they feel the need to combat such organisms? How urgent an issue for the team was the question of hospital-resistant staphylococci in the late 1950s? Already by the early 1950s four broad-spectrum antibiotics effective against both gram-negative and gram-positive bacteria were in common use – tetracycline, *Terramycin* (oxytetracycline: Pfizer), *Aureomycin* (chlortetracycline: Lederle) and chloramphenicol. All these were developed in the USA. However, a new family that emerged in the late 1950s was famously developed here – the cephalosporins – and among the most interesting features in this development was the role played by the National Research Development Council (NRDC), which had been set up in the late 1940s partly because of the debacle over the patenting of penicillin.<sup>8</sup> In the House of Commons debates over the NRDC, the story of penicillin comes up time and time again and we are fortunate to have the testimony of Dr Basil Bard who played an important role in the patenting process. A distinctive feature of some of the semisynthetic penicillins and the cephalosporins was their immunity to penicillinase which had given a certain bacterial immunity and the first occasion of clinical immunity to penicillin was as early as 1942. In 1947 Mary Barber<sup>9</sup> found that 38 per cent of strains of *Staphylococcus aureus* were penicillin-resistant, and more the following year, and we are fortunate to have with us several people who worked with Mary Barber. Since then of course anxieties have increased. The emergence of the semisynthetics in the late 1950s provided new weapons against penicillinase-producing bacteria. By the mid-1960s, however, the methicillin-resistant bacteria had been observed, and Gordon Stewart – and we are fortunate to have him with us – pointed out as early as 1965 that in academic circles resistance to penicillin has provoked about as much interest as therapy.<sup>10</sup> And, of course, this is even more true today. Ladies and gentlemen, I think we are fortunate to have a very rich feast laid out before us and I hope to have many fond assumptions overturned and others given some substance.

Booth: Well, thank you very much, Dr Bud, that's a useful introduction to what we are about today, and I think we should just go straight on to talk firstly about

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<sup>8</sup> The National Research Development Corporation (NRDC) was established in 1949, set up under the Development of Inventions Act 1948 as a Corporation by the Board of Trade, to safeguard and commercialize inventions arising principally from publicly funded research. op. cit. note 5 above.

<sup>9</sup> Professor Mary Barber (1911–1965) was Professor in Clinical Bacteriology at the Postgraduate Medical School, Hammersmith Hospital, London, from 1964 until her sudden death in 1965, where she had been lecturer from 1947 to 1948 and Reader from 1957 to 1964. See Barber M. (1947) Coagulase-positive staphylococci resistant to penicillin. *Journal of Pathology and Bacteriology* 59: 373–384.

<sup>10</sup> Stewart G T. (1965) *The Penicillin Group of Drugs*. Amsterdam: Elsevier. See biographical note 69 below.

streptomycin and what happened there and I think Douglas Eveleigh would like perhaps to start us off.

Professor Douglas Eveleigh:<sup>11</sup> Well, first of all, thank you for inviting me. As you can hear from my accent it's not American, it's Croynge, that is somewhere halfway between Croydon and Penge. I have been at Rutgers now for 25 years, so I did meet Selman Waksman, while Boyd Woodruff<sup>12</sup> is also a good friend and we've had considerable historical discussions. Dr Waksman and Rutgers are famous for four useful antibiotics: actinomycin, discovered in 1940 through Boyd Woodruff's PhD studies, streptomycin in 1944 by Albert Schatz, and two antibiotics, neomycin in 1949 and candicidin in 1953, via Hubert Lechevalier's studies. Four major antibiotics and all from actinomycetes.<sup>13</sup>

Selman Waksman came to the United States from Russia, joined Rutgers, and received his undergraduate degree in 1915, then studying soil protozoa and bacteria.<sup>14</sup> Subsequently in his MSc in 1916, he focused very heavily on actinomycetes. At that time it was very clear that most microbiologists did not understand what actinomycetes were. Actinomycetes were his solid base. He gained his PhD in Biochemistry from the University of California in 1917, and wrote a text with Davison on enzymes<sup>15</sup> – he had a heavy biochemical training. Dr Waksman returned to Rutgers and remained there for the rest of his career. Most of his tenure was in the classical Agricultural School. I am in the Agricultural School and I should just point out to Robert [Bud] not at the Waksman Institute. I am an old Aggie. We have friendly rivalry between the two groups. We always say 'we' found the antibiotics and 'they' spend the royalties. But to history.

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<sup>11</sup> Professor Douglas Eveleigh (b. 1933) has been Professor of Microbiology, Cook College, at Rutgers, the State University of New Jersey, since 1970.

<sup>12</sup> Dr Boyd Woodruff (b. 1917) was a graduate student of Waksman at Rutgers University from 1939 to 1942. His 1942 PhD thesis was 'The production of antibiotic substances by soil microorganisms'. He then joined the Merck Research Laboratory in Rahway, New Jersey, for a period of 40 years, heading research on natural products derived from microorganisms. In retirement, in a home laboratory, he continues research on the ecology of soil actinomycetes. He was elected to the US National Academy of Sciences in 1998. See Woodruff H B, Burg R W. (1986) The antibiotic explosion. In Parnham M J, Bruinvels J. (eds) *Discoveries in Pharmacology*. vol. 3. Pharmacological methods, receptors and chemotherapy. Amsterdam: Elsevier, 303–351.

<sup>13</sup> See Waksman S A, Woodruff H B. (1940) The soil as a source of microorganisms antagonistic to disease-producing bacteria. *Journal of Bacteriology* **40**: 581–600. Schatz A, Bugie E, Waksman S A. (1944) Streptomycin, a substance exhibiting antibiotic activity against gram-positive and gram-negative bacteria. *Proceedings of the Society for Experimental Biology and Medicine* **55**: 66–69. Waksman S A, Lechevalier H A. (1949) Neomycin, a new antibiotic active against streptomycin-resistant bacteria including tuberculosis organisms. *Science* **109**: 305–307. Lechevalier H, Acker R F, Corke C T, Haenseler C M, Waksman S A. (1953) Candicidin, a new antifungal antibiotic. *Mycologia* **45**: 155–171.

<sup>14</sup> Dr Selman Waksman (1888–1973) was born in Ukraine, and took US nationality in 1916. His 1916 MSc thesis focused very heavily on actinomycetes. He became Professor of Microbiology at Rutgers University in 1930 and was awarded the Nobel Prize in Physiology or Medicine in 1952 for his discovery of streptomycin. See Waksman S A, Curtis R E. (1916) The actinomycetes of the soil. *Soil Science* **1**: 99–134. Waksman S. (1954) *My Life with the Microbes*. New York, NY: Simon and Schuster.

<sup>15</sup> Waksman S A, Davison W C. (1926) *Enzymes: Properties, distribution, methods and applications*. Baltimore, MD: The Williams & Wilkins Company.



It's very clear, as Boyd Woodruff has emphasized many times, that as soon as Waksman heard of the effectiveness of penicillin, he returned to the lab and completely changed the direction of his research.<sup>16</sup> Up until that time, he was extremely well known as a physiological soil microbiologist. He had been elected to the US National Academy for his 'microbiology of peat' – really quite an accomplishment. He was a soil microbiologist. But he switched research direction from the fertility of soils and said, 'We must now look at actinomycetes' (of which he had a vast collection) 'and look for antibiotics'.<sup>17</sup> That began with Boyd Woodruff's study. Later with Albert Schatz, the programme was more rationally developed. I emphasize rational. Compare the new Rutgers's screening system to the Dubos studies in 1939 in which he discovered tyrocidine.<sup>18</sup> Dubos would take bacteria, put them in soil as a substrate, enrich for maybe a month then add a few more bacteria, let it enrich for a further month, and then a few more. Clearly a long enrichment procedure was considered essential. Waksman showed that the enrichment procedure was not necessary: one could plate soil and directly screen the many hundreds of cultures for antibiosis. This direct plating was a conceptual advance. So simplistic, but so essential in large-scale screening. As noted previously the ingrained concept was that one must perform long enrichment. Furthermore, Waksman also introduced the use of *Mycobacterium tuberculosis*,<sup>19</sup> to address these waxy gram-positive pathogens – a clinical development in a soil microbiological laboratory. The concept of the early Rutgers's antibiotic studies was to develop a facile screening methodology. Within that screen they looked at productivity, and subsequently there was a clinical medical programme including the use of animals. These were all critical points in the development for actinomycete antibiotics, including streptomycin.

From that methodology one could search for other antibiotics and most subsequent screens followed that model: isolate a diverse collection of soil microbes (especially actinomycetes), screen massively, plus, in industry there was considerable financial backup for further analyses. In contrast, I assure you that Waksman did not have major financial backing at that time: his was really quite a small programme. So point 1 was

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<sup>16</sup> See Woodruff H B. (ed.) (1968) *Scientific Contributions of Selman A Waksman: Selected articles published in honor of his 80th birthday, July 22, 1968*. New Brunswick, NJ: Rutgers University Press.

<sup>17</sup> Professor Douglas Eveleigh wrote: 'Waksman had continually addressed the production of antimicrobial products by soil microbes. Waksman's first studies with actinomycetes were during World War I. International communication was difficult and Krainsky's cultures from Russia were unavailable. Krainsky was a pioneer in this sphere. Waksman noted Krainsky's publication "helped me greatly in my future work. ...In characterizing our newly isolated cultures we tried to give Krainsky the maximum possible credit for his work."' E-mail to Mrs Lois Reynolds, 3 November 1999. See Waksman S A. (1975) *The Antibiotic Era*. Tokyo: The Waksman Foundation of Japan Inc. Quotations on pages 7, 8.

<sup>18</sup> Dubos R.J. (1939) Studies on a bacterial agent extracted from a soil bacillus. *Journal of Experimental Medicine* 70: 1–17. Professor David Greenwood wrote: 'René Dubos (1901–1982) had been a pupil of Selman Waksman but was at the Rockefeller Institute when he discovered tyrothricin, the first true antibiotic, later shown to be a mixture of two antibiotics, tyrocidine and gramicidin.' Letter to Mrs Lois Reynolds, 24 March 1999. See Hotchkiss R D. (1990) From microbes to medicine: Gramicidin, René Dubos and the Rockefeller. In Moberg C L, Cohn Z A. (eds) *Launching the Antibiotic Era*. New York, NY: Rockefeller Press, 1–18.

<sup>19</sup> op. cit. note 12 above.

the development of a facile and rational screening method. Point 2, I think quite clearly Waksman introduced the world to the use, the fuller potential, of the actinomycetes. They were a relatively unknown group and I think we can extrapolate on that as we go along. Point 3 was faith: penicillin and streptomycin were dominant, and there was absolute faith in them. Parenthetically perhaps, the rapid rise of antibiotic resistance was in part because there was such faith in, and use of, single antibiotics.

But I will put faith in a further context. Boyd Woodruff tells me that at Merck they developed the streptomycin system and that process went so well, they did not bother to screen any other soils for further antibiotic producers. In fact the Merck research focused on curing pernicious anaemia, a major disease, and thus their research was to optimize vitamin B<sub>12</sub> production via fermentation. One of the Merck fermentation cultures produced the antibiotic grisein, which had been received from Donald Reynolds, a Rutgers graduate student.<sup>20</sup> Yet the focus on this culture at Merck was the production of vitamin B<sub>12</sub>, not grisein. Perhaps the Merck decision was correct in that grisein never made it to the market place, while the development of vitamin B<sub>12</sub> by Karl Folkers was a major achievement.<sup>21</sup>

I also mention one historical side of the story, which is not well known, regarding streptomycin large-scale fermentation. Merck made their first streptomycin run in a small pilot plant.<sup>22</sup> It worked beautifully, but when they ran it again it failed. So they ran it again and it failed, and again and again. They tried for six months and they did not get another production run, due to 'classical infections'. As a result, when the first Merck large-scale fermentation tank was built, on the recommendation of Jackson Foster, it had trays inside for surface culture in case the submerged fermentation could not be solved. There was no impeller [stirrer]. Simply a stack of trays to grow the microorganisms in still culture. Finally Merck worked out the mechanics of submerged fermentation and bulk-scale streptomycin came to fruition, and the trays were never used.

Let me return to the faith Merck had in the new antibiotics, penicillin and streptomycin. It was so strong that it was Parke-Davis, Lederle and other companies that developed further antibiotics. Only then did Merck renew screening, presumably based on the Rutgers system, and they soon discovered novobiocin.

My fourth point is regarding the implications of industrial–university relationships. Yes, in the 1940s there were such cooperative ventures. They were not a product of the 'New Biotechnology'. The implications of the Merck-Rutgers agreement are

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<sup>20</sup> See Waksman S A, Schatz A, Reynolds D M. (1946) Production of antibiotic substances by actinomycetes. *Annals of the New York Academy of Sciences* 48: 73–86.

<sup>21</sup> Wagner A F, Folkers K A. (1964) *Vitamins and Coenzymes*. New York, NY: Interscience Publishers.

<sup>22</sup> Dr Boyd Woodruff wrote: 'The Merck antibiotic fermentation referred to was penicillin and not streptomycin, and the confusion is that the deep-tank fermentation was worked out first with the penicillin production and then the expertise transferred to the streptomycin production.' E-mail to Mrs Lois Reynolds from Professor Douglas Eveleigh, 29 May 1999. For discussion on the introduction of the deep culture penicillin fermentation method to Britain by Glaxo, see Davenport-Hines R P T, Slinn J. (1992) *Glaxo: A history to 1962*. Cambridge: Cambridge University Press, 141–149, see also streptomycin development, 179–181.

important. In brief, Merck supported Rutgers's research and for that support, Merck had the rights to university results: as it turned out, for actinomycin and streptomycin.

**Booth:** Can I just get something clear here, because the patenting side of streptomycin was rather important. Who held patents, were there any patents? Where were Rutgers involved in that?

**Eveleigh:** The initial aspect was the agreement that Merck held the patents for all rights.<sup>23</sup> However, when streptomycin came along Waksman went back to Merck and simply noted that conceptually 'this discovery is major and could you change the patent agreement?' It was changed in two senses. One the university became the beneficiary and secondly the university set up a non-exclusive licence. As such, seven companies actually took out the licence at that time.

**Booth:** So it was free for anybody to get in on any act if they wanted to?

**Eveleigh:** Absolutely. Waksman said that he felt streptomycin was so important that he wanted to ensure that it could be widely developed on a humanitarian basis. As there could be a problem with production, he wanted development via a non-exclusive rights agreement. This was practical at that time. Subsequently in hindsight the non-exclusive rights decision has been criticized as not necessarily a well-founded, wise decision. Thus when neomycin was discovered, there were several other competing antibiotics ready for commercial development, and naturally an industrial company wanted exclusive rights. In spite of that competitive commercial status, the Rutgers patent policy did not change from a non-exclusive basis until 1976. Those are my four main points: the screening; the actinomycetes themselves; the complete dominance and faith in one system; and then the implications for the non-exclusive patent status.

**Dr Milton Wainwright:**<sup>24</sup> Thank you, Doug, for that very good overview of the situation. I would like to make a couple of comments. First of all, I would like to take issue with the fact that Waksman was the first person to look at actinomycetes antibiotics. In fact there had been some work by Belgian scientists Gratia and Dath in the 1930s,<sup>25</sup> and also the Russians were quite active in the late 1930s looking at

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<sup>23</sup> Dr Boyd Woodruff wrote: 'Rutgers owned the patent on streptomycin. Merck had the exclusive marketing rights. At Waksman's request, after streptomycin became famous, Merck gave up its exclusive position, so marketing rights became non-exclusive. Merck received certain benefits for doing so by being able to deduct a portion of the initial development costs from the royalty payments.' E-mail to Mrs Lois Reynolds from Professor Douglas Eveleigh, 29 May 1999.

<sup>24</sup> Dr Milton Wainwright (b. 1950) was appointed Lecturer at the University of Sheffield in 1975 and Senior Lecturer in Microbiology from 1988. His interests include active research on unorthodox aspects of microbiology, the history of antibiotics and the role of non-virus microorganisms in cancer aetiology. See Wainwright M. (1990) *Miracle Cure: The story of penicillin and the golden age of antibiotics*. Oxford: Blackwell.

<sup>25</sup> See, for example, Gratia A, Dath S. (1924) De l'action bactériolytiques des streptothrix. *Comptes Rendus Société de Biologie* 91: 1442–1443. See also Wainwright M. (2000) Andre Gratia (1893–1950): Forgotten pioneer of research into antimicrobial agents including colicins. *Journal of Medical Biography* 8 (in press).

actinomycetes. Some people have said one of the great advantages that Waksman had was his ability to read Russian, and he may well have got many of his ideas from the Russian literature. The name that comes to mind straightaway is a man called Krassilnikov, who did a lot of work on actinomycetes.<sup>26</sup>

The other point that I think I would like to make is that we must emphasize the work of Albert Schatz<sup>27</sup> in this. I think if we talk about Florey and Chain getting credit with Fleming, then I think Schatz should get partial credit at least with Waksman, and also the names of Feldman and Hinshaw must be included because they actually brought the therapeutic potential of streptomycin into the fore. So my view of streptomycin is not of an antibiotic discovered by Waksman, but one co-discovered by Waksman and Schatz, and developed for medicine by Feldman and Hinshaw.<sup>28</sup>

Booth: Thank you very much. I think we might move on to the effect of streptomycin on medicine. Sir John Crofton, you very kindly came to join us from Edinburgh and I know you were one of the pioneers of using streptomycin. I don't know whether you actually carried out that first trial with Bradford Hill.

Sir John Crofton:<sup>29</sup> I was a very junior person. The first trial was different in two ways I think. One was that it was the first well-known control trial of any therapy and a model for all later trials. That was enormously important. I gather Philip D'Arcy Hart<sup>30</sup> had a trial in some other field, which was negative rather earlier on, but that tends to be forgotten. The other important thing was that it was the first really cooperative trial which occurred in many centres throughout the UK. My function was a very junior one, I had been three months as a registrar at the Brompton and was then asked to coordinate the Brompton side of that trial. The control trial was ethically acceptable, because there was a limited amount of

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<sup>26</sup> Krassilnikov N A, Koreniako A I. (1938) The phenomenon of autobacteriolysis in *Actinomycetales*. *Mikrobiologija* 7: 708–720; 829–837. *idem* (1939) The bactericidal substance of the actinomycetes. *ibid.* 8: 673–685.

<sup>27</sup> Dr Albert Schatz (b. 1920) was a PhD student of Waksman at Rutgers University from 1942 to 1945, and later became a Professor at Temple University. See note 13 above. Schatz A. (1965) Antibiotics and dentistry. Part I: Some personal reflections on the discovery of streptomycin. *Pakistan Dental Review* 15: 125–134. *idem* (1993) The true story of the discovery of streptomycin. *Actinomyces* New Series 4: 27–39. We thank Dr Alan Yoshioka for drawing our attention to these articles. For details of the case for Schatz's recognition as co-discoverer of streptomycin, see Wainwright M. (1991) Streptomycin: Discovery and resultant controversy. *History and Philosophy of the Life Sciences* 13: 97–124.

<sup>28</sup> Hinshaw H C, Feldman W H. (1945) Streptomycin in treatment of clinical tuberculosis: A preliminary report. *Proceedings of the Staff Meetings of the Mayo Clinic* 20: 313–317.

<sup>29</sup> Sir John Crofton Kt FRCP (b. 1912) was Professor of Respiratory Diseases and Tuberculosis at the University of Edinburgh from 1952 until his retirement in 1977. From 1947 to 1950, he worked part-time at the MRC Tuberculosis Unit at the Brompton Hospital, London, and as Lecturer, later Senior Lecturer, at the Royal Postgraduate Medical School, Hammersmith Hospital, London, from 1947 to 1951. He was a member of the MRC Tuberculosis Chemotherapy Trials Committee from 1952 to 1963.

<sup>30</sup> Dr Philip D'Arcy Hart CBE FRCP (b. 1900) trained in medicine at University College Hospital, London, where he became a Consultant Physician. He was Director of the MRC Tuberculosis Research Unit from 1948 until his retirement in 1965. See also note 54 below.

streptomycin,<sup>31</sup> so it was ethically reasonable to randomize these advanced pneumonic tuberculosis cases to a streptomycin and non-streptomycin group.<sup>32</sup> The original idea was that they should be treated for six months, but in fact resistance developed quite quickly with subsequent deterioration in many patients. Before the trial was finished the Medical Research Council (MRC) decided that this was only an adjunct to treatment of tuberculosis and they reduced the treatment period to three months. It's interesting looking back at that. It's interesting also to look at when resistance developed. The World Health Organization (WHO) now accepts people into trials and regards them as new patients if they have had less than a month of treatment, assuming that no resistance could have developed. But if you look back at the original streptomycin trial, and Denny [Mitchison] can probably tell us more about that, several of the patients developed resistance really quite early towards the end of the first month. That is something which we ought to remember.

Booth: When you say they became resistant, was this in a laboratory sense or a clinical one?

Crofton: In a laboratory sense and then deterioration, and that was why the MRC subsequently controlled treatment. But of course there were quite a number of successes. I had a letter from a patient just a month or two ago, who was in the original streptomycin trial, and obviously survived. So there were some successes, but there were a very appreciable number of failures.<sup>33</sup> But fortunately PAS [*para*-aminosalicylic acid] came the next year and the second trial was streptomycin alone, PAS alone, and streptomycin plus PAS. The resistance rate came down and the failure rate came down.<sup>34</sup> *Para*-aminosalicylic acid was developed in Sweden.<sup>35</sup> There was another little bit of serendipity in this first trial. We had quite a lot of patients after about six

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<sup>31</sup> Yoshioka A. (1999) Streptomycin, 1946: British central administration of supplies of a new drug of American origin with special reference to clinical trials in tuberculosis, PhD Thesis, University of London. For details of the constraints on the supply of streptomycin, see Hill A B. (1990) Memories of the British streptomycin trial in TB. *Controlled Clinical Trials* 11: 77–79.

