

CLINICAL PHARMACOLOGY IN THE UK, c. 1950–2000: INDUSTRY AND REGULATION

The transcript of a Witness Seminar held by the Wellcome Trust Centre
for the History of Medicine at UCL, London, on 25 September 2007

Edited by L A Reynolds and E M Tansey

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Abbreviations

ABPI	Association of the British Pharmaceutical Industry
BMA	British Medical Association
BPS	British Pharmacological Society
CDSM	Committee on Dental and Surgical Materials
CHM	Commission on Human Medicines
CRA	Clinical research associate
CRM	Committee on Review of Medicines
CRO	Clinical research organization
CSD	Committee on Safety of Drugs
CSM	Committee on Safety of Medicines
CTX	Clinical trial exemption
DHSS	Department of Health and Social Security
DoH	Department of Health
FDA	Food and Drug Administration (US)
GMC	General Medical Council
GPRD	General practice research database
GSL	General sales list
ICI	Imperial Chemical Industries
IMP	Investigational medical product
ISIS	International studies of infarct survival
MCA	Medicines Control Agency
MDA	Medical Devices Agency
MHRA	Medicines and Healthcare products Regulatory Agency
MoH	Ministry of Health

MRC	Medical Research Council
NICE	National Institute for Health and Clinical Excellence
OTC	Over the counter
P medicine	Pharmacy medicine
POM	Prescription only medicine
PPRS	Pharmaceutical price regulation scheme
SEAR	Safety and Efficacy, Adverse Reactions Subcommittee of the CSM
TCT	Therapeutics and Clinical Trials Subcommittee
UCH	University College Hospital
UCL	University College London
WHO	World Health Organization

WITNESS SEMINARS: MEETINGS AND PUBLICATIONS¹

In 1990 the Wellcome Trust created a History of Twentieth Century Medicine Group, associated with the academic unit of the Wellcome Institute for the History of Medicine, to bring together clinicians, scientists, historians and others interested in contemporary medical history. Among 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 potential benefits of working jointly, and to encourage the creation and deposit of archival sources for present and future use. In June 1999 the governors of the Wellcome Trust decided that it would be appropriate for the academic unit to enjoy a more formal academic affiliation and turned the unit into the Wellcome Trust Centre for the History of Medicine at UCL from 1 October 2000. The Wellcome Trust continues to fund the Witness Seminar programme via its support for the Centre.

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 come together to discuss, debate, and agree or disagree about their memories. To date, the History of Twentieth Century Medicine Group has held more than 50 such meetings, most of which have been published, as listed on pages xiii–xxii.

Subjects are usually proposed by, or through, members of the Programme Committee of the Group, which includes professional historians of medicine, practising scientists and clinicians, and once an appropriate topic has been agreed, suitable participants are identified and invited. This inevitably leads 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 to initiate and stimulate further discussion.

¹ The following text also appears in the 'Introduction' to recent volumes of *Wellcome Witnesses to Twentieth Century Medicine* published by the Wellcome Trust and the Wellcome Trust Centre for the History of Medicine at UCL.

Each meeting is fully recorded, the tapes are transcribed and the unedited transcript is sent to every participant. Each is asked to check his or her 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 forms assigning copyright to the Wellcome Trust.³ Copies of all additional correspondence received during the editorial process are deposited with the records of each meeting in archives and manuscripts, Wellcome Library, London.

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 will be 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 historians with new insights, fresh material for study, and further 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.

**Members of the Programme Committee of the
History of Twentieth Century Medicine Group, 2008–09**

Professor Tilli Tansey – Professor of the History of Modern Medical Sciences, Wellcome Trust Centre for the History of Medicine at UCL (WTCHM) and Chair

Sir Christopher Booth – WTCHM, former Director, Clinical Research Centre, Northwick Park Hospital, London

Mrs Lois Reynolds – Senior Research Assistant, WTCHM, and Organizing Secretary

Dr John Ford – Retired General Practitioner, Tonbridge

Professor Richard Himsworth – former Director of the Institute of Health, University of Cambridge

Professor Mark Jackson – Centre for Medical History, Exeter

Professor John Pickstone – Wellcome Research Professor, University of Manchester

Dr Helga Satzinger – Reader in History of Twentieth Century Biomedicine, WTCHM

Professor Lawrence Weaver – Professor of Child Health, University of Glasgow, and Consultant Paediatrician in the Royal Hospital for Sick Children, Glasgow

² Sir Iain Chalmers authorizes the Wellcome Trust to publish his work and to report or reproduce it in any form or media, including offprints, provided that it is understood that the Wellcome Trust's right to do so is nonexclusive.

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‘Clinical pharmacology in the UK, c. 1950–2000’ was suggested as a suitable topic for a Witness Seminar by Dr Jeffrey Aronson, who assisted us in planning the meeting. We are very grateful to him for his input and to Professor Rod Flower for his excellent chairing of the occasion. We are particularly grateful to Professor Parveen Kumar for writing such a helpful Introduction to these published proceedings. Our additional thanks go to Professor Desmond Laurence, who read through earlier drafts of the transcript, and offered helpful comments and advice. We thank Dr Jeffrey Aronson and Professor Brian Prichard for their help with the Glossary; and for permission to reproduce images included here, we thank Professor Desmond Laurence and AstraZeneca.