<sup>32</sup> Medical Research Council. (1948) Streptomycin treatment of pulmonary tuberculosis: A Medical Research Council investigation. *British Medical Journal* ii: 769–782. First controlled investigation of its kind to be reported of 107 cases, admitted between January and September 1947, aged 15 to 25 (later 30), allocated on random sampling basis to those receiving streptomycin in the form of hydrochloride ( $n=55$ ) or bed rest only ( $n=52$ ). Fifty-one per cent (28) receiving streptomycin showed considerable improvement ('a reasonable prospect of recovery' by radiological assessment) after six months, compared with eight per cent (4) of the control group on bed rest. Seven per cent (4) of the streptomycin group died, compared with 27 per cent (14) of the control group.

<sup>33</sup> op. cit. note 32 above.

<sup>34</sup> Medical Research Council, Joint Subcommittee of the Streptomycin in Tuberculosis Trials Committee and the Research Committee of the British Tuberculosis Association. (1950) Treatment of pulmonary tuberculosis with streptomycin and *para*-aminosalicylic acid: A Medical Research Council investigation. *British Medical Journal* ii: 1073–1085. Three concurrent groups, aged 15 to 30, assigned by random selection: receiving PAS alone (P group,  $n=59$ ); streptomycin (sulphate) alone (S group,  $n=54$ ); streptomycin plus PAS (SP group,  $n=53$ ), accepted on the trial between December 1948 and October 1949 for three-month treatment followed by a month of observation, with two further months of additional treatment (collapse therapy or streptomycin). At the end of six months, improvement was found in 56 per cent of the PAS group, 74 per cent of the S group and 87 per cent of the SP group. Streptomycin-resistant strains were found in 33 of the 49 S patients and 5 of the 48 SP patients.

<sup>35</sup> Lehmann J. (1946) *Para*-aminosalicylic acid in the treatment of tuberculosis. *Lancet* i: 15–16.

weeks who started vomiting. We thought that because it had occurred at that time this might be an allergic reaction. We did a little double-blind trial at the Brompton, and found that antihistamine drugs stopped the vomiting. Well, it soon disappeared as a problem. It was obvious that this was due to a not very pure streptomycin. Somebody else picked up our publication and this was the beginning of the anti-seasick treatment with antihistamines, an interesting bit of serendipity. These are my main introductory points. Of course, there were lots of later trials which we can comment on, and also drug resistance. Denny Mitchison I am sure will talk about these.

Professor D A Mitchison:<sup>36</sup> Now the question is do you want it put a little bit straighter than John's? I mean John has done a good introduction, but he has left out some very important things. The point that I wanted to make was that there were two separate studies, both started in 1947.<sup>37</sup> One of these was the trial in pulmonary TB.<sup>38</sup> The point about that trial was that there was a limited amount of streptomycin available from Merck, and the MRC took the opportunity of doing a strict randomized comparison between streptomycin and just bed rest alone. Otherwise one would have had no assessment of streptomycin, because all the American streptomycin went to individual physicians and no scientific assessment was possible. This was really the start of the controlled clinical trial that went all the way through medicine. That's the first really important point.

Booth: Denny, can we just stop you one minute there. Who was behind that? Why was it done?

Mitchison: There were three people who were the leaders in the study. Philip D'Arcy Hart, who was Secretary of the MRC Committee for Streptomycin in Tuberculosis Trials.<sup>39</sup> The Tuberculosis Research Unit (TRU) was partly at Mill Hill and partly in Hampstead.<sup>40</sup> Philip [D'Arcy Hart], its director, went from one to the other. In the afternoon he travelled

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<sup>36</sup> Professor D A Mitchison CMG FRCP FRCPath (b. 1919) was Professor of Bacteriology at the Royal Postgraduate Medical School, Hammersmith Hospital, London, from 1971 until his retirement in 1985 (Emeritus Professor until 1993) and Emeritus Professor at St George's Hospital Medical School, London, since 1993. He was Director of the Medical Research Council's Unit for Laboratory Studies of Tuberculosis from 1956 until 1984, and collaborated with the MRC Tuberculosis Research Unit (later the Tuberculosis and Chest Diseases Unit) in developing effective chemotherapy for tuberculosis and research laboratories in East Africa, Madras, Hong Kong, Singapore and Prague. He performed the laboratory tests for the 1948 Tuberculosis Chemotherapy Committee Report and was a member of the 1952 Committee.

<sup>37</sup> Medical Research Council, Streptomycin in Tuberculosis Trials Committee. (1948) Streptomycin treatment of tuberculous meningitis. *Lancet* i: 582–596. Report on 105 cases of tuberculous meningitis and acute miliary tuberculosis in young children aged nine and under and some adults, admitted between January and 18 August 1947, treated with streptomycin (hydrochloride), intramuscularly and intrathecally, for a minimum of 120 days. Thirty-three per cent survived a minimum of seven months. Clinical work was coordinated by Dr Marc Daniels and the pathological data was analysed by Dr Mary Barber.

<sup>38</sup> op. cit. note 32 above.

<sup>39</sup> op. cit. note 37 above and Appendix 2.

<sup>40</sup> Thomson A L. (1987) *Half a Century of Medical Research*. vol. 2. The programme of the Medical Research Council (UK). London: MRC, 238–239. See also D'Arcy Hart P. (1999) A change in scientific approach: From alternation to randomized allocation in clinical trials in the 1940s. *British Medical Journal* 319: 572–573.

to Mill Hill and back, so he was working in both places. He was the driving force behind the study, together with Marc Daniels.<sup>41</sup> Bradford Hill,<sup>42</sup> of course, was the statistician and he insisted on randomized allocation. I think that's probably the first time randomized allocation was used. The patulin trial<sup>43</sup> that came before this didn't have randomized allocation, so that it was a statistical innovation, but I think the real problem was how you persuaded chest physicians, who were not so easily persuaded by science as they are nowadays, to actually consider treatment as a scientific adventure.

The other study that went on at the same time was on the use of streptomycin in TB-meningitis and miliary TB.<sup>44</sup> This was not a randomized trial, but one must remember that these diseases were 100 per cent fatal at the time. The finding that a number of the patients survived and did well in that trial spurred Merck to go on producing streptomycin in large amounts. The interesting thing too about this is that whereas practically all the patients in the pulmonary TB trial developed drug resistance, very few of those in the meningitis trial did so, presumably because the number of bacteria in TB-meningitis is much smaller than in pulmonary TB. That's got a very important theoretical implication, because at that time the people who thought about drug resistance thought in terms of one of two possibilities: either you had mutations followed by selection and the whole idea of mutation was really very new, only really thought of in the few years previously, or it was an adaptation, which was Hinshelwood's idea.<sup>45</sup> If it was adaptation, then you should get drug resistance appearing in miliary and meningitis as well as in pulmonary TB, so it set the scene for mutation followed by selection, and that was the theoretical basis on which the trial of streptomycin, PAS and streptomycin plus PAS was set up. It's very important to get the theory right as well as the actual practice.

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<sup>41</sup> Dr Marc Daniels (1907–1953) joined what later became the MRC Tuberculosis Research Unit from 1948, with Daniels as Deputy Director until his early death in 1953. He had been a Scholar to the Prophit Tuberculosis Survey at the Royal College of Physicians from 1942 to 1945. He was appointed to the MRC Streptomycin in Tuberculosis Trials committee as coordinator of its controlled clinical trials. See [unsigned with an appreciation following by A B Hill]. (1953) Obituary: Marc Daniels. *British Medical Journal* i: 567–568. Anon. (1953) Marc Daniels. *Lancet* i: 551–552.

<sup>42</sup> Sir Austin Bradford Hill CBE Kt FRS (1897–1991) was Professor of Medical Statistics at the London School of Hygiene and Tropical Medicine from 1945 until 1961. Doll R. (1994) Austin Bradford Hill. *Biographical Memoirs of Fellows of the Royal Society* 40: 128–140. For details of Hill's first attempt to introduce the concept of randomization in controlled trials, see Wilkinson L. (1997) Sir Austin Bradford Hill: Medical statistics and the quantitative approach to prevention of disease. *Addiction* 92: 657–666.

<sup>43</sup> Medical Research Council, Patulin Clinical Trials Committee. (1944) Clinical trials of patulin in the common cold. *Lancet* ii: 373–375. Clinical trials ran from December 1943 to April 1944, supervised by Dr Joan Faulkner. For details of the earlier work, see Wilkinson L, Hardy A. (2000) *Prevention and Cure: The London School of Hygiene & Tropical Medicine. A twentieth century quest for global public health*. London: Kegan Paul. Especially chapter 7, 'The wider spectrum of public health: Basic research in developing biochemistry; and applied science and statistics in occupational health'.

<sup>44</sup> op. cit. note 37 above. Medical Research Council, Streptomycin in Tuberculosis Trials Committee. (1950) Streptomycin in acute miliary tuberculosis. *Lancet* i: 841–846.

<sup>45</sup> Sir Cyril Hinshelwood FRS (1897–1967), physical chemist, was Dr Lee's Professor of Chemistry at the University of Oxford from 1937 until his retirement in 1964. He was awarded the Nobel Prize for Chemistry in 1956 jointly with Nikolai Nikolaevich Semenov (1896–1986) for his contributions to chemical kinetics. See Thompson H. (1973) Cyril Norman Hinshelwood. *Biographical Memoirs of Fellows of the Royal Society* 19: 375–431.

Booth: Thank you very much indeed. The TB-meningitis work was Honor Smith<sup>46</sup> in Oxford?

Mitchison: Mary Barber, I think, at Hammersmith. [From the floor: St Mary's] Well it was several different places.

Booth: And in other countries?

Mitchison: That was an MRC organization. It was a smallish group to start with, Hammersmith, Liverpool and Glasgow to begin with, and then it expanded later to Great Ormond Street and I am sure to Edinburgh and various other places. It got to be a big study. And St Mary's I am sure, yes.

Booth: Did you all expect resistance to appear to streptomycin as it had with penicillin? Was it expected or was it a surprise or how did people react?

Crofton: It was much worse than with penicillin. With penicillin there was sort of ecological development of resistance in environments. With streptomycin it was in the individual patient. So it was rather unexpectedly worse, because to begin with there hadn't been a great problem with penicillin.<sup>47</sup>

Booth: I think the other thing I would like to ask Professor Mitchison is one of the key features of being able to look at the bacterium was being able to grow it. Was that a major problem?

Mitchison: It was quite a problem to begin with. There was a small bacteriological committee set up with Robert Cruickshank, who went to Edinburgh eventually, as Chairman [of the Pathological Subcommittee of the MRC Streptomycin in Tuberculosis Trials Committee].<sup>48</sup> I was a member of that very small group of four people at the very beginning of the pulmonary TB trial. It later expanded to be a big collaborative exercise. We were trying out the new Dubos media that had been worked out at the Rockefeller Institute, mainly of course by Middlebrook, not by René Dubos, and these actually were not the best methods to

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<sup>46</sup> Dr Honor Smith FRCP (1908–1995), neurologist, was physician in charge of Tuberculous Meningitis Unit, Oxford, from 1948 until 1971. See Smith H V, Daniel P. (1947) Some clinical and pathological aspects of tuberculosis of the central nervous system. *Tubercle* 28: 64–80.

<sup>47</sup> Crofton J, Mitchison D A. (1948) Streptomycin resistance in pulmonary tuberculosis. *British Medical Journal* ii: 1009–1015.

<sup>48</sup> Professor Robert Cruickshank FRCP (1899–1974) was the first Director of the Central Public Health Laboratory, Colindale, London, from 1945 until 1948. He was appointed Professor of Bacteriology at St Mary's Hospital Medical School, London, from 1949 to 1955 and Principal of the Wright–Fleming Institute of Microbiology at St Mary's from 1955 to 1957. He was Chairman of the MRC Pathological Subcommittee of the Streptomycin in Tuberculosis Trials Committee. He moved to the University of Edinburgh as Professor of Bacteriology in 1958 until his retirement in 1966. Professor D A Mitchison wrote: 'As far as I can remember, Robert Cruickshank used to be a Co-Professor with Alexander Fleming (they had tea at the opposite ends of a very long table and appeared usually not to be on speaking terms!).' Letter to Mrs Lois Reynolds, 29 March 1999.



use.<sup>49</sup> It just happened that they were fashionable, just as many areas are now fashionable.

Booth: If I remember rightly you had a green-fingered senior technician who happened to be able to do things that other people couldn't, is that right?

Mitchison: I think all the people involved in the early work managed to get the techniques to work, but they weren't actually very efficient. This was the problem.

Crofton: Can I just comment on that particular point, because later on in Edinburgh we studied failures. We found we had some patients who had reason to have become streptomycin resistant, because of their previous treatment, and behaved clinically as such, but the tests showed sensitivity. We found that the original Dubos [test] didn't show up these low degrees of resistance to streptomycin which proved to be clinically significant and then the techniques were changed.

Mitchison: I don't think that's true. I think the actual situation was that the Tween 80 in the medium pushed the MICs [minimum inhibitory concentration (mg/ml)] down. If one had used the right definition of resistance with the original Tween medium, one would have detected these resistant strains.<sup>50</sup>

Crofton: I think we were using the same techniques and the same criteria of resistance as you did.

Mitchison: And got equally bad or rather worse results.<sup>51</sup>

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<sup>49</sup> Professor D A Mitchison wrote: 'Solid medium tests were almost universally adopted a little later on. What happened worldwide was that sensitivity tests were originally set up in Tween albumen liquid medium (Dubos media). There was then a move to the use of solid media, mainly because they were much easier to deal with and far less often contaminated than the liquid medium tests. In most countries, the solid medium was Löwenstein-Jensen egg medium and numerous problems arose with this because the activity of streptomycin was greatly affected by the method of preparation of the medium, the size of the bottles, the volume on the slope, etc. Thus, it was very difficult to standardize the tests. In America, some centres use agar-based media but these tend to be much more expensive and also may be dangerous. There is a huge history of controversy about methods that has gone on for years. Although there was this worldwide shift to solid media of various sorts, all of the recently introduced automated systems for culturing mycobacteria (for instance the BACTEC system made by Becton Dickinson Microbiology Systems) uses liquid media culture because of its greater sensitivity. The media never include Tween 80.' Letter to Mrs Lois Reynolds, 29 March 1999. For example, details on diagnostic microbiology, see Richardson H. (1999) Blurring the boundaries. *Chemistry and Industry* (16.8.99): 625–630.

<sup>50</sup> Professor D A Mitchison wrote: 'Tween 80 is a surfactant which decreases the minimum inhibitory concentration of many antituberculosis drugs.' Letter to Mrs Lois Reynolds, 29 March 1999. See also Medical Research Council, Pathological Subcommittee of the Streptomycin in Tuberculosis Trials Committee. (1948) Specific laboratory tests in streptomycin therapy of tuberculosis. *Lancet* ii: 862–865.

<sup>51</sup> Sir John Crofton wrote: 'That's why we changed the technique! – to make it concordant with clinical results.' Letter to Mrs Lois Reynolds, 19 March 1999. Professor Mitchison's response to this comment, dated 22 October 1999, and Sir John's full letter will be deposited with the tapes, correspondence and other documentation from the Witness Seminar in the Contemporary Medical Archives Centre of the Wellcome Library.

Dr David Tyrrell:<sup>52</sup> A point about the preceding placebo-controlled trial on patulin, as a common cold treatment. It's a long sorry story which we haven't got time for now, but people like Joan Faulkner supported D'Arcy Hart,<sup>53</sup> ran round the country, thousands of people were given patulin on a double-blind placebo-controlled basis.<sup>54</sup> The only difference was that patients were not treated by random allocation, but as alternate cases, but it was all under code so nobody could know which were given patulin. This was essential as the results were entirely based on clinical assessment. Previously there had been a *Lancet* report of a dramatically successful use of patulin which, in retrospect, must have been due to faulty trial design; but Stuart-Harris<sup>55</sup> and one or two others with practically no resources, had done another trial which showed that it didn't work. But this big trial carried conviction – patulin did no good. It was earlier than the TB trial and I like to think of it as a good 'dry run'. Probably people like Bradford Hill looked at those results and said, 'Well, would alternate cases be really the best way of allocating the placebo and the controls?' and therefore went one step further and improved the design when it came to the TB trial. But of course that trial also had the advantage that there were more objective assessments, blinded X-ray assessment and so on. One other quickie, I think Sheffield was involved in the TBM (tuberculous meningitis) trial because I remember doing the lumbar punctures. It was a daily chore for the Professor's house physician.<sup>56</sup>

Wainwright: Anyone who's interested in the patulin trial, by the way, the Public Record Office is just releasing a large archive on it, if you would like to research that, it's a very interesting story.

Going back to streptomycin. There's a connection here between streptomycin and penicillin. If you look at the Fleming archive, there are about six notebooks concerned with streptomycin. I wonder if anyone remembers Fleming actually being involved? I would also like to ask the question, was the problem of streptomycin affecting the eighth cranial nerve ever observed during the trials?

Crofton: Eighth cranial nerve damage came up very early, at the beginning. Also patients often complained of paraesthesia around the mouth, but that tended to

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<sup>52</sup> Dr David Tyrrell CBE FRCP FRCPATH FRS (b. 1925) trained in medicine at Sheffield and was Stuart-Harris's house physician from 1948 to 1949. He was a member of the scientific staff of the MRC Common Cold Unit at Salisbury from 1957 and its Director from 1982 until his retirement in 1990, where he worked on antiviral drugs in volunteers. From 1970 until 1982 he ran the Division of Communicable Diseases at the Clinical Research Centre, Northwick Park Hospital, Harrow, where he was Deputy Director.

<sup>53</sup> Dr Joan Faulkner (Lady Doll) was then Principal Medical Officer at the Medical Research Council. See D'Arcy Hart's biographical note 30 above.

<sup>54</sup> op. cit. note 43 above.

<sup>55</sup> Sir Charles Stuart-Harris FRCP (1909–1996) was in the Royal Army Medical Corps at the time of the patulin trial. He was Sir George Franklin Professor of Medicine at the University of Sheffield from 1946 until his retirement in 1972. Stansfeld J M, Francis A E, Stuart-Harris C H. (1944) Laboratory and clinical trials of patulin. *Lancet* ii: 370–372. See Crane W A J. (1979) Professor Sir Charles Stuart-Harris. *Postgraduate Medical Journal* 55: 71–72. op. cit. note 43 above.

<sup>56</sup> op. cit. note 37 above.

disappear with purer streptomycin.<sup>57</sup>

Booth: Was it recorded in the first clinical trial as a complication?

Crofton: Oh yes, I am pretty sure it was, because we did a lot of tests, but there was little deafness. There was a later modification to streptomycin which produced more deafness, if less giddiness, leading to its abandonment for clinical use.<sup>58</sup>

Dr Derek Bangham:<sup>59</sup> In connection with some of the reactions to streptomycin, it might be worth while drawing attention to the quality and potency of streptomycin. The sterility of penicillins was tested on behalf of the Therapeutic Substances Regulations<sup>60</sup> by adding penicillinase which would knock out specifically penicillin, and then a sterility test was done on what remained. But with streptomycin it was difficult because there was no actual antagonist to streptomycin. Drs J W Lightbown<sup>61</sup> and John Cornforth<sup>62</sup> at Mill Hill did eventually isolate a group of antagonists to streptomycin.<sup>63</sup> It was not used for a test. However, Lightbown then devised a test for sterility in which a solution of streptomycin was passed through a filter membrane, which was then cultured. Membranes invented by Elford at the NIMR were used at first.<sup>64</sup> Thereafter this test for sterility was used for all antibiotics and made official in the *British Pharmacopoeia 1963*.

I would like to mention other basic contributions that England made to antibiotics. First was the problem of measuring preparations of penicillin, and the early penicillins

<sup>57</sup> For a description of streptomycin's toxicity and side-effects, see, for example, Barber M, Garrod L P. (1963) *Antibiotic and Chemotherapy*. Edinburgh: E & S Livingstone Ltd, 98–101.

<sup>58</sup> Sir John Crofton wrote: 'The modification to streptomycin referred to was in fact dihydrostreptomycin.' Letter to Mrs Lois Reynolds, 2 November 1999.

<sup>59</sup> Dr Derek Bangham FRCP (b. 1924) was Head of the Division of Biological Standards at the National Institute for Medical Research (NIMR) from 1961 to 1972. He was later Head of the Hormones Division of the National Institute for Biological Standards and Control (NIBSC), from 1972 to 1987.

<sup>60</sup> Therapeutic Substances Regulations issued under the Therapeutic Substances Act 1925, revised 1956, related to standards of strength, quality and purity of substances, and the tests to be used.

<sup>61</sup> Dr James W Lightbown was a member of the scientific staff in the Division of Biological Standards at the National Institute for Medical Research (NIMR) from 1949 to 1972, and Head of the Division of Antibiotics at the National Institute for Biological Standards and Control (NIBSC), Potter's Bar, Hertfordshire, until 1983.

<sup>62</sup> Sir John Cornforth Kt CBE FRS (b. 1917) was a member of the scientific staff in chemistry at the National Institute for Medical Research (NIMR) from 1946 to 1962. He became co-director of the Milstead Laboratory of Chemical Enzymology of Shell Research Ltd and Associate Professor of Molecular Sciences at University of Warwick from 1962 until 1975 when he was appointed Royal Society Research Professor at the University of Sussex until his retirement in 1982, now Emeritus. In 1975 he shared the Nobel Prize for Chemistry with Vladimir Prelog (b. 1906) for his work on the chemistry of enzyme action.

<sup>63</sup> See Lightbown J W. (1950) An antagonist of dihydrostreptomycin and streptomycin produced by *Pseudomonas pyocyanea*. *Nature* **166**: 356–357. Lightbown J W. (1954) An antagonist of streptomycin and dihydrostreptomycin produced by *Pseudomonas aeruginosa*. *Journal of General Microbiology* **11**: 477–492. Cornforth J W, James A T. (1956) Structure of a naturally occurring antagonist of dihydrostreptomycin. *Biochemical Journal* **63**: 124–130.

<sup>64</sup> Dr William Elford FRS (1900–1952) was a member of the scientific staff of the National Institute for Medical Research from 1925 to 1952. Gradocol membranes or Elford membranes were accurately graded collodion membranes used to measure the size of small particles, such as viruses, before the advent of the electron microscope. See Andrewes C H. (1952–53) William Joseph Elford. *Obituary Notices of Fellows of the Royal Society* **8**: 149–158.

were rough stuff; the only way of assaying them was by biological assay developed by J H Humphrey and J W Lightbown.<sup>65</sup> Fortunately in 1944, Sir Henry Dale had chaired an international meeting to decide how to define the potency of penicillin. In his own words, 'by judicious assembly of suitable persons' at this international meeting, under the League of Nations, it was decided to use international units. That unit was based on the 'Oxford unit'.<sup>66</sup> The problem with streptomycin was greater because that had been developed in America, and all the Americans always insisted on talking about microgram equivalents of activity. You can't talk about micrograms of activity.

Eveleigh: You [Booth] commented 'was resistance expected?' and I think scientists delude themselves. The answer is clearly that Ehrlich showed there was resistance back before 1910 to a whole range of drugs. He showed there was combined resistance to drugs back in 1910. Penicillin resistance was shown in 1942, sulphonamide resistance was shown in 1942 and streptomycin was first really used in 1946 and resistance was shown in 1946.<sup>67</sup> So I think we shouldn't be deluded about where we are coming from.

Mitchison: It was certainly one of the major aims of the first bacteriological group to look for drug resistance, and I am also quite sure that these very early reports of streptomycin resistance were already known by the time that the work started, so I don't think there was anything new.

Booth: St Mary's was mentioned. Keith Rogers was at St Mary's in the earlier phase, but was Mary's involved in streptomycin, and did Fleming have any attitude to it?

Dr Keith Rogers:<sup>68</sup> I was a long, long way from St Mary's at that time. I left at the end of the blitz.

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<sup>65</sup> Humphrey J H, Lightbown J W. (1952) A general theory for plate assay of antibiotics with some practical applications. *Journal of General Microbiology* 7: 129–143.

<sup>66</sup> The 'Oxford unit' of activity, described as 0.6 µg of pure penicillin-G, was defined by the standard developed by Norman Heatley for penicillin. See Stewart (1965) op. cit. note 10 above, page 9. See Heatley's biographical note 146 below.

<sup>67</sup> Youmans G P, Williston E H, Feldman W H, Hinshaw H C. (1946) Increase in resistance of tubercle bacilli to streptomycin: A preliminary report. *Proceedings of the Staff Meetings of the Mayo Clinic* 21: 126–127. We thank Dr Alan Yoshioka for drawing our attention to this reference.

<sup>68</sup> Dr Keith B Rogers (b. 1910) worked with Fleming (op. cit. note 5 above) at St Mary's Hospital, London, from 1935 to 1941. Dr Keith Rogers wrote: 'I felt I could not put myself forward as the easily caught guinea-pig, but Fleming used me, as a most willing subject. He was always ready to check if he could, to see if one of his ideas would work. He had some streptomycin which he must have been sent, well before it became generally available. In August 1946 I was about to be posted to Venice after my entry into the RAMC [Royal Army Medical Corps], when I developed an acute antral infection. I was in London and visited my old friends in the Inoculation Department who obtained a heavy pure growth of *Haemophilus influenza* from my post nasal discharge. Fleming suggested that he would get Simpson, the Mary's ENT surgeon, to wash out the antrum and then instil some streptomycin. Unfortunately I must have been sensitive to the streptomycin, or the vehicle in which it was placed, as overnight the antrum blocked and probably everything inside expanded to build up a huge pressure causing severe pain and swelling of that side of my face. Simpson washed the antrum out the next morning and there was no further trouble. This must have been an early use of streptomycin, but I felt it was too trivial to talk about.' Letter to Sir Christopher Booth, 13 May 1998. For details of Dr Rogers's account of a similar experience with penicillin in 1932, see Selwyn S. (1980) *The Beta-Lactam Antibiotics: Penicillins and cephalosporins in perspective*. London: Hodder and Stoughton, 22–23.

Professor Gordon Stewart:<sup>69</sup> I was at St Mary's at that time, and certainly cases were being treated. In fact, one of the events in the late 1940s, which made a more convincing impact than almost any other was the cure of childhood tuberculous meningitis, with streptomycin given intrathecally as well as intramuscularly. Before that the difficulty was that there was little or nothing to compare it with. There was no other drug. A bit of history: Domagk in Germany had found that thiosemicarbazones had a distinct effect upon tubercle bacilli *in vitro*. The Germans were using them for the treatment of tuberculosis. We tried some in guinea-pigs, mice and monkeys, ultimately comparing it with streptomycin.<sup>70</sup> The difference was striking, in that although the thiosemicarbazones had a therapeutic action, they didn't compare with streptomycin, and the toxicity was far too high. So they dropped by the wayside, although these were by no means without activity, and some day we might have to use this chemical lead again, because synthetic antimicrobials have been more useful than antibiotics in the therapy of tuberculosis.

Professor Alan Glynn:<sup>71</sup> I was Senior Registrar on the ward where tuberculous meningitis had been treated at St Mary's. By that time the trial was all over and everything was accepted but there were still a small trickle of patients with tuberculous meningitis coming in. Fleming had just died. Whether he had been involved with them I don't know. I really remember it from the fact that we also gave streptomycin occasionally intracisternally and I had to do this the first time with just brief verbal instructions from Dickson Wright an hour before.<sup>72</sup> The patient wasn't frightened, because he was too ill, but I was.

Booth: If I remember rightly, Alan, at some stage in the treatment of tuberculous meningitis people started using large doses of tuberculin intrathecally as well to promote reactions. Would anybody like to comment on that?

Crofton: That was at Oxford. That was Honor Smith<sup>73</sup> and they set out to do a trial on this, in tuberculosis in general, in South Africa, and I went out with that group to help

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<sup>69</sup> Professor Gordon Stewart (b. 1919) was Professor of Public Health at the University of Glasgow from 1972 until his retirement in 1984, now Emeritus. His long professional interest is in the control of communicable diseases which began with his work with antibiotics in 1944 at the Royal Naval Medical School, Haslar, Portsmouth. See Stewart (1965), note 10 above.

<sup>70</sup> Gerhard Johannes Paul Domagk (1895–1964) was Director of the I G Farbenindustrie Laboratory of Experimental Pathology and Bacteriology from 1927. He was awarded the Nobel Prize for Physiology or Medicine in 1939, although his acceptance was cancelled by the German Government. He received the award in 1947, but not the monetary Prize.

<sup>71</sup> Professor Alan Glynn FRCP FRCPath (b. 1923) practised clinical medicine at St Mary's Hospital, London, from 1956 to 1958. He took up bacteriology at St Mary's, was appointed Professor in 1971 and Head of Department of Bacteriology in 1974. In 1980 he became Director of the Central Public Health Laboratory at Colindale until his retirement in 1988.

<sup>72</sup> Mr Arthur Dickson Wright FRCS (1897–1976) was Consulting Surgeon at St Mary's Hospital, London, from 1927 until his retirement in 1962 and the Prince of Wales General Hospital, London. He was on the Council of the Royal College of Surgeons of England for 16 years from 1952, becoming Vice-President.

<sup>73</sup> *op. cit.* note 46 above.

organize it. Unfortunately, Cairns,<sup>74</sup> who was the leader, who was a professor of neurosurgery in Oxford, developed leukaemia just after he came back and so it all folded up and, I believe, that trial was never done. I don't think it would have worked anyway.<sup>75</sup>

Booth: Did it ever work? Nobody ever believed in it, did they?

Crofton: With the later success of combined treatment using streptomycin with PAS and/or isoniazid, it is understandable that additional tuberculin treatment was not pursued.

Booth: Now at what stage did PAS come in, and none of you have mentioned INAH. What was the function of INAH?<sup>76</sup>

Crofton: I think the PAS trials were started in 1948.

Booth: Why? What was the rationale behind it?

Crofton: PAS was actually discovered before streptomycin, but not publicized. It became available in 1948. It was evolved by Lehmann in Sweden.<sup>77</sup> The rationale was that aspirin had been shown to stimulate the metabolism of the tubercle bacillus. Lehmann speculated that an alteration of the aspirin molecule might inhibit an essential metabolic pathway. The para-amino form of salicylic acid proved to do so. The first MRC trials, having produced all this resistance, they initiated this triple trial, as Denny and I have mentioned – streptomycin alone, PAS alone and the combination.<sup>78</sup> With the combination there was considerably less resistance and less failure. And then in 1952 isoniazid came up and so that was tried up against streptomycin/PAS.<sup>79</sup>

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<sup>74</sup> Sir Hugh Cairns FRCS (1896–1952), an Australian neurosurgeon, held the Nuffield Chair of Surgery at Oxford University from 1937 until his early death in 1952. During the war he became the first adviser to the Ministry of Health on head injuries, organized the Head Injuries Hospital in St Hugh's College, Oxford, and was Consultant Neurosurgeon to the Army with the rank of Brigadier. He and Florey organized the field trials of penicillin in North Africa in 1943.

<sup>75</sup> Sir John Crofton wrote: 'As far as I remember we were primarily planning to see if the use of tuberculin would improve the results in the treatment of *pulmonary* tuberculosis. I think we outlined the components of such a trial but, for the reasons I stated, do not think they got as far as any final protocol or formed an actual trial.' Letter to Mrs Lois Reynolds, 19 March 1999. See Cairns H, Duthie E S, Smith H V. (1946) Intrathecal streptomycin in meningitis: Clinical trial in tuberculous, coliform and other infections. *Lancet* ii: 153–155.

<sup>76</sup> Isoniazid (isonicotinic acid hydrazide – INAH) was first synthesized in 1912 and is often a primary drug for treatment of tuberculosis. In 1952 three isoniazid products were under trial in Britain: *Rimifon*, Roche; *Nydrazid*, Squibb; *Pycazide*, Herts Pharmaceuticals. Anon. (1952) Notes and News: Isonicotinic acid derivatives in tuberculosis. *Lancet* i: 571. See Fox H H. (1953) The chemical attack on tuberculosis. *Transactions of the New York Academy of Sciences* 15: 234–242.

<sup>77</sup> op. cit. note 35 above.

<sup>78</sup> Medical Research Council, Joint Subcommittee of the Streptomycin in Tuberculosis Trials Committee and the Research Committee of the British Tuberculosis Association. (1950) Treatment of pulmonary tuberculosis with streptomycin and PAS. A Medical Research Council investigation. *British Medical Journal* ii: 1073–1085.

<sup>79</sup> Medical Research Council, Tuberculosis Chemotherapy Trials Committee. (1952) The treatment of pulmonary tuberculosis with isoniazid. An interim report to the Medical Research Council. *British Medical Journal* ii: 735–746. *idem* (1953) Isoniazid in combination with streptomycin or with PAS in the treatment of pulmonary tuberculosis. *ibid.* ii: 1005–1014. *idem* (1955) Various combinations of isoniazid with streptomycin or with PAS in the treatment of pulmonary tuberculosis. *ibid.* i: 435–445.

Booth: And isoniazid was known in the laboratory to have antituberculous effects or not? Why was it introduced? There must have been some reason.

Crofton: It was the result of Domagk's work in Germany. All the German patents were disallowed at the end of the war, and both the Americans and the Swiss developed isoniazid from Domagk's work. I think I am correct.

Booth: Let's move back to Professor Mitchison, with your bugs in your laboratory. Here you have got PAS and INAH, and everybody says, 'OK this is stopping resistance', so how did that happen? What did it do?

Mitchison: Well, the idea was that you have mutations to, say, streptomycin resistance, occurring rarely, one in perhaps  $10^7$ ; you have resistance to PAS in say one in  $10^6$ . To have double resistance to both of these would be one in  $10^{13}$  bugs, and that's more than you would actually get in the lungs. It doesn't work quite like that because streptomycin is not a very good anti-TB drug and some multiplication goes on despite its presence, and the same is certainly true of PAS. You really have to wait until you get to isoniazid to have a very much better drug. Isoniazid was originally developed in America, but it's been through the hands of other laboratories. It had been through the hands of Burroughs Wellcome pharmaceutical company [The Wellcome Foundation] in this country and was missed as an antituberculous drug. They used the wrong test organism. That's a very sad story, but it's true. It was screened in the right way in America and brought out in 1952 with a great burst of publicity. It went immediately, as far as this country went, into MRC studies both of isoniazid alone and then isoniazid in combination with PAS and/or streptomycin over a period of several years.<sup>80</sup>

Dr Alan Yoshioka:<sup>81</sup> A comment on St Mary's Hospital. Fleming was actually Chair of a much lesser known MRC Committee on the use of streptomycin in non-tuberculous conditions. These included typhoid fever, *Haemophilus influenzae* meningitis. It was also tried at St Bartholomew's and at several other centres.<sup>82</sup>

I take issue with the statement that all the supplies in the United States were allocated to individual physicians. There was a very large programme organized by the Committee on Chemotherapeutic and Other Agents of the National Research Council and doctors such as Feldman and Hinshaw who were involved in

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<sup>80</sup> op. cit. note 79 above.

<sup>81</sup> Dr Alan Yoshioka (b. 1963) was awarded his PhD for his thesis on streptomycin by the University of London shortly after this seminar, see note 31 above. See also Yoshioka A. (1998) Use of randomization in the MRC's clinical trial of streptomycin in pulmonary tuberculosis in the 1940s. *British Medical Journal* 317: 1220–1223.

<sup>82</sup> Wilson C. (1948) Streptomycin in non-tuberculous infections: Summary of a report to the Medical Research Council. *Lancet* ii: 445–446. Sir Alexander Fleming was Chairman of this MRC Committee and Professor Clifford Wilson, Professor of Medicine at the University of London and Director of the Medical Unit at the London Hospital, was Secretary.

quite a large programme which was funded by industry, a large consortium of manufacturers.<sup>83</sup>

Professor Graham Ayliffe:<sup>84</sup> Can I just make a comment on other uses of streptomycin? When I was a house surgeon in the mid-1950s, penicillin and streptomycin were widely given for surgical infections. I wonder whether this combination was really very effective, as it has been shown in recent years that *Bacteroides* is one of the main causative organisms of surgical infections and is usually resistant to both antibiotics. The other use of these agents is, of course, for bacterial endocarditis. Penicillin–streptomycin was used successfully as a synergic combination for many years, particularly for enterococcal infections. I wonder whether we could persuade Pamela Waterworth to say something about this. Professor Garrod and Miss Waterworth were particularly interested in the treatment of endocarditis.<sup>85</sup>

Miss Pamela Waterworth:<sup>86</sup> I am sure that there can be a synergic effect between penicillin and streptomycin, but this is only of significance when the treatment needs to kill all the infecting organisms present. Penicillin alone always leaves a few [bacterial] survivors, which are normally disposed of by the body's natural defences. If this does not happen, the infection recurs when treatment is withdrawn. The main example of this is the treatment of bacterial endocarditis due to enterococci or other relatively resistant streptococci. The organism needs to have normal sensitivity to streptomycin, then the synergic effect of this (or indeed other aminoglycosides) with penicillin normally produces total bactericidal action *in vitro*, and frequently succeeds in treatment.

At Bart's we did have some evidence of the efficacy of this many years after the introduction of streptomycin, when we had a patient with an enterococcal endocarditis, and his streptococcus was highly resistant to streptomycin, and I could

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<sup>83</sup> The Committee on Chemotherapeutic and Other Agents was one of the National Research Council's medical subject committees, created in World War I to advise the US Government's military on scientific and technological matters. For the large-scale trials run by the US Public Health Service and Veterans' Administration after the report of Hinshaw and Feldman's research in 1945 (op. cit. note 28 above), see Marks H M. (1997) *The Progress of Experiment: Science and therapeutic reform in the United States, 1900–1990*. Cambridge: Cambridge University Press. See Chapter 4, 'War and peace', pages 98–128, especially 113–116.

<sup>84</sup> Professor Graham Ayliffe FRCPATH (b. 1926) was Professor of Medical Microbiology at the University of Birmingham from 1980 until his retirement in 1990, now Emeritus. He was a member of the scientific staff at the Medical Research Council and Consultant Bacteriologist at the Hospital Infection Research Laboratory, Birmingham, from 1963 to 1994. See Lowbury E J L, Ayliffe G A J. (1974) *Drug Resistance in Antimicrobial Therapy*. Springfield, IL: Charles C Thomas.

<sup>85</sup> Professor Lawrence P Garrod FRCP (1895–1979) was Professor of Bacteriology, University of London, from 1934 until his retirement in 1961, when appointed Emeritus. After retirement he was made Honorary Consultant in Chemotherapy at the Royal Postgraduate Medical School, Hammersmith Hospital, London. He had been Bacteriologist at St Bartholomew's Hospital, London, from 1925 to 1961. He was an original member of the MRC's Penicillin Clinical Trials Committee. See Shooter R A. (1984) Lawrence Paul Garrod. *Munk's Roll 7*: 203–204.

<sup>86</sup> Miss Pamela Waterworth (b.1920) worked with Professor L P Garrod at St Bartholomew's Hospital, London, from penicillin's introduction in 1944 until his retirement in 1961. She then joined Mary Barber at the Royal Postgraduate Medical School, Hammersmith Hospital, London. In 1971 she moved to the Department of Microbiology at University College Hospital, London, until her retirement in 1981.



get no enhanced killing effect with penicillin and streptomycin. We treated the patient with a very full course, a long course, of high-dosage penicillin, and unfortunately his blood culture became positive about three weeks later with the same organism. Then, the only suggestion we had was the use of neomycin instead of streptomycin, because I had in fact demonstrated that whereas streptomycin did nothing to help kill the streptococcus, neomycin produced a very excellent synergic effect. The patient was, of course, told that if he had neomycin that he would be deaf after it, but he chose to be deaf. We did give him a course of the combined treatment, he was cured of his infection, but he was stone deaf after his treatment. This was published by Professor Garrod in the *British Medical Journal* under the title of 'Deaf or dead'.<sup>87</sup> And I think that is evidence that there is an effect, a genuine effect, in certain circumstances, between the two drugs.

Dr Ralph Batchelor:<sup>88</sup> I wonder how much it was realized, and I suspect not at all at that time, that there was interaction between the penicillin molecule and the aminoglycosides, because  $\beta$ -lactams can acylate the amino groups of aminoglycosides, particularly when the two are together in high concentration making them pharmaceutically incompatible. If you left the two together for any length of time before giving them to the patient, you would be giving partially inactivated drugs leading to treatment failures, the cause of which was not understood in the early days.

Crofton: Penicillin and streptomycin combination was used very extensively for respiratory infections in the Third World. This was always a worry, because if there was cryptic tuberculosis, you might be getting streptomycin resistance, so there was a lot of propaganda against this use. I think it is not widely used now. Some people also thought it was effective in bacterial endocarditis.<sup>89</sup>

Professor Harold Lambert:<sup>90</sup> I think one interesting general point about these years is the time it takes, even after persuasive trials are published, before these new drugs supplant other treatments. I was registrar of a chest department at University College

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<sup>87</sup> Havard D W H, Garrod L P, Waterworth P M. (1959) Deaf or Dead? A case of subacute bacterial endocarditis treated with penicillin and neomycin. *British Medical Journal* i: 688–689.

<sup>88</sup> Dr Ralph Batchelor (b. 1931) was a biochemist at Beecham Research Laboratories, Betchworth, Surrey, from 1956, working his first year in Rome with Professor Sir Ernst Chain. He moved from research to general management in 1970 and was a Director of Beecham Pharmaceuticals from 1978 until his retirement in 1989. He was awarded the Addingham Medal by the City of Leeds in 1966 and the Royal Society Mullard Medal in 1971. Some of the first crystals and early chromatograms showing the presence of 6-APA are in his original notebook, now on display in the Science Museum. See Batchelor F R, Doyle F P, Nayler J H C, Rolinson G N. (1959) Syntheses of penicillin: 6-aminopenicillanic acid in penicillin fermentations. *Nature* **183**: 257–258.

<sup>89</sup> op. cit. note 87 above.

<sup>90</sup> Professor Harold Lambert (b. 1926) trained as a physician, with spells of microbiological research. He was physician in charge of the infectious diseases department at St George's Hospital, London, from 1965, later Professor from 1972, until his retirement in 1984. He has been Visiting Professor at the London School of Hygiene and Tropical Medicine since 1984.

Hospital in 1955–56, and still did 2000 pneumothorax refills;<sup>91</sup> this was of course three years after isoniazid and more years after streptomycin and PAS, and it often takes quite a time of years before the new drugs are seen in relation to pre-existing treatment. It rather reminds me of the meningococcal problem. If one looks at the old 1930s papers, antimeningococcal sera were used in conjunction with sulphonamides in thousands of cases, the serum having been introduced by Flexner in 1908.<sup>92</sup> Only after people got confidence in the sulphonamides, because of course at that time meningococci were all sulphonamide susceptible, did the serum fade away.

**Booth:** If you were doing pneumothoraces, you were probably doing them in a separate clinic, with personnel who were afraid of losing their jobs. Why didn't they give them up?

**Lambert:** I think it was a question of duration. John Crofton will correct me on this, but I think in the early years what was uncertain was relapse rates in relation to durations of therapy. That's my hunch; people didn't really quite have the confidence to say 'that was it' when you gave a particular course of treatment, but Denny [Mitchison] and John [Crofton] would know more about this than I would.

**Crofton:** Well a lot of people were not getting very high cure rates, because first of all they didn't go on long enough. We very early analysed our relapse rates, and discovered that if you gave 18 months or more with the old three drugs you didn't get relapses and you did cure them. I went to Edinburgh at the beginning of 1952 and we never did a pneumothorax after that. And it took about 20 years, before most chest physicians in the UK were giving good tuberculosis treatment.

**Booth:** Was it because their livelihoods were at stake?

**Crofton:** Oh no, it was just conservatism.

**Mitchison:** Well, there's a very much more fundamental point than this, that there are some drugs to which a high proportion of the bacterial population is seen to be phenotypically resistant. This is true of the aminoglycosides, they are singularly ineffective against persisting tubercle bacilli. I wouldn't like to say what they do about enterococci, I am just talking for the moment about TB. Isoniazid is a bit better, but it's not very good, and PAS is hopeless. Now, no drug actually kills all the tubercle bacilli in lesions. You do never get a complete cure in tuberculosis. All you do is to bring the number of persisting bacilli down to the level at which immunity can hold them and that's all you can do.