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, and the Medical Photographic Library; Mr Akio Morishima, who has supervised the design and production of this volume; our indexer, Ms Liza Furnival; and our readers, Ms Fiona Plowman, Mrs Sarah Beanland and Mr Simon Reynolds; and Ms Stefania Crowther for editorial and marketing assistance. Mrs Jaqui Carter is our transcriber, and Mrs Wendy Kutner and Dr Daphne Christie assisted us in running this meeting. Finally, we thank the Wellcome Trust for supporting this programme.

Tilli Tansey

Lois Reynolds

Wellcome Trust Centre for the History of Medicine at UCL

HISTORY OF TWENTIETH CENTURY MEDICINE WITNESS SEMINARS, 1993–2008

- 1993 **Monoclonal antibodies**
- 1994 **The early history of renal transplantation**
Pneumoconiosis of coal workers
- 1995 **Self and non-self: A history of autoimmunity**
Ashes to ashes: The history of smoking and health
Oral contraceptives
Endogenous opiates
- 1996 **Committee on Safety of Drugs**
**Making the body more transparent: The impact of nuclear
magnetic resonance and magnetic resonance imaging**
- 1997 **Research in general practice**
Drugs in psychiatric practice
The MRC Common Cold Unit
The first heart transplant in the UK
- 1998 **Haemophilia: Recent history of clinical management**
Obstetric ultrasound: Historical perspectives
Post penicillin antibiotics
Clinical research in Britain, 1950–1980

- 1999 **Intestinal absorption**
- The MRC Epidemiology Unit (South Wales)**
- Neonatal intensive care**
- British contributions to medicine in Africa after the Second World War**
- 2000 **Childhood asthma, and beyond**
- Peptic ulcer: Rise and fall**
- Maternal care**
- 2001 **Leukaemia**
- The MRC Applied Psychology Unit**
- Genetic testing**
- Foot and mouth disease: The 1967 outbreak and its aftermath**
- 2002 **Environmental toxicology: The legacy of *Silent Spring***
- Cystic fibrosis**
- Innovation in pain management**
- 2003 **Thrombolysis**
- Beyond the asylum: Anti-psychiatry and care in the community**
- The Rhesus factor and disease prevention**
- The recent history of platelets: Measurements, functions and applications in medicine**

- 2004 **Short-course chemotherapy for tuberculosis**
- Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth**
- Public health in the 1980s and 1990s: Decline and rise?**
- 2005 **The history of cholesterol, atherosclerosis and coronary disease**
- Development of physics applied to medicine in the UK, 1945–90**
- 2006 **Early development of total hip replacement**
- The discovery, use and impact of platinum salts as chemotherapy agents for cancer**
- Medical ethics education in Britain, 1963–93**
- Superbugs and superdrugs: The history of MRSA**
- 2007 **The rise and fall of clinical pharmacology in the UK, c. 1950–2000**
- The resurgence of breast-feeding, 1975–2000**
- DNA fingerprinting**
- The development of sports medicine in twentieth-century Britain**
- 2008 **History of dialysis, c. 1950–2000**
- History of cervical cancer and the role of the human papillomavirus over the last 25 years**
- Clinical genetics in Britain: Origins and development**

PUBLISHED MEETINGS

'...Few books are so intellectually stimulating or uplifting'.
Journal of the Royal Society of Medicine (1999) **92**: 206–8,
review of vols 1 and 2

'...This is oral history at its best...all the volumes make compulsive reading...they are, primarily, important historical records'.
British Medical Journal (2002) **325**: 1119, review of the series

Technology transfer in Britain: The case of monoclonal antibodies **Self and non-self: A history of autoimmunity**

Endogenous opiates

The Committee on Safety of Drugs

Tansey E M, Catterall P P, Christie D A, Willhoft S V, Reynolds L A. (eds)
(1997) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 1. London:
The Wellcome Trust, 135pp. ISBN 1 869835 79 4

Making the human body transparent: The impact of NMR and MRI **Research in general practice**

Drugs in psychiatric practice

The MRC Common Cold Unit

Tansey E M, Christie D A, Reynolds L A. (eds) (1998) *Wellcome*
Witnesses to Twentieth Century Medicine. Volume 2. London: The Wellcome
Trust, 282pp. ISBN 1 869835 39 5

Early heart transplant surgery in the UK

Tansey E M, Reynolds L A. (eds) (1999) *Wellcome Witnesses to*
Twentieth Century Medicine. Volume 3. London: The Wellcome Trust, 72pp.
ISBN 1 841290 07 6

Haemophilia: Recent history of clinical management

Tansey E M, Christie D A. (eds) (1999) *Wellcome Witnesses to*
Twentieth Century Medicine. Volume 4. London: The Wellcome Trust, 90pp.
ISBN 1 841290 08 4

Looking at the unborn: Historical aspects of obstetric ultrasound

Tansey E M, Christie D A. (eds) (2000) *Wellcome Witnesses to*
Twentieth Century Medicine. Volume 5. London: The Wellcome Trust, 80pp.
ISBN 1 841290 11 4

Post penicillin antibiotics: From acceptance to resistance?