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<sup>91</sup> The reversal of 'collapse therapy', or closure of tuberculous cavities through relaxation of the lung, used a number of methods, including artificial pneumothorax. By 1960, for those with resistance to the standard drugs (streptomycin, PAS and isoniazid) or who failed to comply with treatment, the treatment of choice was pulmonary resection of the lesions. See, for example, Davidson S. (1961) *The Principles and Practice of Medicine: A textbook for students and doctors*. Fifth edition. Edinburgh: E & S Livingstone Ltd, 387–388.

<sup>92</sup> Flexner S, Jobling J W. (1908) An analysis of 400 cases of epidemic meningitis treated with the anti-meningitis serum. *Journal of Experimental Medicine* 10: 690–733.

Tyrrell: I was at the Northwick Park Hospital, doing infectious diseases and treating tuberculosis, but I have a feeling that we went on treating with streptomycin and PAS, in triple therapy, after a lot of other people had changed to rifampicin.<sup>93</sup> The reason was, that there were clinical trials that said, provided you did your triple therapy properly, you got long-term clinical recovery, never mind whether or not a few organisms were alive. I was prepared to persuade patients to put up with the injections so I could say, 'And if you stick with it, you are going to have a solid clinical cure'; let other people see whether rifampicin and the other combinations of drugs will do equally well. I think it is not a term really of abuse to say that's conservative, I think that is careful therapy.

Dr Geoffrey Scott:<sup>94</sup> It may be of interest that the current consultants in a very famous neurological hospital not a million miles from here are still convinced that streptomycin is a mainstay of the treatment of tuberculous meningitis, which it probably is not.

Booth: That's the National Hospital [for Nervous Diseases] at Queen Square, I presume you are referring to. Well, on that note I think we should move on. We have got other things to discuss and I think we should go on to semisynthetics at this stage.

Dr Peter Doyle:<sup>95</sup> What I propose to do is to set the scene, since I was personally involved in it. To set the scene properly for Beecham's involvement in this story, we need to go back to 1947. In 1947 Mr Lazell, who later became the Chairman of the Beecham Group, decided that it was about time Beecham's had a research group, so he bought an old house in the midst of Surrey, Brockham Park, and set up a central research group there.<sup>96</sup> Initially that was a general purpose research group, that did all sorts of things, studied the effect of light on the colour of Lucozade, studied the use of cysteine in Silvikrin hair tonic, and various things of that sort. One of the interesting points was that it was officially opened by Sir Alexander Fleming in 1947. Now this might have been a coincidence, but there was no doubt that his shadow fell over Brockham Park for some years afterwards. I joined the company in 1952 when the labs had been going for about five years and by which time they had moved more

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<sup>93</sup> Rifampicin, one of 500 derivatives of rifamycin (introduced into therapy in 1968), was considered to be an improvement on the standard triple therapy of streptomycin, PAS and isoniazid, as it could be taken orally with improved antibacterial activity. See, for example, Garrod L P, Lambert H P, O'Grady F. (1973) *Antibiotic and Chemotherapy*. Fourth edition, Edinburgh: Churchill Livingstone, 220, 446. For the nomenclature of the rifamycins, see Aronson J. (1999) When I use a word... That's show business. *British Medical Journal* 319: 972.

<sup>94</sup> Dr Geoffrey Scott (b. 1948) has been Consultant Clinical Microbiologist at University College London Hospitals since 1984. His main preoccupation is the inexorable rise in antibiotic resistance.

<sup>95</sup> Dr Peter Doyle OBE (b. 1921) has been a chemist in industry since graduating from the University of London in 1944. He joined Beecham Laboratories in 1952 and was Director of Research of Beecham Pharmaceuticals from 1962 until his retirement in 1983. Among other honours, he received the Worshipful Society of Apothecaries Gold Medal in Therapeutics in 1964 jointly with Dr G N Rolinson (op. cit. note 101), the Royal Society Mullard Medal in 1971 jointly with Dr Ralph Batchelor (op. cit. note 88), Dr J H C Nayler (op. cit. note 102) and Dr Rolinson. He was awarded the OBE for services to the pharmaceutical industry in 1977.

<sup>96</sup> Lazell H G. (1975) *From Pills to Penicillin: The Beecham story, a personal account*. London: Heinemann.

in the direction of what we used to call 'ethical pharmaceuticals', but we now call prescription medicines. Mr Lazell felt that the introduction of the National Health Service in 1948 was going to destroy the over-the-counter pharmaceutical business and, as you probably realize, Beecham had a big commercial interest in Beecham's Powders, Beecham's Pills, Veno's Cough Cure etc. You name it, they were all on the shelves in Boots. By 1952 the emphasis was changing, and it was decided we ought to be doing more on research into new prescription medicines.

At the time I joined the company in 1952 as Head of the Chemistry Department, it consisted of three graduates and about four technicians. My ex-colleague, David Brown, joined at the same time as Head of Pharmacology and he set up the first pharmacology department. For the first three years, between 1952 and 1955, our main work was confined to compounds related to atropine, because we were interested in problems of gastric and duodenal ulcers, and also in antitubercular compounds. David Brown set up an animal house and we were using the conventional 21-day mouse test, using H37RV.<sup>97</sup> For those who have just been talking about streptomycin, it might be interesting that the compounds we were working with, were derivatives of British anti-Lewisite (BAL).<sup>98</sup> British anti-Lewisite has good antitubercular activity, but it is a foul-smelling compound. At the same time Dr Snow and his colleagues at ICI were working on derivatives of ethylmercaptan (diethyl disulphide). We were both working on extremely smelly compounds. We got as far as considering a clinical trial, but the human experiments we did were so revolting, our volunteers complained so bitterly of the smell and the taste that this was not pursued. In 1955, Mr Lazell, obviously affected by the numbers of the new antibiotics that were appearing on the scene, considered that if we were to go anywhere in this business we had to be in the antibiotic field. The senior consultant to the company at that time was Sir Charles Dodds.<sup>99</sup> After a discussion with Mr Lazell, Sir Charles suggested that he should go and talk to Ernst Chain, who was in Rome at that time. Mr Lazell sent his number two, Mr McGeorge, to Rome to talk to Professor (later Sir Ernst) Chain.

Chain's first love was always penicillin<sup>100</sup> and he suggested we should go back to penicillin. He suggested that we should make para-aminobenzyl penicillin and chemically modify it. It's got an amino group, one can do all sorts of things with amino groups if you are a chemist and we did have some quite good chemists. We had no facilities at all for producing para-aminobenzyl penicillin, since at that time we

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<sup>97</sup> Professor David Greenwood wrote: 'A standard strain of *Mycobacterium tuberculosis* often used in antibiotic susceptibility testing as a control'. Letter to Mrs Lois Reynolds, 16 October 1998.

<sup>98</sup> British anti-Lewisite (dimercaprol) – an antidote to lewisite, an arsenical war gas, which caused blistering, used in World War II, with a disagreeable odour typical of mercaptans. A collection of papers, Sir R A Peters and British anti-Lewisite, CMAC/GC/197, is held in the Contemporary Medical Archives Centre of the Wellcome Library. See also Peters R A, Stocken L A, Thompson R H S. (1945) British anti-Lewisite (BAL). *Nature* **156**: 616–619.

<sup>99</sup> Sir Charles Dodds Bt FRS (1899–1973), medical biochemist, first isolated diethylstilboestrol, a synthetic oestrogen, in 1938. See Dickens F. (1975) Edward Charles Dodds. *Biographical Memoirs of Fellows of the Royal Society* **21**: 227–267.

<sup>100</sup> Abraham E. (1983) Ernst Boris Chain. *Biographical Memoirs of Fellows of the Royal Society* **29**: 43–91. A collection of his papers, CMAC/PP/EBC, is held in the Contemporary Medical Archives Centre of the Wellcome Library.

had no fermentation pilot plant and no fermentation facilities. There was no factory and Beecham was virtually non-existent in the prescription medicine field. The first thing to do was to send appropriate colleagues to Rome. One of them is here, Ralph Batchelor; the other, Dr Rolinson,<sup>101</sup> is not unfortunately. Using Chain's pilot plant, they produced quantities of para-aminobenzyl penicillin. These were sent back to Brockham Park and my colleague, Dr Nayler,<sup>102</sup> who unfortunately died a few years ago, was put in charge of a small group of chemists working with para-aminobenzyl penicillin. The obvious thing to do, using Schotten–Baumann techniques,<sup>103</sup> under mild conditions, to acylate it with all sorts of things. This we did for most of 1956 and the early part of 1957.

At the same time we thought it might be useful to make other possibly modifiable benzylpenicillins, such as benzylpenicillins with a methylamino group, hydroxy group, carboxy group, or whatever, on the benzene ring. During the course of that work it was noted by Ralph Batchelor that the assays were throwing up funny results.<sup>104</sup> The microbiological assay was giving a figure of 'x', the chemical assay was giving a figure of '2x'. Now my early training was as an analyst and I didn't like this. It seemed wrong. We thought about it and obviously there were a number of possibilities. It could have been a weakly active penicillin, something like methylpenicillin. After all, a culture medium has plenty of acetate and propionate floating around, and there's no reason why it shouldn't have incorporated those. One suggestion I made, and perhaps it was a good thing that I was totally ignorant of the biochemistry, was that maybe the mould had been trying to make penicillin, but can't make it all, it can only make the nucleus. It has all the necessary bits and pieces to make the nucleus – the valine, cysteine, etc. – without putting on side chains. That was just out of the blue. Could it be that? We thought about it and both my colleague, John Nayler, and I said, 'Well it's simple, all you have to do is add a bit of phenylacetylchloride to the brew to make some penicillin-G and the assay should

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<sup>101</sup> Dr George Rolinson (b. 1926) was Associate Director of Research and Senior Microbiologist at Beecham Pharmaceuticals at Brockham Park, Betchworth, Surrey, from 1955 to 1988. See Rolinson G N. (1998) Historical Perspective: Forty years of  $\beta$ -lactam research. *Journal of Antimicrobial Chemotherapy* 41: 589–603. Dr Rolinson was unable to attend the Witness Seminar, but has seen and commented on the transcript as indicated in the relevant footnotes.

<sup>102</sup> Dr John Nayler FRSC (1927–1993) joined the newly formed Chemistry Department at Beecham Research Laboratories in 1948, and was Head of the Department of Organic Chemistry there from c. 1960 to 1989. Nayler and his colleagues' demonstration of the existence of the penicillin nucleus (6-aminopenicillanic acid) in certain penicillin fermentation solutions led to the synthesis of most of the commercially and clinically important semisynthetic penicillins marketed by Beecham from 1959 to 1972. Nayler's name appears on the majority of the many patents and publications during this period. From Doyle P. (1993) John Nayler, 1927–93. *Chemistry in Britain* 29: 531. See also *Nature* (1959), op. cit. note 88 above.

<sup>103</sup> Dr Peter Doyle wrote: 'The Schotten–Baumann method of acylation was originally developed some 120 years ago for the synthesis of esters by the reaction of acid chlorides with alcohols under alkaline conditions. It was later applied to the synthesis of amides by the reaction of acid chlorides with amines. The method is exemplified in most textbooks of practical organic chemistry.' Letter to Mrs Lois Reynolds, 5 April 1999.

<sup>104</sup> Dr George Rolinson wrote: 'This is not quite correct. The discrepancy between the two assays was noted much earlier by Rolinson and Batchelor, right at the beginning of the work on p-aminobenzyl penicillin in 1956.' Letter to Mrs Lois Reynolds, 8 June 1999. See also note 101 above, page 590.

agree' and that's what happened. We talked about it on the Monday, by the Thursday we had shown that in that culture medium there was something that was probably 6-APA as we now know it. Later on Ralph Batchelor showed more elegantly, using paper chromatography, that you could show the same thing. That was in May 1957. It took us something like six months to see solid 6-APA.<sup>105</sup>

Meantime in the chemistry labs, we were working with more and more concentrated solutions. Various extraction methods were giving us material we could work with. We did not see crystallized 6-APA until later that year, perhaps early the following year. By using simple Schotten–Baumann-buffered reactions we were able to acylate this 6-APA. That went on for some time, all of 1957 and 1958, it was even better when we got the crystalline material, but during the course of that work we came across a number of different properties. One was very interesting. As soon as a sterically-hindered side chain was introduced into a penicillin nucleus, you got resistance to some -lactamases. That was the first clue and it was fairly obvious to continue with that.

At this stage I must pay a tribute to the late Dr Nayler's contribution.<sup>106</sup> It was Dr Nayler who was in charge of the chemistry group and it was mainly his ideas that led to methicillin, to isoxazole penicillins, ampicillin, and later on to amoxicillin, carbenicillin, and most of the other penicillins that we eventually produced. It was his contribution to the chemistry that we have much to be indebted to. We published the work, the initial discovery of 6-APA in January of 1959 and then of course the roof fell in because we were approached by practically every pharmaceutical company in the world. Beecham had nothing, we had no antibiotic factory, we had a small microbiology pilot plant, we had a chemical pilot plant in Brockham Park, we had no sales organization, we had just nothing. Everything had to be created from 1959 onwards. To do that Beecham obviously had to tie up with other companies. I was made Director of Research in 1963, and all this was happening about this time. The company decided to tie up with the Bristol Laboratories in the States and the *quid pro quo* was very simple, they were going to help us into the penicillin-G business. They were going to supervise the building of our factory at Worthing, which they did, and supplied us with strains of organism to produce the penicillin-G. By late 1959, I think it was, I was called in to see the Deputy Chairman. He had had an approach from the Bayer company who had found a way of splitting the side chains from penicillin-G, obviously a much more efficient way of producing 6-APA than trying to brew the thing in culture without any side chain. Obviously then the company had to tie up with Bayer again on a *quid pro quo* basis and

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<sup>105</sup> Dr Peter Doyle wrote: 'I have no doubt that Drs Rolinson and Batchelor were aware of this assay discrepancy while working in Rome with Professor Chain during 1956. However, they certainly did not communicate this problem to myself or Dr Nayler nor as far as I am aware to Professor Chain nor to Dr Farquharson, then Director of Research at Brockham Park. The discrepancy was in fact well known to other workers in the field, particularly in several USA companies, notably Eli Lilly, Pfizer, and Bristol Labs. The speculation that it might be due to the presence of a penicillin without a side chain had also occurred to Japanese workers. However, no-one previous to Dr Nayler and I had thought of proving it by acylating the mixture *in situ* to convert the biological inactive penicillin nucleus to produce biologically active material. It is interesting to speculate that if Dr Nayler and I had been aware of these assay differences earlier, Beecham might have made the discovery of 6-aminopenicillanic acid at a much earlier date than May 1957.' Letter to Mrs Lois Reynolds, 27 October 1999.

<sup>106</sup> *op. cit.* note 102 above.

they supplied us with information about their process which was worked on by my own colleagues at Brockham.<sup>107</sup> By the beginning of 1960 we had the process of producing large quantities of 6-APA, we had the clues that had already led us into what to do with it when we got it, and the whole story went on from there. I don't think there's much more I want to say. I should mention, of course, that apart from Sir Ernst Chain and Sir Charles Dodds, who were our two senior consultants, Sir Ian Heilbron and Professor A H Cook at Imperial College were also our consultants. Later on many other scientists came into the picture, for instance Dr Stewart who's sitting at the back there, so we had the benefit of a lot of advice and for which we were very grateful.

Batchelor: If I can pick up some other points outside the ones that Peter Doyle has made. It's perhaps worth reminding everyone that after penicillin-G and the recognition that by adding a precursor to the fermentation you could get other penicillins, Otto Behrens and his co-workers at Eli Lilly made many such penicillins and published their work in 1948.<sup>108</sup> Penicillin-V was actually one of the penicillins they made in this way but they didn't recognize its special properties. It wasn't until Brandl and Margreiter in 1954 that the acid stability and oral absorption of penicillin-V was recognized. There had been some chemical modification of penicillin-X, p-hydroxybenzyl penicillin by Coghill and his group, which had been published in 1949.<sup>109</sup> This was essentially the situation when we at Beecham came into the picture.

When I first got involved and went to work in Rome, I didn't even know the structure of penicillin or have any other preconceptions about the substance, which as it turned out, was probably a good thing.

People ask what part did Sir Ernst Chain play?<sup>110</sup> I think one of the essential things he provided was the environment for us to work in and he convinced the company we should be allowed to do certain work. Without him I think we would never have discovered 6-APA and developed the semisynthetic penicillins. Another thing about Chain was his enormous enthusiasm – if you weren't enthusiastic, you didn't work with him for long. That, I believe, was another important contribution.

What I do remember clearly was the discrepancy<sup>111</sup> in the antibiotic assays? We were

<sup>107</sup> Dr George Rolinson wrote: 'Perhaps it could be mentioned that enzymatic splitting of a penicillin to produce 6-APA was first achieved in our own laboratories (Beecham Research). The Beecham patent for this process was filed in March 1959; the patent for the Bayer process was not filed until September 1959.' Letter to Mrs Lois Reynolds, 8 June 1999. See also note 101 above, page 591.

<sup>108</sup> Behrens O K, Corse J, Edwards J P, Garrison L L, Jones R G, Soper Q F, Van Abeele F R, Whitehead C W. (1948) Biosynthesis of penicillins. IV. New crystalline biosynthetic penicillins. *Journal of Biological Chemistry* 175: 793–809.

<sup>109</sup> Brandl E, Margreiter H. (1954) Ein saurestabiles biosynthetisches Penicillin. *Österreichische Chemiker-Zeitung* 55: 11–21. Coghill R D, Stodola R H, Wachtel J L. (1949) Chemical modifications of natural penicillins. In Clarke H T, Johnson J R, Robinson R. (eds) *The Chemistry of Penicillin*. Princeton, NJ: Princeton University Press, 680–687.

<sup>110</sup> See Chain's biographical note 5 above.

<sup>111</sup> Dr George Rolinson wrote: 'I introduced the chemical assay myself right at the beginning of our work on p-aminobenzyl penicillin, for the reasons given in my article (Rolinson 1998, op. cit. note 101 above, page 590) and the discrepancy between the chemical and the microbiological assay was clearly apparent in the very earliest fermentation studies long before we began the work on the isolation of p-aminobenzyl penicillin.' Letter to Mrs Lois Reynolds, 8 June 1999.

making p-aminobenzyl penicillin to ship back to the chemists in England, and the discrepancy was noticed because I was very impatient, wanting rapid assay results in order to isolate and purify the material. The bioassay was too slow and so I used a chemical one. It was then we became aware of the discrepancy but kept very quiet about it while still in Rome, obviously for very good industrial and commercial reasons. If we then go on from the initial experiments to which Peter [Doyle] referred, that is acylating some no-precursor broth with phenylacetylchloride and showing that penicillin-G was formed. I can clearly remember taking the chromatograms which had been placed on agar seeded with *Bacillus subtilis* to reveal the presence of any antibiotics, out of the incubator. I thought at the time it had been a very nice experiment with a good clear-cut positive result. I don't believe, however, that there was any great optimism that we might finish up with some useful products or so many useful semisynthetic penicillins. We had already made many derivatives from p-aminobenzyl penicillin, none of which were of any interest. My own personal view is that we really had no conception of what it was going to lead to.<sup>112</sup>

It's worth reminding people that the amount of 6-APA we were dealing with in the fermentation was at the most 0.1 mg/ml and usually rather less. One of the reasons for this low concentration we now know to be because 6-APA reacts very rapidly with carbon dioxide leading to a stable degradation product which Marvin Johnson at Wisconsin identified as his factor VI in his early studies with radioactive tracer studies. This, of course, limits the amount that can be made by fermentation.

There were other limitations imposed by this low concentration of 6-APA, which was responsible for isolation and crystallizing. Peter [Doyle] mentioned the enzymic reactions. Not only was it difficult to recover and purify but we also needed dry, solid 6-APA for some of the chemical reactions needed to make important semisynthetic penicillins – methicillin, for example.

We did look for an organism to remove the side chain and found a penicillin acylase in a *Streptomyces* spp., which was unfortunately both exocellular and penicillin-V specific. However, it did provide a route to 6-APA from which many of the early laboratory samples of semisynthetic penicillins were made.

It was interesting, as Peter [Doyle] mentioned, that Bayer came on the scene with a bacterial culture which was very good at splitting penicillin-G. We then picked this up and developed it on a large scale and it was only a very short time before we were visiting Bayer and putting our own bacterial process, which was a modification of theirs, into production in their factory in Germany.

The situation in the 1950s is interesting, and I think answers one of the questions raised earlier as to whether resistance due to penicillinase (now  $\beta$ -lactamase) was recognized as a problem. I think the answer is that we at Beecham certainly did. When Bristol-Myers became involved with Beecham their interest was commercially orientated to getting a 'new penicillin' to the market as quickly as possible, which was why

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<sup>112</sup> For a contemporary view of the developments between 1956 and 1961 written by another observer, see note 100 above, pages 63–65.



phenethicillin (*Broxil*: Beecham) was the first semisynthetic penicillin to be launched. To those of us at Beecham the slightly later methicillin was the jewel in the crown,<sup>113</sup> because it solved the problem of penicillin-resistant staphylococci, at that time responsible for the closing of many hospital wards. This was when we came to feel we had achieved something worthwhile.

I won't go into any more detail on this, except to say that it is worth noting that this one piece of work led to almost 30 semisynthetic penicillins becoming available to medicine with different uses, ranging from phenethicillin through methicillin, the isoxazoles, ampicillin, amoxicillin, carbenicillin and even the lactamase inhibitors, sulbactam and tazobactam.<sup>114</sup>

It's interesting that just after the publication of the isolation of 6-APA, the *British Medical Journal* carried an editorial on 14 March [1959], which said it was very uncertain about the value of 6-APA and to what it was going to lead.<sup>115</sup> In this context I should just point out that today some 11 000 tonnes of 6-APA is made every year, which among other things is used to make 6500 tonnes of ampicillin, and over 10 000 tonnes of amoxicillin. It's not the first time the *British Medical Journal* has got it wrong, but by the time of the publication of 6-APA those of us at Beecham were already seeing useful compounds in the pipeline.

The total tonnage of semisynthetic penicillin today is in excess of 18 000 tonnes – interesting when we consider the total for cephalosporins, which we shall be talking about later, is only some 5500. Perhaps I should stop at that point and let other people say a few things.

**Booth:** A thing I would ask is you talk about bringing these things on the market. This was before the establishment of the Committee on Safety of Drugs and so on.<sup>116</sup> How did you get your stuff onto the market? Did you just advertise it and let the doctors prescribe it?