Tansey E M, Reynolds L A. (eds) (2000) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 6. London: The Wellcome Trust, 71pp.
ISBN 1 841290 12 2

Clinical research in Britain, 1950–1980

Reynolds L A, Tansey E M. (eds) (2000) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 7. London: The Wellcome Trust, 74pp.
ISBN 1 841290 16 5

Intestinal absorption

Christie D A, Tansey E M. (eds) (2000) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 8. London: The Wellcome Trust, 81pp.
ISBN 1 841290 17 3

Neonatal intensive care

Christie D A, Tansey E M. (eds) (2001) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 9. London: The Wellcome Trust Centre for the History of Medicine at UCL, 84pp. ISBN 0 854840 76 1

British contributions to medical research and education in Africa after the Second World War

Reynolds L A, Tansey E M. (eds) (2001) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 10. London: The Wellcome Trust Centre for the History of Medicine at UCL, 93pp. ISBN 0 854840 77 X

Childhood asthma and beyond

Reynolds L A, Tansey E M. (eds) (2001) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 11. London: The Wellcome Trust Centre for the History of Medicine at UCL, 74pp. ISBN 0 854840 78 8

Maternal care

Christie D A, Tansey E M. (eds) (2001) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 12. London: The Wellcome Trust Centre for the History of Medicine at UCL, 88pp. ISBN 0 854840 79 6

Population-based research in south Wales: The MRC Pneumoconiosis Research Unit and the MRC Epidemiology Unit

Ness A R, Reynolds L A, Tansey E M. (eds) (2002) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 13. London: The Wellcome Trust Centre for the History of Medicine at UCL, 74pp. ISBN 0 854840 81 8

Peptic ulcer: Rise and fall

Christie D A, Tansey E M. (eds) (2002) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 14. London: The Wellcome Trust Centre for the History of Medicine at UCL, 143pp. ISBN 0 85484 84 2

Leukaemia

Christie D A, Tansey E M. (eds) (2003) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 15. London: The Wellcome Trust Centre for the History of Medicine at UCL, 86pp. ISBN 0 85484 087 7

The MRC Applied Psychology Unit

Reynolds L A, Tansey E M. (eds) (2003) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 16. London: The Wellcome Trust Centre for the History of Medicine at UCL, 94pp. ISBN 0 85484 088 5

Genetic testing

Christie D A, Tansey E M. (eds) (2003) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 17. London: The Wellcome Trust Centre for the History of Medicine at UCL, 130pp. ISBN 0 85484 094 X

Foot and mouth disease: The 1967 outbreak and its aftermath

Reynolds L A, Tansey E M. (eds) (2003) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 18. London: The Wellcome Trust Centre for the History of Medicine at UCL, 114pp. ISBN 0 85484 096 6

Environmental toxicology: The legacy of *Silent Spring*

Christie D A, Tansey E M. (eds) (2004) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 19. London: The Wellcome Trust Centre for the History of Medicine at UCL, 132pp. ISBN 0 85484 091 5

Cystic fibrosis

Christie D A, Tansey E M. (eds) (2004) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 20. London: The Wellcome Trust Centre for the History of Medicine at UCL, 120pp. ISBN 0 85484 086 9

Innovation in pain management

Reynolds L A, Tansey E M. (eds) (2004) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 21. London: The Wellcome Trust Centre for the History of Medicine at UCL, 125pp. ISBN 0 85484 097 4

The Rhesus factor and disease prevention

Zallen D T, Christie D A, Tansey E M. (eds) (2004) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 22. London: The Wellcome Trust Centre for the History of Medicine at UCL, 98pp. ISBN 0 85484 099 0

The recent history of platelets in thrombosis and other disorders

Reynolds L A, Tansey E M. (eds) (2005) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 23. London: The Wellcome Trust Centre for the History of Medicine at UCL, 186pp. ISBN 0 85484 103 2

Short-course chemotherapy for tuberculosis

Christie D A, Tansey E M. (eds) (2005) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 24. London: The Wellcome Trust Centre for the History of Medicine at UCL, 120pp. ISBN 0 85484 104 0

Prenatal corticosteroids for reducing morbidity and mortality after preterm birth

Reynolds L A, Tansey E M. (eds) (2005) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 25. London: The Wellcome Trust Centre for the History of Medicine at UCL, 154pp. ISBN 0 85484 102 4

Public health in the 1980s and 1990s: Decline and rise?