**Doyle:** Methicillin was an interesting case. We actually made methicillin in the lab I think it was the May of 1959, and it was on the market in the September of the

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<sup>113</sup> Methicillin, or sodium 6-(2,6-dimethoxybenzamido)-penicillate monohydrate, was first known in Beecham Laboratories as BRL 1241, given the trade name of *Celbenin*. It was discontinued in 1993. op. cit. notes 121 and 169 below. Professor David Greenwood wrote: 'Incidentally, the trade name, *Celbenin*, was formed from the name of C E L Bencard, who was, I think, the Managing Director of the Beecham-associate firm, Bencard, who used to market methicillin and the oral antistaphylococcal penicillin, cloxacillin (*Orbenin*).' E-mail to Mrs Lois Reynolds, 5 November 1999.

<sup>114</sup> See Rolinson (1998), op. cit. note 101 above.

<sup>115</sup> Anon. (1959) The penicillin nucleus. *British Medical Journal* i: 701–702. Professor David Greenwood wrote: 'This *BMJ* editorial was later revealed to have been written by Professor L P Garrod. See Waterworth P M (ed.) (1985) L P Garrod on antibiotics – a selection of his *British Medical Journal* editorials. *Journal of Antimicrobial Chemotherapy* 15 (Suppl. B): 1–46. The editorial cited is reproduced on pages 32–33.' Letter to Mrs Lois Reynolds, 24 March 1999.

<sup>116</sup> See Tansey E M, Reynolds L A. (1997) The Committee on Safety of Drugs. In Tansey E M, Catterall P P, Christie D A, Willhoft S V, Reynolds L A. (eds) *Wellcome Witnesses to Twentieth Century Medicine*, vol. 1. London: The Wellcome Trust, 103–132.

following year and being prescribed. It took about 18 months, a bit less than 18 months. Now as you say, that was before the Dunlop Committee, it was before the Committee on the Safety of Medicines, before thalidomide, I think we did two weeks of toxicity studies. It was very minimal.

Booth: Could you do that now?

Doyle: No, of course you can't. Today, it would take between eight to ten years.

Booth: Which increases the cost enormously.

Dr Geoffrey Asherson:<sup>117</sup> Sheehan makes a great point about patents in this area.<sup>118</sup> Was this work in general protected by a patent? Or was it your knowledge of your process, which rival firms did not have, that enabled you to produce semisynthetic penicillins to advantage?

Doyle: The patent situation was interesting. We were able to take out a patent for crystalline 6-APA which we published all over the world and of course all the materials from it, methicillin, etc. We had a general patent on acylation and then specific patents covering everything that we could think of. So everyone that marketed those products had to pay a royalty. Now synthesis routes were a bit complicated, because Professor Sheehan, as you probably know, had done a lot of work on the synthesis of penicillin-V. He published something like seven papers I think, and in one of the Ciba Foundation symposia he contended that 6-APA would be unstable and couldn't exist.<sup>119</sup> Later on he claimed that he had made 6-APA by his synthetic route and I think he got a patent in the USA for that. I believe that Bristol Laboratories had to pay him a royalty on their marketing of our penicillins, which I thought was a bit puzzling. We got involved in tremendous patents arguments in the United States and on top of that there was an anti-Trust action as well, so it all got rather involved.<sup>120</sup> An extremely good chemist that I had working with me at the time repeated Sheehan's work. He

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<sup>117</sup> Dr Geoffrey Asherson (b. 1929) was Head of the Division of Immunological Medicine at the Clinical Research Centre, Northwick Park Hospital, Harrow, from 1970 to 1995. He was interested in patients who failed to make antibodies and in the control of the immune response.

<sup>118</sup> Dr Geoffrey Asherson wrote: 'John C Sheehan was the first to prepare a fully synthetic penicillin. [In his book] he shows the American side of the story of the semisynthetic penicillins and devotes a lot of space to rival patent claims in which John Peter Clayton and J H C Nayler, then of Beecham's, played an important role. He notes that Beecham "became interested in the penicillin field at just about the time I was finishing my penicillin synthesis" at MIT. Beecham and the American company, Bristol, agreed to join in a venture producing synthetic and semisynthetic penicillins. There was argument over patents between Sheehan and Beecham's which involved processes for preparing and acylating free APA. Part of the argument was that the Sheehan disclosure was "insufficient ...to enable one of ordinary skill in the art to follow the disclosure and produce what Sheehan alleges he obtained".' Letter to Mrs Lois Reynolds, 18 January 1999. See Sheehan J C. (1982) *The Enchanted Ring: The untold story of penicillin*. Cambridge, MA: MIT Press. Quotes above on pages 160, 185.

<sup>119</sup> Wolstenholme G E W, O'Connor C M. (eds) (1958) *Ciba Foundation Symposium on Amino Acids and Peptides with Antimetabolic Activity*. London: J & A Churchill Ltd, 257-258.

<sup>120</sup> See Federal Trade Commission. (1958) *Economic Report on Antibiotics Manufacture*. Washington, DC: Government Printing Office. We thank Dr Alan Yoshioka for drawing our attention to this reference.

tried to repeat it twice, but could not repeat Sheehan's claim to the synthesis of 6-APA. I think that is all I need to say.

Stewart: This is a marvellous, modest account by Peter Doyle and Ralph Batchelor of what was a remarkable series of observations. Although they say that some of it was accidental, a great deal was well planned with astonishing speed. From the time that I first received methicillin, it was like penicillin-G all over again. We were able to see, without the possibility of a balanced trial, that there were cases who were then so ill with penicillinase-forming, highly-resistant staphylococci that one simply had to take a chance. The first cases of septicaemia, osteomyelitis and so on, had to be treated on that basis in 1959, and include some that were treated by Dr Trafford and Dr Douthwaite.<sup>121</sup> This made it quite clear that these drugs had a most unusual level of activity as indeed ampicillin and some of the other semisynthetics had later.

I should comment on Peter Doyle's reference to John Sheehan at MIT. There was a competitive enterprise operating in the USA. The waters are quite murky in some ways at that period, and they were claiming to have isolated 6-APA, or even to have synthesized it. But the practical point was that despite all the talk about this, the only way to do it commercially was the way the Beecham Group did it, and, considering the modest facilities that were described, in a remarkably ingenious fashion very quickly. This opened the door to all kinds of things. It wasn't just a therapeutic advance. It was perhaps the first step forward in strategic biochemical chemotherapy, because we began to understand from this work how it was that certain functional groups could be introduced and would make an enormous difference to spectrum, to allergy, to all kinds of things.

Tyrrell: I'd like just to tell you about a side issue which illustrates what's been said before on the tremendous enthusiasm of Ernst Chain and his belief that penicillin would be the source of all the very best future antibiotics. He was sure that it would also be the source of the best antivirals. He built partly on the work that Shope<sup>122</sup> had done, showing that from fungal cultures you could extract an antiviral substance, which cured mice with the lethal virus infections. To cut a long story short, through work at Merck and elsewhere, it turned out that these fungi were carrying double-stranded-RNA-containing fungal viruses and if you extracted the double-stranded RNA then that would act as an antiviral agent by inducing interferon. It worked beautifully in mice. And Chain was so persuasive that he got Beecham to do a lot of

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<sup>121</sup> Douthwaite A H, Trafford J A R. (1960) A new synthetic penicillin. *British Medical Journal* ii: 687–690. This is the first reported controlled trial of BRL 1241, *Celbenin*.

<sup>122</sup> Richard Edwin Shope (1902–1966) was an American pathologist and virologist, then at the Department of Animal and Plant Pathology of the Rockefeller Institute for Medical Research, Princeton, New Jersey, and the Merck Institute for Therapeutic Research, Rahway, New Jersey. Professor David Greenwood wrote: 'Shope isolated the antiviral from a fungus growing on the "isinglass cover of a photograph of my wife, Helen, on Guam, near the end of the war in 1945". He named the substance 'helenine' – "largely out of recognition of the good taste shown by the mold ...in locating on the picture of my wife".' Letter to Mrs Lois Reynolds, 16 October 1998. See also Shope R E. (1953) An antiviral substance from *Penicillium funiculosum*. *Journal of Experimental Medicine* 97: 601–650, quotes on pages 601, 614–615.

the development work and while Merck were making synthetic poly-IC preparations, he produced biologically produced double-stranded RNA, which protected mice but was too toxic to use in man.

Dr Martin Cole:<sup>123</sup> Ralph [Batchelor] referred to splitting penicillin-V, and I was rather interested in this as a microbiologist and a biochemist. At that time there was a lot of work going on on the microbiological transformation of all sorts of drugs and we wondered whether it might be possible to do microbiological transformation on 6-APA. Hydroxylation of one of the methyl groups would be an example. We started having a look at 6-APA and thought we'll have a protected form of it as well, that is protection on the amino group, for which we'll use benzylpenicillin. We decided to look at some bacteria which we already had in the laboratory; they were in the bacteriologist's culture collection. Within a week or two of starting these experiments we found a strain of *Escherichia coli* which would readily cleave the side chain in penicillin-G. As Peter Doyle said, the Bayer company in Germany discovered a similar thing, and they pipped us to the post on the patent, but I want to illustrate how facile that reaction was. I looked back through my notes and saw that one of these strains of *E. coli* came from Eleanor's [one of the laboratory's technicians] rainwater butt, this was just an environmental strain of *E. coli*. We grew the organism up and I think Ralph Batchelor carried out the reaction. If you collected the cells and suspended them in a 2 per cent penicillin-G solution, they would split that penicillin-G to 6-APA, 95 per cent yield in four hours. Once we had done that, I think it is true to say, Ralph, it had a dramatic effect on the availability of 6-APA. Yes, it's true as Peter says, we couldn't scale these things up readily, we didn't have the facilities, we looked to others to do this. I don't know whether either of you [Doyle or Batchelor] can confirm this, but I do remember those who were designing our factory at Worthing were very unhappy about the idea of having to change the design from a direct 6-APA fermentation process using *Penicillium chrysogenum*, to having to have a double fermentation process, one to make penicillin-G and then another to grow up the *E. coli* to knock off the side chain to make the 6-APA, but maybe they would like to comment on that?

Batchelor: That's absolutely right, what Martin says. Eleanor was actually one of the technicians in the lab and it was her water butt that it came from, but what is interesting is that we worked very quickly, within five months. It was the week before Christmas that that reaction was spotted, and by May the next year we had made enough 6-APA to be ready for the marketing of methicillin. Without that material, we wouldn't have been able to market methicillin at the time, and I remember when we first ran the pilot plant production with this and I was there directing operations and even had my boss working for me at the time, turning knobs and controlling pH. We

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<sup>123</sup> Dr Martin Cole (b. 1933) joined the Department of Microbiology, headed by Dr G N Rolinson, at Beecham Research Laboratories at Brockham Park, Betchworth, Surrey, in 1958. He became Head of the Biochemical Services Department and then Research Coordinator, until 1990. See Cole M. (1980) ' -Lactams' as -lactamase inhibitors. *Philosophical Transactions of the Royal Society of London B* **289**: 207-223.

finished up, as one of the shift workers said, 'We had more 6-APA in our fingernails at the end of the reaction, than we normally made in a week's production' and I was collecting the *E. coli* cells in a Sharples super centrifuge. Health and Safety at Work Regulations didn't exist in those days, and the easiest way to get it out was to put one's hand down the tube of the Sharples and get up the *E. coli* sludge. What's interesting, of course too, are the things that 6-APA has led to, and it's a pity that Malcolm Lilly<sup>124</sup> is not here, but of course with his collaboration Beecham devolved an immobilized enzyme system for this, which I think was probably the first commercial immobilized enzyme used on a large scale, and all of that 6-APA that I was talking about is now made all over the world using immobilized enzyme technology and very efficiently.

From the floor: His pilot plant is in the Science Museum on display.

Booth: I wonder if I could ask the clinicians present to talk about the impact of these. What I remember so well of that period is being able to give penicillin by mouth. This was a fantastic change from having to give injections, particularly to children.

Stewart: This of course was the substitution of the  $\beta$ -carbon atom which conferred acid stability. It had been apparent before, but this was what made such an enormous difference in treating children with the semisynthetic penicillins generally. There were two advantages for the price of one, because along with those substituents there were also possibilities of hindering, if that is the word, the attachment of  $\beta$ -lactamase to penicillin. In terms of the structure–activity relationship, this was an enormous breakthrough. But clinically, the other point was that, although not to quite the same extent, the new derivatives lacked the toxicity of penicillin-G, being substances which reacted on muramic acid in cell walls.<sup>125</sup> Since there is no counterpart in mammalian cells, these penicillins were virtually non-toxic, quite unlike almost all the other antibiotics, though subject a year later to a totally different chain of resistance patterns in previously sensitive bacteria.

Batchelor: I think it's interesting to realize that those of us involved certainly thought that methicillin was a good compound, although we would have liked one a bit more active, and quickly found one. My own memory is that of course we had the mixture of isomers of ampicillin, before we had the D(-) form which effectively doubled the activity. I still believed then that many of us felt that if it perhaps was an interesting

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<sup>124</sup> Professor Malcolm Lilly FRS (1936–1998) was the first British Professor of Biochemical Engineering at University College London, from 1979 until his death in 1998. He was unable to attend the Witness Seminar and sent a three-page contribution, which was circulated at the meeting. '...In 1964 I decided that one of the enzymes I wanted to work on was penicillin acylase (or penicillin amidase) which was the enzyme which was able to remove the side chain from benzyl penicillin and which Beecham's routinely grew in very large fermenters. They would then use the whole microorganism to carry out the conversion of benzyl penicillin to 6-aminopenicillanic acid as a single batch process...'. Letter to Dr Tilli Tansey, 12 May 1998. The full text will be deposited with the tapes, correspondence and other documentation from the Witness Seminar in the Contemporary Medical Archives Centre of the Wellcome Library.

<sup>125</sup> For a description of the characteristics of muramic acid, see note 10 above, pages 89, 92–93.

compound, and we would have liked it to have been more active. I think it was very much marketing pressure from Bob Wilkins that pushed ampicillin along the road and it is interesting to consider how much marketing has affected things around the world. This is perhaps not the place to talk about it, but it's interesting to look at dosages around the world, and what is the right dosage in one country isn't the right dosage in another.<sup>126</sup> Clinical practice is quite different. It's interesting to think that when I gave you those figures for semisynthetic uses, China has virtually no semisynthetic penicillin usage, just a little ampicillin sodium by injection, even though it's the largest producer of penicillin-G. There's no ampicillin or amoxycillin orally really to speak of at all. So it's interesting to think about that when we come to talk about resistance later on today. But I think there's certainly an effect of marketing on what has happened with these things.

**Booth:** Doctors are very gullible aren't they?

**Batchelor:** They are not only very gullible. We heard earlier that they are very conservative, and I can remember how difficult it was to convince them that you could use amoxycillin three times a day because they all wanted to stick to four times a day and in some countries it is actually used as infrequently as twice a day.

**Booth:** Now there must be somebody here from the clinical side who has some comment to make on that. I am just intrigued to know that at that stage marketing was a crucial thing and it must be what determined what practice was in the hospital. There was no accepted practice or was there? There were no infection committees in those days or were there?

**Batchelor:** Can I just add one other thing? One of the things that was always said was the desire to have a narrow-spectrum antibiotic, a rifle rather than a shotgun. It's interesting to consider that we did develop something like a rifle for the gram-negatives, temocillin, which was singularly unsuccessful in the market place and maybe the medical profession say they want a rifle, but they prefer the broad spectrum.

**Booth:** I do remember at Hammersmith certainly that our late-lamented friend, Mary Barber,<sup>127</sup> was very much involved in guidance over antibiotic usage through the 1960s until her unfortunate death. I think she must have died in 1965. But what was the position when she was there? Did she run a policy on antibiotics? Pamela [Waterworth], can you answer that? Did she run a policy for the clinicians on the use of antibiotics? Was advice given?

**Waterworth:** Oh yes, extensively. Graham Ayliffe should answer that. He was working with her then.

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<sup>126</sup> Dr Batchelor wrote: 'Generally the UK and USA work to a minimum effective dose while Germany would recommend a maximum tolerated dose.' Letter to Mrs Lois Reynolds, 24 March 1999.

<sup>127</sup> See biographical note 9 above.

Ayliffe:<sup>128</sup> Yes, I think we are now going into the problems of resistance at this stage, but in about 1957 Mary Barber was perhaps the first person in the country to introduce an antibiotic policy for most of the hospital [Hammersmith]. In this policy she reduced or tried to eliminate the use of penicillin apart from a few conditions such as endocarditis, to reduce the use of antibiotics as much as possible, and to give all antibiotics in combination. This was actually followed by a reduction in the numbers of penicillin-resistant strains of *Staphylococcus aureus* isolated. She mainly used erythromycin and novobiocin as a combination therapy, and resistance didn't emerge for a while, but gradually, over the years, it did. When methicillin appeared this policy was no longer needed. But she still had a written policy which she enforced with a hand of iron in Hammersmith Hospital as long as she was there.<sup>129</sup>

Dr Tilli Tansey:<sup>130</sup> Did she develop that because of her concern about resistance? And were other people influenced by her decision, or was she alone in doing this?<sup>131</sup>

Ayliffe: No, I think there were a number of others who were also worried about resistance at that time. In particular, Edward Lowbury was working on burns patients in Birmingham.<sup>132</sup> He found in the 1950s that resistance emerged rapidly to tetracycline, erythromycin and novobiocin and there was really little else left at that time for treating systemic staphylococcal infections.<sup>133</sup> The use of combinations only delayed the onset of resistance.

Booth: I think so far as individual clinicians were concerned, and Mary Barber, there was little doubt that you did what you were told or else. She was a very persuasive person.

Tyrrell: The Northwick Park Hospital was being designed about the time these things were going on and there were two other things which were mentioned and thought

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<sup>128</sup> See biographical note 84 above.

<sup>129</sup> Professor Gordon Stewart wrote: 'In retrospect, and with all respect to Mary Barber, I would like to make the point that, despite freewheeling, there was always an antibiotic policy with penicillin from 1944 onwards in the UK. This was partly because of shortage, but also because it soon became apparent that staphylococci, coliforms and gonococci became resistant to alternative drugs. The problem became acute in 1954 in many major clinical centres internationally. The use of antituberculous drugs from 1952 onwards was also strategic.' Letter to Mrs Lois Reynolds, 14 October 1998.

<sup>130</sup> Dr Tilli Tansey is Convenor of the History of Twentieth Century Medicine Group and Historian of Modern Medical Science, Wellcome Institute for the History of Medicine, The Wellcome Trust.

<sup>131</sup> Miss Pamela Waterworth wrote: 'I think that Professor L P Garrod was the first to try to prevent resistance developing, by limiting the use of new drugs when they first became available. He saw that the indiscriminate use of these, when they were introduced rapidly, led to untreatable infections so when the manufacturers brought him a new drug he put pressure on them not to push its use, but to hold it in reserve for genuine emergencies. When the next antibiotic arrived the last was released. This continued until methicillin arose, and was undoubtedly the main reason why resistance rates in this country were, at that time, lower than in most others.' Letter to Mrs Lois Reynolds, 9 October 1998.

<sup>132</sup> Professor E J L Lowbury (b. 1913) was Head of Bacteriology at the Medical Research Council Industrial Injuries and Burns Unit at the Birmingham Accident Hospital from 1949 to 1979; Honorary Director of the Hospital's Infection Research Laboratory from 1964 to 1979; and Honorary Professor of Medical Microbiology at the University of Aston from 1979. He was unable to attend the Witness Seminar and sent reminiscences to Dr Tilli Tansey, dated 14 April 1998, which will be deposited with the tapes, correspondence and other documentation from the Witness Seminar in the Contemporary Medical Archives Centre of the Wellcome Library.

<sup>133</sup> Lowbury E J L, Topley E, Hood A M. (1952) Chemotherapy for *Staphylococcus aureus* in burns. *Lancet*: 1036–1042.

about, but some of them never eventuated. One was the importance of isolation of people who are producing and shedding organisms which are resistant. We were in favour of having isolation rooms in the hospital, but this was very unfashionable and thought to be retrograde. The days when you had to worry about infection were in the past and not something which the 1970s hospital needed to concern itself with!

Another thing which I remember discussing with Robert Blowers<sup>134</sup> was to try and get someone to study, in a rigorous way, the effects of different concentrations and durations of antibiotic treatment. I don't think anybody ever took that very seriously, but the point was that we felt that prolonged treatment was likely to induce prolonged selection of drug-resistant organisms, and that often the standard durations of treatment were rather pulled out of the hat, or were the ones that had been used for the last drug. They weren't actually ascertained by careful study of the patients – and I think that's a message for the present as well.

Lambert: Just to back up David Tyrrell on that point, I think there has been an extraordinary gap in this whole field. In the recent Select Committee of the House of Lords on antibiotic resistance,<sup>135</sup> one of the special points made was the extraordinary ignorance about dosage duration and dose interval, in which there are quite superficial leaps from bits of pharmacokinetics to clinical implications. After the initial trials which get the drugs through the Committee of Safety on Medicines, these aspects are never taken up again. It is still a very fundamental gap in our knowledge of how to use these drugs.

Mitchison: Can I make one comment about Mary Barber and her interest in staphylococci, because I was trying to organize a record system using computers for the first time. The reason for doing this was Mary wanted her records solely in terms of staphylococcal infections, whereas the other clinicians and bacteriologists wanted them in different forms. But it is true that there was this initial concentration on staphylococci that later, of course, expanded to gram-negative organisms.

Dr Basil Bard:<sup>136</sup> I would like to make a point about [Ernst] Chain. He once said to me that he would not have been able to do his work today because of the impurities in his non-lethal drugs, but he insisted that no-one came to any harm over this.

Booth: Chain was a remarkable man and I remember his enthusiasm. He once took me round his newly founded department at Imperial College after he came back from

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<sup>134</sup> Dr Robert Blowers FRCP FRCPath was Head of the Division of Hospital Infection and Microbiology at the Clinical Research Centre at Northwick Park Hospital, Harrow.

<sup>135</sup> *op. cit.* note 4 above.

<sup>136</sup> Dr Basil Bard (b. 1914) was called to the Bar in 1939, joining the staff of the Coal Commission in 1940. During the war he served with the Ministry of Supply from 1941 to 1943 and the Ministry of Aircraft Production from 1943 to 1945. In 1945 he joined the Confederation of British Industry, moving to the newly established National Research and Development Corporation in 1949. He was Managing Director of the NRDC from 1972 until his retirement in 1975.



Rome, and showed me six huge fermentation vats and said he was very proud that he was the only professor of biochemistry in the country that had such a department. It was based on what you had all been doing.

We are going to move on now firstly to cephalosporins, and resistance in bacteria. Bugs come from all sorts of funny places. I remember when Rank Hovis McDougall were trying to manufacture protein from a microorganism. They went all over the world looking for a bug and finally found it in a small quarry just down the road from the factory near Darlington. Cephalosporins don't quite have that story, but there is something of that in it and we were going to ask Dr Basil Bard, but he is going to ask his son to speak for him.

Bard: That's correct. I am going to ask my son to deliver my script, as I am not able to do so myself. I would just like to make a point that Austin Bide<sup>137</sup> was the chap with whom I had to negotiate at Glaxo, because he was in charge of the patents at that time, and he eventually became Chairman, which was very considerate of him.

Prepared text read by Dr Basil Bard's son, Nicholas Bard: I first came into contact with the cephalosporins in 1953, when I was at NRDC. I had been invited to Professor Florey's laboratory at Oxford to check up why he had not received 25 grams of cephalosporin-C: they should have been delivered to him from a Professor Brotzu<sup>138</sup> in Sardinia, but appeared to have 'not been received'.

It was Professor Brotzu who had first discovered cephalosporins,<sup>139</sup> in 1952; he found that the technology was too difficult for him in Sardinia, and he passed it over to Professor Florey at Oxford. Cephalosporin-C was a fraction of the result, the others being penicillins,<sup>140</sup> and so was really unknown. We circulated information to the industry, and found that only Glaxo had the resources to develop and produce cephalosporin-C; accordingly, we granted them a worldwide licence to do so.

Glaxo insisted on doing this at their expense, although NRDC was quite willing to pay the cost. The American firm Eli Lilly said that they wished to participate in the development of cephalosporin-C, and we permitted them to do so, granting them a non-exclusive licence, (a) which excluded the United Kingdom and other British and Commonwealth territories; (b) on terms that they were to hand over their results to Glaxo, and license Glaxo to utilize those results. We described this as a 'penicillin in reverse' agreement.

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<sup>137</sup> Sir Austin Bide Kt FRSC (b. 1915), Honorary President of Glaxo Holdings plc since 1985, was unable to attend the Witness Seminar.

<sup>138</sup> Professor Guisepe Brotzu isolated an aerobic mould from the sea, near a sewage outfall in Sardinia, which eventually yielded cephalosporin. See Brotzu G. (1948) Ricerche su di un nuovo antibiotico. *Lavori dell' Istituto d'Igiene di Cagliari*, 1-11.

<sup>139</sup> Professor David Greenwood wrote: 'Brotzu isolated the mould that was eventually shown to produce cephalosporin-C in July 1945, as he makes clear in his original paper.' Letter to Mrs Lois Reynolds, 24 March 1999.

<sup>140</sup> Professor David Greenwood wrote: 'Three components were eventually found to be present: cephalosporin-N, a penicillin; cephalosporin-P, a steroid-like antibiotic; and cephalosporin-C, a minor component of the antibiotic complex first detected by E P Abraham of Oxford.' Letter to Mrs Lois Reynolds, 16 October 1998.

A consequence of this was that Eli Lilly discovered a commercial route to cephalosporanic acid: whereas Professor Abraham<sup>141</sup> at Oxford had earlier identified this material, and had discovered a theoretical route which only yielded 1 per cent production, Eli Lilly's route could achieve production of 80 per cent. Cephalosporanic acid had two points where groups could be attached, and so it was possible to make cephalosporins which were highly selective, e.g. for eyes, or for taking in materials orally instead of by injection.

In 1957, both Glaxo and Eli Lilly produced their materials for the market, cross-licensing one another. We did not find that either the difficulties of licensing, or the relatively unknown material, was viewed by the industry as inhibiting. We soon had, in addition to the British and American licensees, a Swedish licensee and a Japanese licensee, to whom we explained that they could evolve their own cephalosporin product and secure patent rights on it, and need only pay us 4 per cent for the privilege – although we charged progressively higher rates for the option and licence. This work was supervised by Sir Howard Florey, Sir Robert Robinson<sup>142</sup> and Sir Charles Dodds.<sup>143</sup>

I always had confidence in the cephalosporins and felt sure that they would find their place in medicine, because they were uniquely resistant to penicillinase. The consequences of this project for NRDC and Oxford University were receipt, over the years, of a wholly unprecedented £125 million in royalties, together with widespread recognition for both these institutions and the principal individuals involved.

Booth: Well, that's a very clear account. Thank you very much indeed, Dr Bard. I wonder if Dr Stewart would like to carry on at this point.

Stewart: The story of cephalosporins<sup>144</sup> is in its way, I suppose, quite as interesting, quite as complicated, and quite as romantic, as that of the penicillins. I have been asked to talk about the cephalosporins and I am very glad to do so, but before embarking on it I should regret the absence of one person perhaps more than any

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<sup>141</sup> Professor Sir Edward Abraham Kt CBE FRS (1913–1999) was largely responsible for the purification of penicillin and describing its chemical structure, the discovery of the enzyme penicillinase and the isolation of the antibiotic, cephalosporin-C. He was Professor of Chemical Pathology at the Sir William Dunn School of Pathology, University of Oxford, from 1964 until his retirement in 1980, when appointed Emeritus. He founded the Edward Penley Abraham [EPA] Research Fund and the EPA Cephalosporin Fund Lectures with part of his personal share of the cephalosporin royalties. He was unable to attend the Witness Seminar. See Anon. (1999) Sir Edward Abraham. *The Times* (12 May 1999), 21. A video interview with Sir Edward Abraham, conducted by Professor Richard Thomas, is in the archives of the Biochemical Society.

<sup>142</sup> Professor Sir Robert Robinson Kt FRS (1886–1975), chemist, was Waynflete Professor of Chemistry at the University of Oxford from 1930 until his retirement in 1955. During the war he became involved in the development of penicillin, publicly supporting one view of its chemical structure. He was President of the Royal Society from 1945 to 1950 and received the Nobel Prize for Chemistry in 1947 for his work on the chemistry of natural products. See Todd A R, Cornforth J W. (1976) Robert Robinson. *Biographical Memoirs of Fellows of the Royal Society* 22: 415–527.

<sup>143</sup> See biographical note 99 above.

<sup>144</sup> A useful extension can be found in Stewart (1965) op. cit. note 10 above, pages 159–172, 185–191.

other who should be here today and that is Sir Edward Abraham<sup>145</sup> who, with Lord and Lady Florey, and others, notably Norman Heatley,<sup>146</sup> not only confirmed the microbiological activity of the original penicillins and cephalosporins, several of them, but also came very near to a complete chemical identification within a period of two or three years. So we had not only 6-APA in the late 1950s, we also had 7-ACA, 7-aminocephalosporanic acid, the difference being that the penicillin sulphur-containing ring was five-membered, whereas this was a six-membered dihydrothiazine ring, but otherwise a lactam structure very similar to the penicillins, similar in structure, similar in lack of toxicity, similar in action on the muramic acid peptide of the bacteria cell wall. This was fascinating. I came across it, not because of what we now use as the therapeutic cephalosporins, but because of cephalosporin-N, which in fact was a penicillin with a straight side chain with an amino group which foresaw what Peter Doyle and Ralph Batchelor have already referred to, as the widening effects of the spectrum of the basic group on the side chain. This brought into focus the possibility of widening the entire  $\beta$ -lactam spectrum and that has indeed proved to be the case. This was foreseeable in the mid-1950s before there was a therapeutic cephalosporin available, but work proceeded and apart from the wonderful chemical work done by Abraham and Newton,<sup>147</sup> it became possible to work out all kinds of other complex structure–activity relationships and to produce new antibiotics with better, wider spectra which we depended upon for years. But the first two were very disappointing. Cephalothin, which was made by Lilly with a thioenyl side chain, was actually quite disappointing clinically, so an effort was made by Glaxo, who were the other people in the field with the support (I had the same support myself at that time) from the National Research Development Corporation, thanks to Dr Bard. This led to elaboration of the more complex side chain of cephaloridine which was very active indeed, except that it was highly unstable. The reason was quite simple and emerged accidentally. It polymerizes and it is also light sensitive, so the only way to make it for therapeutic use was to grow it under nitrogen in the dark. In patients it was very effective indeed at the right time, because it had combined action against gram-positive cocci and gram-negative bacilli, which made it useful in respiratory infections and in urinary infections, which were becoming an increasing problem as organisms learned to be resistant to ampicillin.

This went on on both sides of the Atlantic intensively, and the support of the NRDC in Britain in making cephalosporins available on a semicommercial basis to interested scientists was, I think, quite unique. They deserve a great deal of belated recognition

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<sup>145</sup> See biographical note 141 above.

<sup>146</sup> Dr Norman Heatley OBE (b. 1911), chemist, who worked with both Chain and Florey, devised a test to determine the strength of penicillin, the 'Oxford unit', also a technique and the equipment in which to grow penicillin. He spent his working life from 1936, except for secondments or sabbaticals, at the Sir William Dunn School of Pathology, Oxford, and from 1942 as a Senior Research Officer, later University Lecturer, until his retirement in 1978. See Heatley N G. (1990) Penicillin and luck. In Moberg C, Cohn Z A. (eds) *Launching the Antibiotic Era: Personal accounts of the discovery and use of the first antibiotics* New York, NY: Rockefeller University Press, 31–41.

<sup>147</sup> Newton G G F, Abraham E P. (1954) Degradation, structure, and some derivatives of cephalosporin-N. *Biochemical Journal* **58**: 103–111.

for what they did. I think we would not have cephalosporins without them, just as we wouldn't know anything else without Brotzu, Florey, and Abraham. The clinical trial started at the medical school of the University of Indiana. Other trials went on in this country and elsewhere, and very soon found their place. The more complex molecular structures offered the possibility for alternative substitutes, and a much wider range of derivatives became available very quickly. We are using many of them still. They keep outpacing each other. It was like the barbiturates in the 1930s and 1940s, the chemists learned how to make permutations and very soon there were all kinds of derivatives with varying usefulness and patents by improvement and what not. Many of these things had a very short life, and I am sorry to say that this was true of the two original cephalosporins, cephalothin and cephaloridine, because they were quickly outpaced.

Other things happened too. It appeared that the allergenicity, which was a problem with the penicillins, did not apply to the cephalosporins. Nothing was quite so allergenic as penicillin-G because it was so extremely reactive, in particular when conjugated with protein. These  $\beta$ -lactams have all kinds of interesting properties outside the therapeutic field. For example, they make wonderful chemical colours, and all kinds of things which have been used in other fields. The cephalosporin molecule appeared able to evade some of the cross-allergenicity. There is some marginal overlap, probably because of minor determinants in the antigenic process, but it's not nearly so bad. Hence cephalosporin came to replace penicillin in highly allergic subjects, although these problems began to be dealt with by the discovery that penicillin could in fact be rendered clear and free from the allergenic protein, and again this was work in which Beecham's played a very, very large part. The other thing was the toxicity. Cephalosporins were nephrotoxic<sup>148</sup> up to a point but that was overcome by chemical changes and then the final problem was polymerization which is an unresearched chapter, because both the  $\beta$ -lactam antibiotics, cephalosporins and penicillins, are highly liable to polymerization. This is a phenomenon in itself (biopolymerization), which played a part naturally in the mode of action in the cell wall and also in the complication of allergy by providing a base to which proteins became linked, during manufacture or clinically.

Professor David Greenwood:<sup>149</sup> I am always fascinated by the way that Lady Luck seems to be hiding in the wings in drug discovery and I think that cephalosporins are a very good example of this. After all, Brotzu published his original description in Italian, in a journal that he is said to have founded for that purpose,<sup>150</sup> and anything more likely to relegate it

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<sup>148</sup> For a description of the nephrotoxicity of cephalosporins, see Selwyn (1980), op. cit. note 68 above, page 109.

<sup>149</sup> Professor David Greenwood (b. 1935) was born in the year that Prontosil, the first sulphonamide, was described. He has been at the University of Nottingham Medical School since 1974 and Professor of Antimicrobial Science since 1989. He held a Wellcome Trust History of Medicine Fellowship for Clinicians and Scientists from October to December 1993.

<sup>150</sup> Professor Greenwood wrote: 'I suspect that the claim may be apocryphal. It is more likely that *Lavori dell'istituto d'Igiene di Cagliari* was an occasional publication, which Brotzu used to document his discovery. *The World List of Scientific Periodicals* (1964) lists a journal with a very similar title – *Lavori dell'istituto d'Igiene dell'Università di Cagliari* with issues from 1940.' Letter to Mrs Lois Reynolds, 24 March 1999. op. cit. note 138 above.

to obscurity can hardly be imagined. It was only through a British contact, Blyth Brooke, a British medical officer who worked in Italy at the end of the war, that the *Cephalosporium* mould was brought to England and drawn to the attention of the Oxford group. Moreover, the antimicrobial activity of the *Cephalosporium* mould that Brotzu discovered was not due to a cephalosporin, it was due to a penicillin and a steroid antibiotic; cephalosporin-C was a very minor component. So I think we should remember that we owe Lady Luck quite a debt of gratitude in this, as in many other discoveries.

**Booth:** If it was found in the penicillin part, why did people go on looking at the cephalosporin side of it?

**Batchelor:** I was just going to say that luck yes, but one has to accept that when Guy Newton and Edward Abraham found an impurity in their penicillins, they recognized cephalosporin-C by its unique effect,<sup>151</sup> so at least they made an observation again and did something about it. I think that's the important thing.

**Dr Leo Hepner:**<sup>152</sup> I wonder if we could have some comments about another feature which follows on from cephalosporin-C and 7-ACA. Dr Bard mentioned cephalosporanic acid, but in fact there were two cephalosporanic acids: 7-ACA and 7-ADCA. The latter was developed by Eli Lilly almost as a way of circumventing the NRDC patent, thereby entering into the cephalosporin business through the back door. Once this 7-ADCA route was established, half the cephalosporin business was removed from the orbit of the NRDC. Perhaps we could hear about this?

**Bard:** I left the NRDC in 1975, and during that time I had no intimation that they [Eli Lilly] had cephalosporanic acid.

**Stewart:** Yes, I am wondering what back door is being referred to, because there were a number of back doors and side doors in this whole industry. It was quite complex. There's no doubt that there were several cephalosporins and of course at that time, since the structure of penicillin itself was in some doubt, the President of the Royal Society [Sir Robert Robinson<sup>153</sup>], for example, thought that it was a oxazolone and not

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<sup>151</sup> Professor Greenwood wrote: 'Because it was found to be stable to staphylococcal  $\beta$ -lactamase, which was causing increasing problems in the treatment of staphylococcal infections at the time.' Letter to Mrs Lois Reynolds, 16 October 1998. Professor Greenwood later wrote: 'Professor Sir Edward Abraham has made this clear in print on several occasions. A suitable reference would be Abraham E P. (1990) Oxford, Howard Florey, and World War II. In Moberg C L, Cohn Z A. (eds) *Launching the Antibiotic Era*. New York: Rockefeller University Press, 19–30. See page 29 for the statement about resistance to staphylococcal penicillinase.' Letter to Mrs Lois Reynolds, 24 March 1999.

<sup>152</sup> Dr Leo Hepner (b. 1930) has been a management consultant in fermentation biotechnology since 1970. He founded the biotechnology journal, *Process Biochemistry*, in 1965 and has established extensive contacts with companies and personalities involved in the area of penicillins and cephalosporins.

<sup>153</sup> Clarke H T, Johnson J R, Robinson R. (eds) (1949) *The Chemistry of Penicillin*. Report on a collaborative investigation by American and British chemists under the joint sponsorship of the Office of Scientific Research and Development, Washington DC, and the Medical Research Council, London. Princeton, NJ: Princeton University Press. op. cit. note 142 above. See also Sheehan J C. (1982), op. cit. note 118 above, pages 92–122.

a ring structure at all and that held things up for quite a long while, because people don't usually go round contradicting the President of the Royal Society when he is a chemist. But what became quite clear was the essential antimicrobial activity resided in the 7-ACA derivatives, that what was cephalosporin-N would now be called penicillin-N and it's not really a cephalosporin at all. The essential activity was different from penicillin and quite distinguishable, and belonged to the 7-ACA nucleus and its appropriate side chains. But without the side chains it's like 6-APA, relatively inert.

Lambert: In the early years in which the first cephalosporins were introduced I would have said that there was always an earlier drug – I think David [Greenwood] will back me up on this – which was accessible. Even in those years the problem of resistance was already very much in the forefront of our minds, the effort was already being made to restrict antibiotic usage. Where I worked, mainly at St George's Hospital, for many years our drug policy only included one cephalosporin which was rather rarely used, so I think with reference to the early years, there was very limited extension of the existing range except for certain specific infections, as Professor Stewart has indicated. I wouldn't quite agree with him about allergy. There's enough cross-allergy to make cephalosporins undesirable where there is profound danger like anaphylaxis or angioedema, but where so often the story of allergy is an indefinite or vague or mild one, then of course, they made a lot of difference.

Scott:<sup>154</sup> I started my career in infectious diseases very early on in the 1970s, and oral cephalosporins were just becoming available then, and I do remember that they were being used for some patients with *Staphylococcus aureus* abscesses who were allergic to penicillins. The general feeling was that they were not particularly effective against gram-positive infections, and that feeling has continued all the way through until now. In fact, as new cephalosporins have been developed they have been less and less active against gram-positive infections, and more active against gram-negatives. The other point about them, which is interesting to me from a historical point of view, is that their development and spread was very, very extensive in the United States of America, whereas the penicillins held sway here and that is something which is really quite difficult to understand for me. It must be something to do with marketing or the particular preferences of clinicians or the drug companies and maybe someone here has got some answers to that.

Lambert: I did make an attempt to quantify the point that Geoff [Scott] has just made some years ago by finding from various friends in the industry the tonnage of injectable cephalosporins used in three countries – the UK, Japan and the United States of America – and by simple extrapolation of populations I found, if I remember rightly, that if you counted the tonnage of injectable cephalosporins per patient as one

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<sup>154</sup> See biographical note 94 above.

in the UK, it was eight in the US and 13 in Japan, and I think that there is nothing that I know about epidemiology of infectious diseases which would explain that!<sup>155</sup>

**Bard:** The point that I would like to make, Mr Chairman, is very simple: that we had experience in the UK that, in confirmation of the figures that Dr Lambert has given, there was a bias against cephalosporins in the UK. But on the other hand, we always took the view that they were useful in three conditions: where penicillin didn't work, where it was inactive, and where penicillin was contraindicated.

**Batchelor:** There are actually a number of reasons for this sort of thing and it's certainly not epidemiology. Let's take Japan. The answer is actually very simple why Japan has a very large number of cephalosporins. It's all to do with the reimbursement of doctors, who get a percentage of the cost of the product that they prescribe, and with the way that the Japanese Government works. They reduce prices regularly so that it's the latest product that has the highest price and therefore the doctor prescribes the most recent products, which were developed by Japanese companies, and he gets the most money, so there's a very simple situation in Japan. In the United States there are a number of reasons, it's undoubtedly partly marketing, it's partly historical situations. As an aside, at the moment, semisynthetic penicillins of course, which are very big in the UK and in the USA, are almost zero in Germany because Germany is still a sulphonamide market, it still goes back to the pre-war, so it's quite interesting there, custom and practice come into it. Apart from the marketing strength of different companies, and certainly the US had a very high marketing strength. Beecham was actually relatively weak in the States, Bristol-Myers didn't do as good a job as [Eli] Lilly did, that's one of the reasons. The other reason with some of the newer injectable products, is that there is also prescription by fear in the United States, fear of a lawsuit by the doctor having to face a lawyer that's saying, 'Doctor, did you know that this drug was the latest and most efficient, why didn't you prescribe it to my patient?' and that affects what happens in the United States, and I think you will have to take all of these things into account before you start thinking whether it was the epidemiology or not.

**Eveleigh:** I hope this isn't too frivolous, but just before I left the States to come to this meeting, I phoned Richard Ellander at Bristol-Myers and he commented that the current world sales for antibiotics were \$22 billion, basically the  $\beta$ -lactams were \$12 billion, in other words over half, of which the cephalosporins dominated.

**Batchelor:** That's absolutely right. The actual sales of cephalosporins in dollar terms are higher than the penicillins, that's partly because of the higher price, but another contributory factor is the fact that most of the cephalosporins are injectable, whereas most of the penicillins, particularly ampicillin and amoxicillin, are mainly oral and

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<sup>155</sup> Professor Harold Lambert wrote: 'I made the analysis for a lecture and never published it.' Letter to Mrs Lois Reynolds, 27 March 1999.

the price of injectable products is obviously much higher because the cost of making a sterile product for injection and packaging in that form is actually much more costly than making an oral product. So that's one of the reasons.<sup>156</sup>

Ayliffe: There was another difference. When cephalosporins were first manufactured, cephaloridine was produced in this country and cephalothin was produced in the USA. Cephaloridine was less stable to  $\beta$ -lactamases than cephalothin and less effective for treating staphylococcal infections. This may be another reason why cephalosporins were less frequently used in this country. I wonder if Pamela would like to comment?

Waterworth: I can't remember.

Greenwood: There must be a large element of marketing in all this. At one time cephalexin was the top-selling cephalosporin in the world, a singularly dull and inactive cephalosporin, the most useful property of which is oral absorption. Cephadrine, when it became available, which is identical in any parameter you care to mention, quickly overtook it in the market because the manufacturers brought out a more expensive, injectable form of this well-absorbed compound. In Italy, there is a compound called pivalexin, which is said to be better absorbed than cephalexin (which is 100 per cent absorbed). When I looked up the world literature on pivalexin, I discovered that there was one paper in Italian in which eight patients had been treated.

Booth: We will now move on to discuss resistance and immunity. I wondered if we could ask Professor Naomi Datta if she would be so kind as to start us on our way.