Berridge V, Christie D A, Tansey E M. (eds) (2006) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 26. London: The Wellcome Trust Centre for the History of Medicine at UCL, 101pp. ISBN 0 85484 106 7

Cholesterol, atherosclerosis and coronary disease in the UK, 1950–2000

Reynolds L A, Tansey E M. (eds) (2006) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 27. London: The Wellcome Trust Centre for the History of Medicine at UCL, 164pp. ISBN 0 85484 107 5

Development of physics applied to medicine in the UK, 1945–90

Christie D A, Tansey E M. (eds) (2006) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 28. The Wellcome Trust Centre for the History of Medicine at UCL, 141pp. ISBN 0 85484 108 3

Early development of total hip replacement

Reynolds L A, Tansey E M. (eds) (2007) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 29. London: The Wellcome Trust Centre for the History of Medicine at UCL, 198pp. ISBN 978 085484 111 0

The discovery, use and impact of platinum salts as chemotherapy agents for cancer

Christie D A, Tansey E M. (eds) (2007) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 30. London: The Wellcome Trust Centre for the History of Medicine at UCL, 142pp. ISBN 978 085484 112 7

Medical Ethics Education in Britain, 1963–93

Reynolds L A, Tansey E M. (eds) (2007) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 31. London: The Wellcome Trust Centre for the History of Medicine at UCL, 241pp. ISBN 978 085484 113 4

Superbugs and superdrugs: A history of MRSA

Reynolds L A, Tansey E M. (eds) (2008) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 32. London: The Wellcome Trust Centre for the History of Medicine at UCL, 167pp. ISBN 978 085484 114 1

Clinical pharmacology in the UK, c. 1950–2000: Influences and institutions

Reynolds L A, Tansey E M. (eds) (2008) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 33. London: The Wellcome Trust Centre for the History of Medicine at UCL, 168pp. ISBN 978 085484 117 2

Clinical pharmacology in the UK, c. 1950–2000: Industry and regulation

Reynolds L A, Tansey E M. (eds) (2008) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 34. London: The Wellcome Trust Centre for the History of Medicine at UCL (this volume). ISBN 978 085484 118 9

The resurgence of breastfeeding, 1975–2000

Reynolds L A, Tansey E M. (eds) (2009) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 35. London: The Wellcome Trust Centre for the History of Medicine at UCL (in press). ISBN 978 085484 119 6

The development of sports medicine in twentieth century Britain

Reynolds L A, Tansey E M. (eds) (2009) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 36. London: The Wellcome Trust Centre for the History of Medicine at UCL (in press). ISBN 978 085484 121 9

History of dialysis in the UK: c. 1950–2000

Reynolds L A, Tansey E M. (eds) (2009) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 37. London: The Wellcome Trust Centre for the History of Medicine at UCL (in press). ISBN 978 085484 122 6

History of cervical cancer and the role of the human papillomavirus over the last 25 years

Reynolds L A, Tansey E M. (eds) (2009) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 38. London: The Wellcome Trust Centre for the History of Medicine at UCL (in press). ISBN 978 085484 123 3

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A hard copy of volumes 21–34 can be ordered from www.amazon.co.uk; www.amazon.com; and all good booksellers for £6/\$10 plus postage, using the ISBN.

Other publications

Technology transfer in Britain: The case of monoclonal antibodies

In: Tansey E M, Catterall P P. (1993) *Contemporary Record* **9**: 409–44.

Monoclonal antibodies: A witness seminar on contemporary medical history

In: Tansey E M, Catterall P P. (1994) *Medical History* **38**: 322–7.

Chronic pulmonary disease in South Wales coalmines: An eye-witness account of the MRC surveys (1937–42)

In: D’Arcy Hart P, edited and annotated by E M Tansey. (1998) *Social History of Medicine* **11**: 459–68.

Ashes to Ashes – The history of smoking and health

In: Lock S P, Reynolds L A, Tansey E M. (eds) (1998) Amsterdam: Rodopi BV, 228pp. ISBN 90420 0396 0 (Hfl 125) (hardback). Reprinted 2003.

Witnessing medical history. An interview with Dr Rosemary Biggs

Professor Christine Lee and Dr Charles Rizza (interviewers). (1998) *Haemophilia* **4**: 769–77.

Witnessing the Witnesses: Pitfalls and potentials of the Witness Seminar in twentieth century medicine

By E M Tansey. In: Doel R, Soderqvist T. (eds) (2006) *Writing Recent Science: The historiography of contemporary science, technology and medicine*. London: Routledge, 260–78.

INTRODUCTION

What exactly is clinical pharmacology and how did it develop? This Witness Seminar gave some fascinating personal historical eye-witness accounts of how the specialty of clinical pharmacology developed. But who are the clinical pharmacologists? How were they trained, where did they work and how were the products they developed regulated? These questions are not easy to answer as the specialty developed in a rather haphazard way over the last half century. The realization –‘Well, perhaps we are clinical pharmacologists’– only came after a number of papers on clinical pharmacology had been published (page 17). Whatever the modest development of the specialty, its importance cannot be underestimated; we are dependent on it for drug innovation, whether it is done by industry alone or in collaboration with academia. We were all taught pharmacology at medical school, but often the basic elements of pharmacology were forgotten unless, of course, there were drug interactions or adverse drug reactions. Often individual interest was only stimulated if clinical trials of new drugs were requested for the completion of the phases of drug development. Many learned their clinical pharmacology while being employed by the industry and, indeed, there was a jointly funded Department of Health/ABPI scheme that was successful in training for a while (pages 29–30). However, the awareness and profile of clinical pharmacology was mainly raised by the development of the diploma of pharmaceutical medicine (DipPharmMed) with a syllabus containing aspects of clinical pharmacology and also the creation of the Faculty of Pharmaceutical Medicine in 1989 (page 28).

So who calls the tune? Much has been written and said about the interaction between industry and the influence of the pharmaceutical industry on everyday medical practice. A parliamentary health select committee considered this issue recently in 2005.³ The general view was that the drug industry influenced medical practice, education and the prescription of non-generic drugs. Its infiltration was often subtle, for example, through support for weekly journal clubs, X-ray sessions and, more nationally, conferences and workshops. The interface was blurred and said to be tainted by ‘drug industry money’.

However, the interface was never thus in the earlier days when the pharmaceutical industry and academia worked alongside each other. Nevertheless, the question remains as to whether new drug development was pushed by the academic

³ House of Commons, Health Committee (2005).

departments of the pharmaceutical industry or by the marketing strategies that they employed. Drug companies are vast empires and often the marketing side does not impinge on the scientific development limb. It was argued that the industry was not a homogenous mass although this wasn't a view held by all.

The question was asked whether the pharmaceutical industry was benign or malign (page 40). Either way, there was a critical problem. There has been declining productivity and little drug innovation: in the past ten years, industry has put an increasing investment into marketing, lobbying and public relations. This has resulted in 'over-medication' of patients, particularly in the US, not an ideal or indeed an acceptable situation. An interesting suggestion that the reason why the pharmaceutical industry was neither benign nor malign was that pharmaceutical companies were 'socially blind'. The web is full of adverts for cheaper drugs, and patients who are influenced by advertising will push their general practitioners into giving them a prescription.

However, the inter-relationship between academia and industry in this country has not always been viewed suspiciously. The interaction, in fact, started with Henry Wellcome and the Burroughs Wellcome Company. Henry Wellcome set up the first research labs in this country and employed people like Henry Dale, George Barger and John Gaddum. As Tilli Tansey explained (page 31), they all started their research careers in the Wellcome laboratories and then moved on either into the MRC or into academia. Henry Dale became the first member from a pharmaceutical industry to be elected an FRS in 1914. There was no prejudice against electing people coming from industry. However, this is different in the US, where, for example, the American Society for Pharmacology and Experimental Therapeutics has not allowed members from industry. Neither could a pharmacologist in industry become a member of a professional body. This situation lasted until 1942 and may account for some of the differences that have been raised about in-house research in British and European companies, as opposed to the US tradition. In this country, pharmacologists could move between the two, but Tilli Tansey, who has a historical interest in this, thought these barriers may have become more firm recently.⁴ This has had the effect that phase I clinical trials have drifted further and further from academia as the establishment felt that industry-sponsored research was somehow tainted. Clearly, this has major implications on training as well as on the experience that young pharmacologists can gain by moving between academia and industry.

⁴ See Church and Tansey (2007).

Regulation has also become more structured and rigid. It is a salutary fact that proper regulation was only forced by the thalidomide tragedy. Alasdair Breckenridge reminded the seminar that it was exactly 50 years ago to that week that thalidomide had been introduced into medicine. In the early 1900s a huge number of drugs were put onto the market and a health select committee was appointed in 1911 to look at the regulation of this but unfortunately reported as the First World War broke out.⁵ Nothing was then done officially until the thalidomide tragedy, which led to the subsequent development of the Committee on Safety of Drugs (CSD) in 1963. The Committee had no power or legal force behind it apart from a moral one and was working on goodwill – much to the surprise of US colleagues. Sir George Godber (Chief Medical Officer, 1960–73) assured the Committee that it would only last three years before the Medicines Act, but in fact it lasted for seven years. The CSD's major concern was safety (pages 43–4), and it considered efficacy only in so far as it concerned safety. However, subsequently, the Committee on Safety of Medicines (CSM) was established and treated efficacy as a major factor, but decisions on safety were difficult, as often the number of patients included in clinical trials was small. 'How do you get a handle on the safety of marketed drugs?' asked Alasdair Breckenridge, a discussion that started in the 1970s and continues today. Post-marketing surveillance was set up. Adverse drug reactions were monitored and later a reporting system on-line (ADROIT) was a major step forwards.⁶ It was commented (page 46) that the reports of these reactions did not mainly come, as was expected, from hospitals but were more often reported by general practitioners. Now, of course, patients can also have an input into this.

The Medicines Act came into being in 1968. Industry was very powerful in determining what would be in the Act. For example, there was no definition of the 'relative' efficacy in clinical practice. There was no concept of whether a medicine was needed or not, or indeed any discussion about the price. The Medicines Act appointed a Medicines Commission that appointed other committees, including the Committee on Safety of Medicines. This regulatory system worked extremely well for almost 40 years. The question of cost didn't come into the equation until the formation of the National Institute for Health and Clinical Excellence in 1999; licensed drugs were now considered on their

⁵ House of Commons, Select Committee (1914).