Professor Naomi Datta:<sup>157</sup> Well I will have to move into molecular biology. We've already heard about bacteria mutating to resistance and in the 1950s it was assumed that that was always the way in which bacteria did it. Then there came the publications from Japan,<sup>158</sup> stating that multiple resistance, that is to four unrelated drugs – streptomycin, tetracycline, chloramphenicol and sulphonamides – could be transferred from one

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<sup>156</sup> Dr Ralph Batchelor wrote: 'Actual tonnage of penicillin produced far exceeds the cephalosporin-ampicillin and amoxycillin alone comes to 16 500 tonnes.' Letter to Mrs Lois Reynolds, 14 October 1998. Dr Batchelor later wrote: 'The paragraph ought to end by saying that the tonnage produced and the number of patients treated is, however, the reverse. The actual tonnage of penicillin produced in 1995 was around 24 000 for penicillin-G and 9000 for penicillin-V, of which only *c.* 4000 tonnes of penicillin-G and 1600 tonnes of penicillin-V were used directly as antibiotics in their own right – most of the rest being converted to semisynthetic penicillins and cephalosporins. Over 6000 tonnes each of ampicillin and amoxycillin were made together with over 1000 tonnes of other semisynthetic penicillins. In the same year the total tonnage for all cephalosporins was 4700. The same source gives the US dollar values as \$9.3 billion for cephalosporins and \$5 billion for semisynthetic penicillins, agreeing well with Dr Eveleigh's figure. The reference for my figures is *Penicillin and Cephalosporin Business Reports*, Michael Barber and Associates, 18 Croydon Road, Caterham, Surrey CR3 6QB.' Letter to Mrs Lois Reynolds, 24 March 1999.

<sup>157</sup> Professor Naomi Datta FRS (b. 1922) was Professor of Microbial Genetics in the Department of Bacteriology, Royal Postgraduate Medical School, Hammersmith Hospital, London, until her retirement in 1984, now Emeritus. She had been a member of staff at the Central Public Health Laboratory, Colindale, before moving to the Hammersmith as Assistant Lecturer in 1957.

<sup>158</sup> *op. cit.* note 6 above.



bacterium to another. This possibility was suggested by the isolation of bacteria of different genera, *Shigella* and *Escherichia*, from clinical material, with the same resistance pattern. Evidence was sought by growing resistant *Shigella* in mixed culture with sensitive *E. coli*. From the mixture, resistant *E. coli* was isolated. This was not thought to be very likely by the people with whom I was in contact at Hammersmith. By that time Bill Hayes's MRC Unit on Microbial Genetics was set up in the Hammersmith. Bill, on the assumption that resistance was acquired by mutation, encouraged the use of multiple antibacterial therapy since that should prevent the emergence of resistance.<sup>159</sup> However, in 1959 we had an outbreak of *Salmonella typhimurium* at Hammersmith Hospital and I collected the many isolates. Afterwards, when we were less busy from the results of the epidemic, I went through them looking for variations between the different isolates, and to my great surprise I found that a few were resistant to the three drugs – streptomycin, tetracycline and chloramphenicol. The Japanese had already published their findings, which I probably wouldn't have noticed if it hadn't been that Denny [Mitchison] had pointed out the paper to me.<sup>160</sup>

Booth: He's very good at pointing out papers to people.

Datta: A very useful function. Anyway, having got these ones, I then tried the test. Would they transfer their resistance in mixed culture from a *Salmonella* to an *E. coli*. Sure enough they did. This was really exciting for me personally but also it was very important for molecular biology,<sup>161</sup> because the DNA molecules which had been transferred from one bacterium to another, plasmids as they are called, can be used as vehicles for, well really any genetic material you like to put into them. That's the whole basis of genetic engineering.

Not only was the finding that the plasmids carrying resistance could be transferred from one bacterium to another, but quite soon afterwards it appeared that individual resistance genes could hop from one plasmid to another. We called these transposons. It turns out that in the DNA of all of us here, there are vast numbers of transposons in our chromosomes. So altogether these little findings to do with clinical bacteriology have made a great difference to the understanding of genetics and molecular biology.

Booth: Can I just ask, in terms of resistance clearly these plasmids became important. Could you see them or extract them? How did you know they were there?

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<sup>159</sup> Professor William Hayes FRS (1913–1994) joined the Postgraduate Medical School at Hammersmith Hospital, London, as Senior Lecturer in bacteriology in 1950 and was invited to set up the MRC Microbial Genetics Research Unit there as director, in 1957. In May 1968, on his appointment to a personal chair at the University of Edinburgh, the Unit moved to Edinburgh and was renamed the Molecular Genetics Unit. The Unit closed on Hayes's departure to the Research School of Biological Sciences at the Australian National University in 1974 where he remained until his retirement in 1979. For a description of the discovery of the transmissible plasmid, see Broda P, Holloway B. (1996) William Hayes. *Biographical Memoirs of Fellows of the Royal Society* 42: 171–189.

<sup>160</sup> op. cit. note 6 above.

<sup>161</sup> See Datta N. (1962) Transmissible drug resistance in an epidemic strain of *Salmonella typhimurium*. *Journal of Hygiene* 60: 301–310.

Datta: Oh, that was very simple, you just grew the mixed culture on a selective medium containing the drug, tetracycline, say, to which resistance was being studied. It's the DNA that's transferred from one to the other. Only DNA. Not protein or RNA at all.

Lambert: I would like to follow Professor Datta directly because the paper which she published, which I have here, gave me one of those extraordinary and vividly exciting moments where fundamental advance in biology links up with one's clinical practice there and then. I'd recently gone from UCH to St George's and we were beginning to see strains, mainly of *Shigella* and *Salmonella*, with multiple resistance to various drugs. I found this intensely mystifying, because we knew that the actual mechanisms of resistance to say tetracycline, sulphonamide, streptomycin, were different one from the other. The idea that they could go as a package was intellectually tormenting me. It didn't make too much difference to patients getting better, but it worried me a lot. My reading of the *Japanese Journal of Experimental Science*<sup>162</sup> hadn't been too fastidious, but I was actually reading the *Journal of Hygiene* religiously and we had here Naomi Datta's transmissible drug resistance in an epidemic strain of *Salmonella typhimurium*, the paper which Naomi has just referred to.<sup>163</sup> I thought it was extraordinarily vivid and it really explained what we were seeing clinically in the wards. As Naomi has said, things have gone on to identify transposons and integrons, and we know a lot more about the way in which bacteria recruit resistant genes and put them into a package which can then act in effect as a virulence factor and be transferred as a whole. But this was the first actual glimmering that we had.

If I might just make one other point. Although the molecular biology has gone on a long way since those years, there is a great deficiency of knowledge about the actual events in the ecosystems in which these transfers take place. Looking back at this paper by Naomi I see that she had the prescience to look at a lot of faecal specimens from stools of patients collected at Hammersmith and found in fact one *Shigella sonnei* and three *E. coli* carrying the same form of multiple resistance. Although this paper is in a prestigious journal of 1962, not many people have done that sort of thing, and it links directly with what we were talking about earlier, that the problem of antibiotic usage is two problems, one of antibiotic use, and the other of control of cross-infection and this still has a long way to go.

Booth: Professor Datta, could I just come back to you. I remember those days and I think I remember that epidemic that you studied. Didn't you call them R factors to begin with? And what did you think they were at the beginning?

Datta: Yes, they were called R factors for resistance factors. Yes, and because of Bill Hayes's unit, I did know a little about genetics. What was already known before the R factors, as we called them, were discovered, was something called the F factor of *E. coli*, fertility factor, and this fertility factor was able to bring about the transfer of genes from one strain of *E. coli* to another. This was the work of Lederberg, and it followed

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<sup>162</sup> op. cit. note 6 above.

<sup>163</sup> op. cit. note 161 above.

on the work of Beadle and Tatum on *Neurospora* about genetic combination in microorganisms.<sup>164</sup> The F factor was transmissible from one bacterium to another. It didn't carry anything with it as a general rule, except itself. In fact, I remember when Bill [Hayes] used to give lectures about the F factor, he would say, 'It's an extraordinary thing that if you put one male into a large population of female bacteria, by the next morning they would all be the males'. And so because that was known already, there was obviously some connection between the F factor and the R factor.

Booth: Transfer of material.

Greenwood: This provoked the famous headline 'Hayes says sex is infectious'.<sup>165</sup>

Ayliffe: Can I give another example of a new plasmid appearing in the late 1960s? *Pseudomonas aeruginosa* was one of the most important causes of infection in burns patients and was resistant to most available antibiotics except polymyxin B and colistin, which were both toxic. Carbenicillin was the first penicillin to be produced which was active against *Pseudomonas* and was a major advance. It was then noticed by Edward Lowbury that *Pseudomonas* strains and other gram-negative bacilli in the unit were resistant to carbenicillin and also to kanamycin, which was not used in the unit at the time.<sup>166</sup> This and other evidence suggested to us that this resistance was probably due to a new plasmid. Professor Richmond<sup>167</sup> transferred resistance to these two antibiotics, and also to tetracycline and ampicillin together and rapidly published the results. This was an important plasmid with an unusual ability to move between species.

Booth: Now can I just get clear in my very thick mind what the plasmid is doing. You have got a ring of DNA that goes from a bacterium to another one and that carries the resistance. I assume that the plasmid must code for an enzyme of some sort which attacks the antibiotic.

Datta: It carries genes determining proteins. Penicillinase is the most obvious one, but there are many others. In tetracycline resistance, some protein prevents tetracycline getting into the cell. In the case of chloramphenicol resistance it's a chloramphenicol transacetylase that inactivates the drug. There are a whole lot of different genes with known functions which are carried on these little molecules.

Booth: Now can that happen in any bacterium, or is it specifically for the four gut bacteria that you were involved with?

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<sup>164</sup> Joshua Lederberg (b. 1925), George Wells Beadle (1903–1989) and Edward Laurie Tatum (1909–1975) shared the 1958 Nobel Prize for Physiology or Medicine for their description of the role of genes in biochemical processes. For F factors and R factors see Hayes W. (1968) *The Genetics of Bacteria and their Viruses: Studies in basic genetics and molecular biology*. Second edition. Oxford: Blackwell Scientific Publications, 746–808.

<sup>165</sup> Professor David Greenwood wrote: 'I am afraid I can give no reference for this headline, though the story was circulating in the late 1960s and was, I believe, true.' Letter to Mrs Lois Reynolds, 24 March 1999.

<sup>166</sup> Lowbury E J L, Kidson A, Lilly H A, Ayliffe G A J, Jones R J. (1969) Sensitivity of *Pseudomonas aeruginosa* to antibiotics: Emergence of strains highly resistant to carbenicillin. *Lancet* ii: 448–452.

Datta: Oh no, staphylococci and streptococci have them too and they are also transmissible.

Mitchison: The one important pathogen in which plasmids don't exist is *Mycobacterium tuberculosis* and that I think is because *M. tuberculosis* doesn't come into contact with other bacteria and so doesn't gain any additional variability, which is what the plasmids are really doing. The other important consequence is that combined treatment works with tuberculosis, because you don't get transmission of multiple resistances, but it works much less effectively when you have plasmid transfection.

The other point I think I should make is because Naomi mentioned transposons. Transposons are the basis of the very good epidemiological classification of different strains of tubercle bacilli. It's where the many copies of the plasmid actually lodge in the tubercle bacillus genome that determines the many million possible combinations of different patterns that you get which remain constant for individual strains.

Booth: What about manufacturers of antibiotics? To what extent was your policy in pursuing newer antibiotics from year to year induced by knowing what was going on about resistance? Did it matter to the way in which you approached your programme?

Cole: Well, the answer to that I think is that it definitely had a major influence on us, but I don't know whether you want to at this point open up the whole subject of  $\beta$ -lactamase inhibitors. Once it became well appreciated and understood that destruction of penicillins by penicillinase was a major resistance mechanism, of course we in the industry were very keen to try and find ways round it. One way, as has been mentioned already, was by selecting molecular structures that had intrinsic stability to these enzymes built in, as in methicillin and isoxazolyl penicillins. But that approach, of course, didn't really apply to the gram-negative bacteria; it was very difficult there to achieve in-built stability to their destructive enzymes. Bearing in mind that penicillinases occurred very widely, and were of all sorts of different types, later to be called  $\beta$ -lactamases, because of their great variety, and the fact that some attacked the cephalosporins as well, this led to the thought that maybe one could have an approach of using an additional substance to inhibit the enzyme. As Edward Abraham's name has been mentioned already, I thought I would just read to you one little snippet here, a rather profound thought that he had which he published in 1972. He said, "The irreversible inactivation of a  $\beta$ -lactamase by an appropriate substrate, though more promising in principle than competitive inhibition as a method of mitigating the contribution of these enzymes to bacterial resistance, is at present more remote from

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<sup>167</sup> Sir Mark Richmond Kt FRCPATH FRS (b. 1931) has been a member of the School of Public Policy at University College London since 1996. He was Group Head of Research of Glaxo Holdings from 1993 to 1995. From 1990 to 1994, he was Chairman of the Science and Engineering Research Council, having been Professor of Bacteriology at the University of Bristol from 1968 to 1981, and Vice-Chancellor and Professor of Molecular Microbiology at the University of Manchester from 1981 to 1990. He was unable to attend the Witness Seminar. See Sykes R B, Richmond M H. (1970) Intergeneric transfer of a  $\beta$ -lactamase gene between *Pseudomonas aeruginosa* and *E. coli*. *Nature* 226: 952-954.

practical application'.<sup>168</sup> What he was getting at was there were some examples where one compound could act as a competitive inhibitor and protect another, but he was thinking that what would be nicer would be if the inhibitor actually inactivated the enzyme, but that really wasn't known at that time.

I think he was the first to observe that cephalosporin-C was actually a  $\beta$ -lactamase inhibitor. That was in 1956, and a few years later George Rolinson and Ralph Batchelor found that methicillin actually acted as an inhibitor also.<sup>169</sup> And of course having discovered methicillin, it was natural to then look at the isoxazolyl penicillins and some of those were really very good, like cloxacillin. Cloxacillin was very extensively investigated in combination with ampicillin; the combination *Ampiclox* [ampicillin with cloxacillin: Beecham], was quite good against some resistant bacteria, but the effect really wasn't extensive enough to make big claims for enhancing the activity of ampicillin.

So there was still a big need for a better compound and in our labs, at Brockham Park, we thought that as it's well established that certain  $\beta$ -lactam compounds can act as inhibitors, maybe we could screen all the penicillins we had made. Well we had made an awful lot of compounds and by the time that I started looking at them, we had in the cupboards over a thousand semisynthetic penicillins. It was not going to be easy to do biochemical tests on that number of compounds, so we devised an automated procedure. Some of you may remember the Technicon equipment where fluid separated by bubbles of air was pumped along tubes; we adapted that methodology and screened all these compounds. We did in fact find some that were a big improvement, and one we published on, BRL 1437, we had high hopes for.<sup>170</sup> The only trouble was that if you wanted to put it together with something like ampicillin or amoxycillin it wasn't going to be much good. In one of those very quick volunteer studies, I think I swallowed a small amount of it, we discovered that the oral absorption was terrible. So we really didn't make much progress on trying to find an inhibitor from the existing semisynthetic penicillins or even the cephalosporins, although the Glaxo people had a look too and they found one or two of their cephalosporins were quite good inhibitors.

At about the same time we started screening microorganisms to see if they produced  $\beta$ -lactamase inhibitors, after all, cephalosporin-C was a microbial metabolite that had been shown to be an inhibitor, so there was some precedent for microorganisms producing  $\beta$ -lactamase inhibitors. We mounted a substantial screen, using not an

<sup>168</sup> Abraham E P. (1972) *Biosynthesis and Enzymic Hydrolysis of Penicillins and Cephalosporins*. Tokyo: University of Tokyo Press, 74.

<sup>169</sup> Rolinson G N, Stevens S, Batchelor F R, Cameron-Wood J, Chain E B. (1960) Bacteriological studies on a new penicillin – BRL 1241. *Lancet* ii: 564-567. op. cit. note 113 above. See also Abraham E P, Newton G G F. (1956) A comparison of the action of penicillinase on benzylpenicillin and cephalosporin-N and the competitive inhibition of penicillinase by cephalosporin-C. *Biochemical Journal* 63: 628–634.

<sup>170</sup> Cole M, Elson S, Fullbrook P D. (1972) Inhibition of the  $\beta$ -lactamases of *Escherichia coli* and *Klebsiella aerogenes* by semisynthetic penicillins. *Biochemical Journal* 127: 295–308. Professor David Greenwood wrote: 'BRL 1437 (2-isopropoxy-1-naphthylpenicillin) was first described by Martin Cole and his colleagues in 1972. Professor Francis O'Grady and I investigated the activity of this compound *in vitro*.' Letter to Mrs Lois Reynolds, 24 March 1999. See Greenwood D, O'Grady F. (1975) Potent combinations of  $\beta$ -lactam antibiotics using the  $\beta$ -lactamase inhibition principle. *Chemotherapy* 21: 330–341.

automated biochemical method in that case, but a simple antibacterial synergy test using *Klebsiella pneumoniae* which was resistant to penicillin-G. If you put in something like methicillin, the methicillin would stop the destruction of the penicillin-G, and now the organism became sensitive to the penicillin-G. This method was devised by Dr Rolinson and we adapted it to the screening of large numbers of organisms.<sup>171</sup> We came up with a *Streptomyces* that produced several extremely potent  $\beta$ -lactamase inhibitors. Later this class of compounds was to be called the olivanic acids. The substances were produced in very small amounts, they were very unstable, and an awful job to isolate. We started to get some information about the properties of these compounds, and there was a hint that they might be  $\beta$ -lactams, because there was a competitive inhibition element in the inhibition of the penicillinases, but we could never isolate enough to do the structural chemistry at that stage.

Then there was an interesting debate that Peter Doyle here may well remember at a meeting we both were at. The cephamycins, the 7-methoxycephalosporins and related compounds, were described by Eli Lilly and by Merck. They didn't mention anything about  $\beta$ -lactamase inhibition by these compounds, but they were novel  $\beta$ -lactam structures and so I remember Peter Doyle saying one day, 'That's what you've got, you've got one of these cephamycins in your *Streptomyces* culture fluid.' Our response to that was not to attempt to get the compounds, which was rather fortunate, but we ordered the culture that produced the substances. Now Eli Lilly had deposited the culture, it was named *Streptomyces clavuligerus* in the American Type Culture Collection, so you could buy it. I think it was \$30 at the time. We purchased the culture and grew it up, with the idea to make these new methoxy-cephalosporins. When we carried out the chromatography on the culture fluid, we found a  $\beta$ -lactamase-inhibitory substance that wasn't a cephamycin nor was it an olivanic acid. What we had found we later called clavulanic acid. So that's how we discovered clavulanic acid and that, of course, was found to be a very good inhibitor of a lot of the penicillinases, but wasn't much good against the cephalosporinases.

Datta: Of course it's important about the penicillinase inhibitor, but then you have to find inhibitors for all the other different proteins that use different resistances. But, of course, penicillinase is a very important one.

Doyle: Talking about luck, and Martin [Cole] has mentioned the luck of picking up that culture, but the other very fortunate thing for us was with clavulanic acid. We wanted to combine it with ampicillin or amoxycillin and it was going to depend on the oral absorption. But first of all it was orally well absorbed and if you looked at the pattern of absorption, it was almost identical with ampicillin. So *in vivo* we had the material [clavulanic acid] there when the ampicillin was also there and that was another stroke of fortune. We knew nothing about that when we started.

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<sup>171</sup> Dr George Rolinson wrote: 'Screening of microorganisms for  $\beta$ -lactamase inhibitors was a programme I initiated myself and I devised the test Dr Cole refers to for the express purpose of doing this work. For the first six months of the programme I carried out the laboratory work myself, single-handed, and I then increased the scale of the work by involving other members of the department and this programme resulted in the discovery of the  $\beta$ -lactamase inhibitors Dr Cole refers to.' Letter to Mrs Lois Reynolds, 8 June 1999. op. cit. note 101 above, page 599.

Mitchison: One of the organisms that produces a potent penicillinase is of course the tubercle bacillus. Now in these days when we have quite a number of multiple drug resistant strains, it would be extremely useful to have a penicillin which worked on these resistant strains. I have been trying to get SmithKline Beecham to do the necessary study of early bactericidal activity, for which the expertise is known, to prove this point. So what one has to say is that here are the chemists doing some very, very useful skilled jobs and the developers at Beecham's failing drastically.

Stewart: All is not lost, Professor Mitchison. There are some things that were left on the shelf or were somehow lost or forgotten. For example, quinacillin, which is a semisynthetic penicillin with a quinoline side chain and unusual activity against tubercle bacilli, as well as being resistant to penicillinase and active against some strains of methicillin-resistant *Staphylococcus aureus* (MRSA). Then there are steroid antibiotics, which include cephalosporin-P<sup>1</sup> and the fusidic acid group, also active against some *Mycobacteria*. The crude cephalosporins, as found by Brotzu and purified by Abraham and his colleagues, therefore had a relatively wide spectrum of activity. There are escape routes for exploration among these rejects, but most of them are probably unsuitable for patenting, because like cephalosporin-N and penicillin-T, they had been messed up by people like me beforehand. They might be of interest otherwise because MRSA, or should I say EMRSA, has a potential for epidemic spread in the community as well as in hospitals, and for causing septicaemias with severe lesions like endocarditis and osteomyelitis. Recent work, mainly in New York, but also in Japan, has identified *mecA* genes in strains of EMRSA, which are prevalent, invasive and come from external sources. Fingerprints of the DNA in these strains, according to Roberts in the New York Hospital, show similarity to 'Archaic strains' in their words.<sup>172</sup> These strains may therefore relate to those which some of us played with in the 1960s, and placed on file with the National Collection of Type Cultures. This is history which may be of relevance to what is going to happen next.