⁶ The database for storing and monitoring suspected adverse reactions to drug substances was started in 1993 by the Medicines Control Agency (MHRA since 2003) with data from 1964, and is available by subscription to AEGIS (ADROIT Electronically Generated Information Services). See www.info.doh.gov.uk/doh/iar.nsf/0/80256F4F0030DD2180256EBE004B5F31?OpenDocument (visited 24 September 2008). See also Wood and Coulson (1993).

cost and clinical effectiveness but clearly there was a limit to the number of drugs that could be considered per year. However, with the changes in regulatory systems in Europe and with the various recognition systems across countries, it was felt that the basic structure of the Medicines Commission and the CSM should be changed. A new Commission on Human Medicines was formed in 2005 to be more compatible with the European regulatory system. Sadly, I was the last chairman of the Medicines Commission as appointed by the Medicines Act of 1968, but I felt that the Commission had done a worthwhile job extremely well over the years.

This Witness Seminar on the history of clinical pharmacology provides an invaluable record of the development of clinical pharmacology. As always, one is grateful to Tilli Tansey, Lois Reynolds and their team for doing the hard work and to Rod Flower and all the participants who gave their personal recollections.

Parveen Kumar

Barts and the London School of Medicine and Dentistry, University of London

CLINICAL PHARMACOLOGY IN THE UK, c. 1950–2000: INDUSTRY AND REGULATION

The transcript of a Witness Seminar held by the Wellcome Trust Centre for the History of Medicine at UCL, London, on 25 September 2007

Edited by L A Reynolds and E M Tansey

CLINICAL PHARMACOLOGY IN THE UK, c. 1950–2000: INDUSTRY AND REGULATION

Participants

Dr Jeffrey Aronson	Professor Tim Mant
Professor Nigel Baber	Professor Denis McDevitt
Sir Alasdair Breckenridge	Professor Michael Orme
Sir Iain Chalmers	Dr Anthony Peck
Professor Joe Collier	Professor Brian Prichard
Professor Donald Davies	Professor Sir Michael Rawlins
Dr Peter Fletcher	Professor John Reid
Professor Rod Flower (chair)	Professor Phil Routledge
Dr Arthur Fowle	Dr Julian Shelley
Professor Sir Charles George	Dr Robert Smith
Professor David Grahame-Smith	Professor Cameron Swift
Professor John Griffin	Dr Tilli Tansey
Dr Andrew Herxheimer	Professor Duncan Vere
Professor Ray Hill	Professor Owen Wade
Dr Peter Lewis	

Among those attending the meeting: Ms Yaa Adjei, Dr Stuart Anderson, Professor Paul Andrews, Dr Fiona MacLaughlin, Dr Clare McVicker, Mr Wesley Miner, Professor Sir Stanley Peart, Professor Laurie Prescott, Dr Ann Marie Swart, Dr Margaret Wade, Dr Naho Yamazaki

Apologies include: Professor David Barnett, Dr Peter Bennett, Professor Sir James Black, Professor Morris Brown, Professor Tony Dayan, Professor Sir Colin Dollery, Professor Sir Liam Donaldson, Professor Robin Ferner, Dr Jeremy Gale, Dr Gerry Haigh, Professor Andrew Hughes, Professor Leslie Iversen, Dr Derrick Jackson, Professor Trevor Jones, Professor Parveen Kumar, Professor Desmond Laurence, Professor Salvador Moncada, Dr John Mucklow, Dr Douglas Munro-Faure, Dr Stuart Murray, Professor Walter Nimmo, Dr Chris Owens, Professor Munir Pirmohamed, Dr John Posner, Dr Anthony Pottage, Dr June Raine, Dr Gill Samuels, Dr Gareth Sanger, Dr Myles Stephens, Dr Malcolm Thomas, Dr Richard Tiner, Dr Martin Todd, Professor John Toy, Professor David Webb, Dr Frank Wells, Dr Gavin Winston, Professor Kent Woods.

Dr Tilli Tansey: I am the convenor of the Wellcome Trust History of Twentieth Century Medicine Group. Several years ago, the Wellcome Trust initiated the group to try to bring together historians of medicine, clinicians and scientists in an effort to create, in particular, archives for future research. One of the devices we've organized is this: having a Witness Seminar where we get together a number of people who've been involved in a particular debate or discovery to sit together to discuss, disagree and have frank discussions about what happened and why, and how.

This is the second meeting we've had on clinical pharmacology.¹ The first one, which focused on individual pharmacologists and relevant institutions, engendered so much debate and interest, even before we held it, that we decided that we should hold a second one to look particularly at regulatory and industrial aspects of the subject. And I'm delighted that Jeff Aronson, who helped organize the first meeting, has helped us very much in organizing the second, and Rod Flower, who chaired the first one, has agreed to do the same for this one. Let me hand over for the rest of this meeting to the chairman, Rod Flower.