Ayliffe: We seem to be discussing staphylococcal resistance again and perhaps at this stage we should say something about the emergence of MRSA and its subsequent progress. As everyone is aware, the first methicillin-resistant strain of *Staphylococcus aureus* was found by Patricia Jevons at Colindale in 1960,<sup>173</sup> soon after methicillin was introduced clinically. Many more strains were isolated in different countries, such as Denmark, Switzerland, Australia, India, over the next few years. At that time Professor Borowski from Poland, and Professor Ång from Turkey were working with Mary Barber on MRSA at Hammersmith Hospital. On returning to their respective countries, both isolated methicillin-resistant strains before methicillin was available for clinical use. Methicillin-resistant strains spread to many hospitals in this country and were often associated with resistance to tetracycline, erythromycin and novobiocin, although these were rarely used for the treatment of

<sup>172</sup> Roberts R B, de Lencastre A, Eisner W, Severina E P, Shopsis B, Kreiswirth B N, Tomasz A. (1998) Molecular epidemiology of methicillin-resistant *Staphylococcus aureus* in 12 New York hospitals. *Journal of Infectious Diseases* 178: 164–171.

<sup>173</sup> Jevons M P. (1960) 'Celbenin'-resistant staphylococci. *British Medical Journal*i: 124–125. op. cit. note 113 above.

staphylococcal infections after the introduction of penicillinase-resistant penicillins. There was no evidence that these were linked on a single plasmid. In the late 1960s and 1970s, MRSA started to disappear from this country, from Denmark, and Australia and several other countries. The reason for this disappearance remained uncertain. It was thought that the discontinuation in use of tetracycline and possibly streptomycin for acute infections might be a possible reason. When we thought the problem of MRSA was over, new strains emerged again in Australia, the USA, Eire and, in the 1980s in Britain and many other countries. The reason remains unknown. Now they are present in most countries of the world and we are unable to eradicate them, although Scandinavia remains relatively free.

**Booth:** What do clinicians do if they get a MRSA in their wards?

**Lambert:** People do sometimes say that in certain problems of resistance we are already up against the buffers, and in MRSA it's not very far from that, because the accepted reserve drug is vancomycin. Such is the resistance problem that people now talk as if vancomycin is a satisfactory, easy, good drug. In fact, as you well know, Chris [Booth], it's a toxic, difficult, pain in the neck to use and in the last few months, well maybe in the last year, both in Japan and in the States, some vancomycin-resistant strains have been reported. There are some new agents coming along which do have activity, but we are almost on the edge of untreatability.

**Greenwood:** May I just add something to that, because it's often said that vancomycin is the last line of defence against MRSA. Strains of MRSA that are sensitive only to vancomycin (and other glycopeptides) are, in fact, extremely rare. Most strains are sensitive to other agents, including fusidic acid and rifampicin, two excellent antistaphylococcal antibiotics. Some are sensitive to aminoglycosides, macrolides or other agents. Doctors who were practising before antibacterial agents became available – effectively, in the year I was born [1935] – or even in the early days of penicillin, would be astounded by the amount of choice now on offer. Claims that we are now approaching the 'postantibiotic era' need to be seen in this perspective.

**Booth:** If these resistances exist in countries that haven't used these antibiotics, what price the idea that we are constantly being bombarded with, that resistance is the result of misuse of antibiotics, either in human disease or in veterinary animals. What's the answer to that?

**Batchelor:** There's just a couple of points I would make. First of all, I think one has to recognize that resistance is the price one pays for having an antibiotic and using it and it shouldn't be at all surprising, because nature abhors a vacuum and is bound to fill up that vacuum if you do something about it. But it always worries me when one talks about misuse of antibiotics, although it's always that the doctor is accused of misusing it and I think the doctor has one job only, and that is of treating the patient sitting in front of him, that's what his real priority has to be. He can't be thinking about posterity. One talks about veterinary usage. To my knowledge, the usage of



these drugs is much lower than is talked about.<sup>174</sup> What one needs to look at sometimes is at a few other places and I give you one example that I know well. A lot of people from the Green side think that making ethanol from sugar cane is a very good, green, sustainable energy source. What I can tell you is that some professors in Rio were looking at the microorganisms in part of Brazil, and wondered why they found multiple-resistant organisms. The answer was very simple. The people with these open-top fermenters, making alcohol from sugar cane, were actually keeping some of the bacteria away by adding multiple doses of mixed antibiotics like penicillin and streptomycin. So it wasn't surprising that the environment was absolutely filled up with multiple-resistant organisms. So I think we have to look at areas outside medicine for some of the problems.

**Ayliffe:** I think I have said before that resistance has emerged to almost every antibiotic introduced. On discontinuing the use of an antibiotic, resistance usually, but not always, decreases. One of the problems with methicillin resistance is that it is not necessarily related to the use of a particular antibiotic. Cephalosporins are possible selecting agents, but discontinuing their use may be difficult in practice.

Plasmids controlling the resistance to several linked antibiotics also means that discontinuing the use of one of them might not reduce resistance to that agent if the others continue to be used. As already mentioned, we should perhaps rely more on the prevention of cross-infection, and increasing the availability of isolation facilities in hospitals.

**Booth:** Let me just take that point to Professor Datta. Suppose you have a culture of a group of organisms that have a named or chosen plasmid, whatever you might call it. If you just watch that culture in successive cell cultures over time, does a plasmid ever disappear spontaneously, or is it there forever?

**Datta:** It sometimes disappears spontaneously, but they vary very much on how stable they are in these conditions.

**Booth:** And the molecular biologists who use plasmids for genetic engineering, presumably are choosing specifically stable ones, are they?

**Datta:** Yes, and smaller ones are usually more stable than big ones.

**Mitchison:** I think there is a specific point about the TB situation and that is that there is a reasonably good evidence now that if you are taking multiple drugs, as you tend to do in the treatment of TB, and you stop taking them for a bit, and then start again, and stop, and start, you get the emergence of drug resistance, often to all of the drugs being used, more or less simultaneously. It's a slightly unusual

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<sup>174</sup> Dr Batchelor wrote: 'In 1995 only 2 per cent of all penicillin-G and -V produced was used in animal feed.' Letter to Mrs Lois Reynolds, 14 October 1998.

mechanism<sup>175</sup> and I won't go into that, but I think that certainly exists as a mechanism. And the second thing is that these multiple-resistant strains do tend to disappear in the community if you try and get more regular drug treatments. This has been shown to some extent in America where they had a great many of these in the big cities, and particularly in New York, and they put a tremendous amount of money into what they call an outreach programme of actually supervising all the doses of drugs, and I believe they have achieved substantial reduction in drug resistance. It is also shown in places like Hong Kong where they supervise all the drug taking, that they have very little multiple drug-resistant (MDR) tuberculosis. There are however one or two strains that get about in the community that seem to have perhaps exceptionally high virulence, and maybe they are exceptions to this rule that you can get rid of the drug-resistant strains.

Crofton: The WHO has recently done a world survey of countries with drug resistance and correlated it with the TB control in that country, and where there's good TB control you get very much less drug resistance. As Denny [Mitchison] says, it tends to disappear and you are not creating new drug resistance if you are giving group treatment. The other thing that they have shown is that where there is a large number of re-treatment patients, you get more drug resistance.

Hepner: No-one has yet mentioned the problem of the likelihood that drug resistance can be transferred from animals to humans. This has been an ongoing problem in animal husbandry since the late 1960s and early 1970s. In this country the Swann Committee, chaired by Michael Swann, was established to advise about this issue. This resulted in the decision by the UK Government to prohibit the use of dosing low-level antibiotics into animal feed, a custom prevalent all over the world. The Swann Committee Report was only accepted by the European Community after the UK's entry into the European Community.<sup>176</sup> The USA has not accepted the Swann Committee findings, because the FDA has never been able to demonstrate that resistance is transferred from animals to humans. To this day, nobody knows whether this is so. It remains an open question.

Lambert: On that last point, I agree with Dr Hepner that rigorous proof is very hard to come by. There are certain examples which I would particularly mention, *Salmonellas* and trimethoprim, and *Salmonellas* and fluoroquinolones, ciprofloxacin, in which the epidemiological and temporal evidence is extremely persuasive. I think

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<sup>175</sup> Mitchison D A. (1998) How drug resistance emerges as a result of poor compliance during short course chemotherapy for tuberculosis. *International Journal of Tuberculosis and Lung Disease* 2: 10–15.

<sup>176</sup> Agricultural Research Council and Medical Research Council, Joint Committee on Antibiotics in Animal Feeding. (1969) *Report on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine*. Cmnd. 4190. London: HMSO. The Committee was chaired by Professor Sir Michael Swann FRS (Lord Swann from 1981) (1920–1990), of Edinburgh University. The UK entered the European Economic Community along with Ireland and Denmark in 1973, endorsed by a referendum conducted by the Labour Government in 1975. See Mitchison J M. (1991) Michael Meredith Swann, Baron Swann of Coln Denys. *Biographical Memoirs of Fellows of the Royal Society* 37: 446–460. See also Datta N. (1969) Penicillin in poultry feed. *British Medical Journal* iv: 741.

where people get a bit confused is thinking it's a general problem of human pathogens. It's in fact a problem restricted mainly to certain genera, *Salmonella*, *Campylobacter*, enterococci, some *E. coli* and one or two others. It's a specific rather than a general problem.

Booth: Well, I think we've had a very good discussion. We could go on and discuss parasites and malarial resistance as well if we wanted, but I think that's a subject on its own. I would like just to quote from a letter that Tilli Tansey received from Edward Lowbury, who very sadly can't be with us here today. He writes,

'In the battle of human wits against bacterial genes, the bacteria are seen to have the advantage of unvarying obedience to their genetic codes, while sadly our codes of practice are fallible and easily disregarded.'<sup>177</sup>

And I suppose that is true. But I would like to thank everyone who has contributed to these discussions this afternoon.

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<sup>177</sup>Letter from E J L Lowbury to Dr Tilli Tansey, 14 April 1998. op. cit. note 132 above.



Date of discovery and source of the more important antibiotics

| Name                                   | Date of discovery | Microbe   | Source                                    |
|--|-------------------|---|---|
| Penicillin                             | 1929–1940         | <i>Penicillium notatum</i>  | Air, London                               |
| Tyrothricin {gramicidin<br>tyrocidine} | 1939              | <i>Bacillus brevis</i>  | Soil, New York, USA                       |
| Griseofulvin                           | 1939<br>1945      | <i>Penicillium griseofulvum</i> Dierckx<br><i>Penicillium janczewski</i>            | Soil, Dorset                              |
| Streptomycin                           | 1944              | <i>Streptomyces griseus</i>   | Soil, New Jersey, USA                     |
| Bacitracin                             | 1945              | <i>Bacillus licheniformis</i>   | Contaminated wound                        |
| Chloramphenicol                        | 1947              | <i>Streptomyces venezuelae</i>  | Mulched field, Venezuela                  |
| Polymyxin                              | 1947              | <i>Bacillus polymyxa</i>  | Soil, UK and USA                          |
| Framycetin (= neomycin B)              | 1947–1953         | <i>Streptomyces lavendulae</i>  | Damp patch on wall, Paris, France         |
| Chlortetracycline                      | 1948              | <i>Streptomyces aureofaciens</i>  | Soil                                      |
| Cephalosporin-C, -N and -P             | 1948              | <i>Cephalosporium</i> sp.   | Sewage outfall, Sardinia                  |
| Neomycin                               | 1949              | <i>Streptomyces fradiae</i>   | Soil, New Jersey, USA                     |
| Oxytetracycline                        | 1950              | <i>Streptomyces rimosus</i>   | Soil                                      |
| Nystatin                               | 1950              | <i>Streptomyces noursei</i>   | Farm soil, Fauquier County, Virginia, USA |
| Erythromycin                           | 1952              | <i>Streptomyces erythreus</i>   | Soil, island in Philippines               |
| Tetracycline                           | 1953<br>1954      | Prepared chemically<br>from chlortetracycline<br><i>Streptomyces</i> (unidentified) | Soil, Texas, USA                          |
| Novobiocin                             | 1955              | <i>Streptomyces spheroides</i><br><i>Streptomyces niveus</i>                        | Pastureland, Vermont, USA                 |
| Cycloserine                            | 1955              | <i>Streptomyces orchidaceus</i><br><i>Streptomyces gaeryphalus</i>                  | Soil, Indiana, USA<br>Soil, Guatemala     |
| Vancomycin                             | 1956              | <i>Streptomyces orientalis</i>  | Soil, Borneo and Indiana, USA             |
| Ristocetin                             | 1957              | <i>Nocardia lurida</i>  | Soil, Garden of the Gods, Colorado, USA   |
| Kanamycin                              | 1957              | <i>Streptomyces kanamyceticus</i>   | Soil, Japan                               |
| Paromomycin                            | 1959              | <i>Streptomyces rimosus</i>   | Soil, Colombia                            |

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## Post Penicillin Antibiotics – Appendix 2

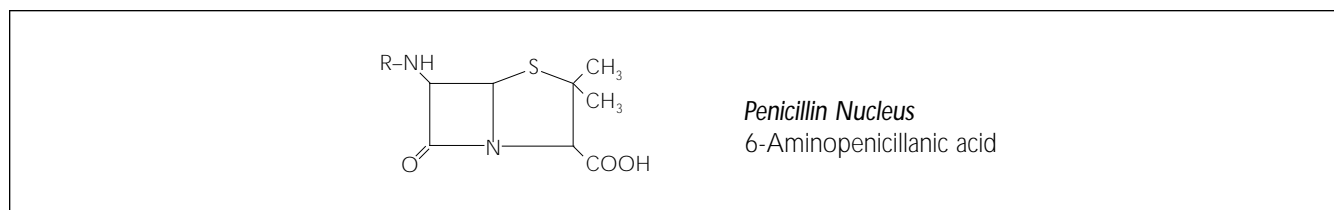
### Selected MRC trials 1944–55

| Date   | Authors   | Title  | Journal,date and pages           |
|--|---|--|----------------------------------|
| <b>i. Trials and reports to the Medical Research Council (MRC)</b> |   |  |                                  |
| 1944   | MRC, Patulin Clinical Trials Committee  | Clinical trials of patulin in the common cold  | <i>Lancet</i> ii (1944): 373–375 |
| 1948   | MRC, Streptomycin in Tuberculosis Trials Committee  | Streptomycin treatment of tuberculous meningitis   | <i>Lancet</i> i (1948): 582–596  |
| 1948   | Smith H V, Vollum R L, Cairns H   | Treatment of tuberculous meningitis with streptomycin. A report to the MRC   | <i>Lancet</i> i (1948): 627–636  |
| 1948   | MRC, Streptomycin in Tuberculosis Trials Committee  | Streptomycin treatment of pulmonary tuberculosis. An MRC investigation   | <i>BMJ</i> ii (1948): 769–782    |
| 1948   | Wilson C [Secretary of the Streptomycin in Non-tuberculous Infections Committee]  | Streptomycin in non-tuberculous infections. Summary of a report to the MRC   | <i>Lancet</i> (1948) ii: 445–446 |
| 1948   | MRC, Pathological Subcommittee of the Streptomycin in Tuberculosis Trials Committee   | Specific laboratory tests in streptomycin therapy of tuberculosis  | <i>Lancet</i> ii (1948): 862–865 |
| 1950   | MRC, Streptomycin in Tuberculosis Trials Committee  | Streptomycin in acute miliary tuberculosis   | <i>Lancet</i> i (1950): 841–846  |
| 1950   | Bignall J R, Clegg J W, Crofton J W, Douglas Smith B J, Holt H D, Mitchison D A, Armitage P   | Intermittent dosage in the treatment of pulmonary tuberculosis with streptomycin. A report to the Streptomycin in Tuberculosis Trials Committee of the MRC | <i>BMJ</i> i (1950): 1224–1230   |
| 1950   | MRC, Joint Subcommittee of the Streptomycin in Tuberculosis Trials Committee and the Research Committee of the British Tuberculosis Association | Treatment of pulmonary tuberculosis with streptomycin and PAS. An MRC investigation  | <i>BMJ</i> ii (1950): 1073–1085  |
| 1952   | MRC, Joint Subcommittee of the Streptomycin in Tuberculosis Trials Committee and the Research Committee of the British Tuberculosis Association | The prevention of streptomycin resistance by controlled chemotherapy. An MRC investigation   | <i>BMJ</i> i (1952) : 1157–1162  |
| 1952   | MRC, Tuberculosis Chemotherapy Trials Committee   | The treatment of pulmonary tuberculosis with isoniazid. An interim report to the MRC   | <i>BMJ</i> ii (1952) : 735–746   |
| 1953   | MRC, Tuberculosis Chemotherapy Trials Committee   | Isoniazid in the treatment of pulmonary tuberculosis. Second report to the MRC   | <i>BMJ</i> i (1953): 521–536     |
| 1953   | MRC, Laboratory Subcommittee of the Tuberculosis Chemotherapy Trials Committee  | Laboratory techniques for the determination of sensitivity of tubercle bacilli to isoniazid, streptomycin and PAS. MRC Isoniazid Trial, Report No. 3       | <i>Lancet</i> ii (1953): 213–217 |

| Date                           | Authors  | Title  | Journal,date and pages  |
|--------------------------------|--|--|---|
| 1953                           | MRC, Laboratory Subcommittee of the Tuberculosis Chemotherapy Trials Committee | Emergence of bacterial resistance in pulmonary tuberculosis under treatment with isoniazid,streptomycin plus PAS, and streptomycin plus isoniazid. MRC Isoniazid Trial, Report No. 4 | <i>Lancet</i> ii (1953): 217–223  |
| 1953                           | MRC, Tuberculosis Chemotherapy Trials Committee                                | Isoniazid in combination with streptomycin or with PAS in the treatment of pulmonary tuberculosis  | <i>BMJ</i> ii (1953): 1005–1014   |
| 1955                           | MRC, Tuberculosis Chemotherapy Trials Committee                                | Various combinations of isoniazid with streptomycin or with PAS in the treatment of pulmonary tuberculosis   | <i>BMJ</i> i (1955): 435–445  |
| <b>ii.Related publications</b> |  |  |   |
| 1944                           | Stansfeld J M,Francis A E, Stuart-Harris C H                                   | Patulin:Laboratory and clinical trials   | <i>Lancet</i> ii (1944): 370–372  |
| 1946                           | Lehmann J  | <i>para</i> -aminosalicylic acid in the treatment of tuberculosis  | <i>Lancet</i> i (1946): 15–16   |
| 1946                           | D'Arcy Hart P  | Chemotherapy of tuberculosis: Research during the past 100 years   | <i>BMJ</i> ii (1946): 805–810; 849–855  |
| 1946                           | Cairns H, Duthie E S, Smith H V  | Intrathecal streptomycin in meningitis: Clinical trial in tuberculous,coliform and other infections  | <i>Lancet</i> ii (1946): 153–155  |
| 1947                           | Smith H V, Daniel P  | Some clinical and pathological aspects of tuberculosis of the central nervous system   | <i>Tubercle</i> 28 (1947): 64–80  |
| 1948                           | Erdei A (with comment by W E Snell)  | Pulmonary tuberculosis treated with <i>para</i> -aminosalicylic acid: Early results in six cases   | <i>Lancet</i> i (1948): 791–793   |
| 1952                           | Daniels M, Hill A B  | Chemotherapy of pulmonary tuberculosis in young adults: An analysis of the combined results of three MRC trials  | <i>BMJ</i> i (1952) : 1162–1168   |
| 1953                           | Ritchie G M, Taylor R M, Dick J C  | The effect of streptomycin and isoniazid on miliary tuberculosis and tuberculous meningitis  | <i>Lancet</i> ii (1953): 419–425  |
| 1953                           | Crofton J  | Desensitization to streptomycin and PAS  | <i>BMJ</i> ii (1953): 1015–1017   |
| 1999                           | Fox W, Ellard GA, Mitchison D A  | Studies on the treatment of tuberculosis undertaken by the British MRC Tuberculosis Units, 1946–86, with relevant subsequent publications  | <i>International Journal of Tuberculosis and Lung Disease</i> 3 (1999): S231–S279 |

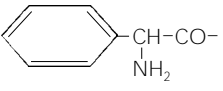
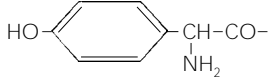
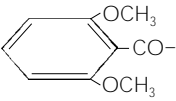
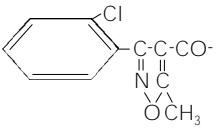
## Post Penicillin Antibiotics – Appendix 3

### Clinically useful penicillins



| Side chain | R= | Accepted name                   | Full chemical name                             | Trade names                       | Important properties |
|------------|----|---------------------------------|--|-----------------------------------|----------------------|
|            |    | <b>Benzyl penicillin</b>        | 6-(Phenylacetamido) penicillanic acid          |                                   |                      |
|            |    | <b>Phenoxymethyl penicillin</b> | 6-(Phenoxyacetamido) penicillanic acid         | <i>Penicillin V</i>               | Acid resistant       |
|            |    | <b>Phenethicillin</b>           | DL-6-( -Phenoxypropionamido) penicillanic acid | <i>Broxil</i>                     | Acid resistant       |
|            |    | <b>Propicillin</b>              | DL-6-( -Phenoxybutyramido) penicillanic acid   | <i>Broclin</i><br><i>Ultrapen</i> | Acid resistant       |
|            |    | <b>Phenbenicillin</b>           | 6-( -Phenoxyphenylacetamido) penicillanic acid | <i>Penspek</i>                    | Acid resistant       |



| Side chain R=   | Accepted name      | Full chemical name  | Trade names                           | Important properties                                   |
|---|--------------------|---|---------------------------------------|--|
|    | <b>Ampicillin</b>  | 6-(D(-)- -Aminophenyl-acetamido) penicillanic acid                          | <i>Penbritin</i>                      | Active against gram-negative bacilli<br>Acid resistant |
|    | <b>Amoxycillin</b> | 6-(D(-)- -Amino-p-hydroxy-phenylacetamido) penicillanic acid                | <i>Amoxil</i>                         | Active against gram-negative bacilli<br>Acid resistant |
|  | <b>Methicillin</b> | 6-(2,6 Dimethoxy-benzamido) penicillanic acid                               | <i>Celbenin</i><br><i>Staphcillin</i> | Penicillinase resistant                                |
|  | <b>Cloxacillin</b> | 6-(5-Methyl-3-ortho-chlorophenyl-isoxazole-4-carboxamido) penicillanic acid | <i>Orbenin</i>                        | Penicillinase resistant<br>Acid resistant              |

# INDEX: SUBJECT

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