Professor Rod Flower:² Thanks very much indeed, Tilli. It's a pleasure to be back here again. We had a very enjoyable meeting on 6 February 2007 and I would like to welcome back colleagues who attended on that occasion. Those of you who couldn't attend ought to know that we tried, during that session, to answer various questions, including: what clinical pharmacology actually was; how it started in medical schools and other institutions; how networks and interactions arose; who became clinical pharmacologists and why; and how they were influenced by government reports and other initiatives. We also discussed the role of various learned societies and journals in the development of the subject and later in the afternoon we touched upon the diversity and expansion of clinical pharmacology.

We decided to split our original Witness Seminar on clinical pharmacology into two sections, because it was evident that the more regulatory side of the discipline deserved a separate airing, and that's why we are here today.

My main job is really to act as a sort of facilitator. It's a very informal format. We will break for tea at 4 o'clock and at 6 o'clock for drinks, and in between those times I will do my best to encourage discussion, to field questions and so on, but it is really your reminiscences we want, not mine, and this is very much your afternoon!

¹ See Reynolds and Tansey (eds) (2008b).

² Biographical notes appear on pages 89–102.

On behalf of Jeff Aronson and myself, I'd like to thank the staff here at the Centre: that is to say, Tilli, Wendy, Daphne and Lois. I'd especially like to thank Jeff as the whole thing was his idea and he has mapped a lot of the important areas for discussion.

I suppose medicine and the law have always been inextricably entwined. We hear, for example, that in ancient Egypt a healer who killed a patient could himself be sentenced to death if it could be shown that he did not follow the exact prescriptions as laid down in the sacred books of Hermes. That was in around 2000 BC but, by extension, the same type of reasoning applies to us today. I guess most of the discussion this afternoon will be about the regulation which arose in the post-thalidomide era, that is to say, the Dunlop Committee and before that its immediate predecessor, the Cohen Committee.³

I would anticipate that events that took place after that are really going to constitute the main subject of our consideration later today.

However, to start off with we are going to call upon Nigel Baber, who is going to talk a little bit about his own experiences in the pharmaceutical industry, the sorts of drugs he was interested in and some of the personalities he encountered. We are then going to talk about the development of the clinical pharmacology industry and then later we are going to talk more about the regulatory side of things. So Nigel, may I kick off with you?

Professor Nigel Baber: Thank you very much, chairman. I'm very aware that the industrialists are probably in the minority here, and my recollections are going to be personal. They are about three major companies for which I've had the honour and privilege, and the fun, to work. The period I'm going to be talking about is 1975 up to 1998. The first company I worked with was ICI Pharmaceuticals, long before it became Zeneca and certainly long before it became AstraZeneca. In fact, funnily enough, Astra was one of its main rivals at the time. The period when I joined was, in some ways, ICI at its zenith. Propranolol had just been registered for hypertension, thanks largely to Professor Brian Prichard's work.⁴ Practolol had gone into decline a little while before because of the oculomucocutaneous syndrome.⁵ That was the end of practolol, though it took a very long time to die. I think the most practical

³ See Glossary, pages 103–4.

⁴ Prichard and Gillam (1964).

⁵ See Mann (2005); Abraham and Davis (2006).

thing I learnt from practolol was how to run a major post-infarction study. Ken Green was then the manager of clinical research.⁶ It was not called clinical pharmacology in those days. So I learnt under him and others how you set up major post-infarction studies. These were the predecessors of ISIS and the Trent study and all that followed from them.⁷ Atenolol was rapidly being developed at that stage. That was the golden hope – to supplant propranolol as the latter faded and became generic. Clofibrate was another drug that bit the dust about a month or so after I joined – I don't think it was cause and effect – with the World Health Organization (WHO) study,⁸ and I can clearly remember the medical director of ICI at the time, Colin Downie, who really had a pretty bad time of it then, wading his way through all the reports on clofibrate and all the reports on practolol.⁹ Tamoxifen was another very important drug for ICI at that time, and we all know what a remarkable medicine that has become in the treatment of breast cancer.¹⁰ But ICI was predominantly a cardiovascular company.

The department there responsible for early-phase evaluation was called 'clinical research' not 'clinical pharmacology' for the first few years after I joined. The manager was Ken Green. When he retired it was taken over by John Nicholls, whom some here may well remember. John did one of the most important things, I think, for clinical pharmacology at ICI, which was to build one of the first in-house clinical trials units, a splendid unit on stilts, over the reservoir, and I think it's still functioning (the South Manchester Unit of AstraZeneca Pharmaceutical Research Laboratories, Alderley Park, Cheshire; see Figure 1).

Our volunteers were employees of ICI, either from the Alderley Edge research site or from the manufacturing site in Macclesfield. I think later, after I left, volunteers were drawn from outside. But the philosophy of ICI was that volunteer studies should be done in-house if at all possible.

⁶ Professor Baber wrote: 'Dr Kenneth Green was manager of clinical research at ICI Pharmaceuticals from about 1975–85. He was a cardiologist, best known for pioneering the first large multicentre, multinational post-infarction trial with a β -blocker (practolol) which set the benchmark for future secondary prevention trials.' Note on draft transcript, 8 July 2008. See Green (1975).

⁷ On the ISIS (International Study of Infarct Survival) study see ISIS-1 (1986); ISIS-2 (1988); ISIS-3 (1992); and Reynolds and Tansey (eds) (2005): 105–7; for the Trent study see Wilcox *et al.* (1986).

⁸ See Heady (1973); Principal Investigators (1978, 1980, 1984).

⁹ On practolol see Wright (1975); Amos *et al.* (1978). On clofibrate see note 8.

¹⁰ See Jordan (1988).



Figure 1: AstraZeneca Clinical Trials Unit, South Manchester

Rod has asked me to talk about the interface between industry and the regulatory authorities as a separate issue, and I will certainly try to do that. So I have compacted nine years into a few words. Perhaps mention should be made of one other very interesting development compound. Professor Breckenridge was involved in this: that was a drug called clobuzarit (Clozic, ICI 55897). This was designed as a disease-modifying agent for the treatment of rheumatoid arthritis and it was related to clofibrate.¹¹ This is quite an interesting bit of history, if you'll forgive me for a few moments. We talk these days about the speed with which translational medicine allows rapid entry into major clinical trials, but we very rapidly did single and repeat dose studies in volunteers with clobuzarit. We then moved quickly to dose-ranging studies, now called 'proof of concept', in patients with early rheumatoid arthritis. This was done in the UK, Switzerland, Germany, Austria, South Africa and Italy, and Arthur Rushton and I managed this programme. This was a drug which we were just about beginning to convince ourselves had disease-modifying properties in terms of falls in C-reactive protein and erythrocyte sedimentation rates in comparison with indomethacin and changes in X-ray scoring.¹² We then had our first three

¹¹ See McConkey *et al.* (1980); Bird *et al.* (1983).

¹² See Jones *et al.* (1982); Lewis *et al.* (1989).

cases of Stevens–Johnson syndrome.¹³ These were scattered all over the world (Austria, South Africa and France) – they weren't just in one centre. We had about 1500 patients exposed to the drug, and Bill Duncan, who was then deputy chairman, technical – I think that was the correct term – called us together and told us, 'We're going to pull the plug on Clozic'.¹⁴ I think he was absolutely right, but there was tremendous resistance from the physicians who were using the drug and who wished to continue with it. It was a most interesting drug to work with – one of the most interesting that I've ever dealt with. So, that's a summary of my experiences at ICI.

I then joined Merck Sharp & Dohme Limited (hereafter Merck), and I think then, Merck, too was probably at the height of its powers. I was there for three and a half years as European director of clinical pharmacology. Keith Jones was overall director of clinical pharmacology based in the US. Between us we took every single new compound of Merck's into human in Europe. The reason was very simple, of course; investigational new drug applications for the US Food and Drug Administration (FDA) were extremely difficult to come by, and that's why European clinical pharmacology was so important to Merck. Merck's philosophy was totally different from ICI's and, as we shall see, from Glaxo's. They did not have in-house trials units of their own: they expected us to go to 'centres of excellence', as we call them now, which could be anywhere in the world, where we could get expert advice in design and conduct of phase I and IIa studies. The main programme that we looked after was the leukotriene programme, and I'm sorry Colin Dollery isn't here, but it was with Colin we did a lot of the work. Donald Davies will remember that as well. The key leukotriene challenge was to develop a leukotriene D₄ antagonist, and this was conducted by Neil Barnes at Kings.¹⁵ I doubt if current regulations would allow such a rapid programme, but it put Merck really in front of the leukotriene race. Of course Merck was, at that time, financially very sound. Its main portfolio consisted of enalapril (Vasotec), simvastatin (Zocor) and mevinolin (lovastatin, Mevacor) in the US. Interestingly, as an aside, nearly all of Merck's clinical pharmacology work on those major drugs

¹³ A severe form of erythema multiforme with lupus-like symptoms, thought to be caused by an allergic reaction to medication.

¹⁴ Professor Baber wrote: 'There was a meeting of all of the principal investigators from the countries listed who presented their results and there was a debate at which Bill Duncan and Colin Downie (medical director) were present, on the future of Clozic. It was following this meeting that Bill Duncan announced the termination of the development programme.' Note on draft transcript, 8 July 2008.

¹⁵ See, for example, Barnes *et al.* (1984); Barnes *et al.* (1987).

was not done in America: everything was repeated in the US. Scandinavia was where most of the enalapril work was done, and the same with the statin programmes, as most of you will know if you read the old literature.¹⁶ Merck was a good place to work. Ed Skolnick was the R&D director, a most fearsome intellect.

After three and a half years at Merck I moved to Glaxo, or rather to the Glaxo Group Research as it was then. Richard Sykes had just become research and development director. I was there for nine years; the latter two years were under the GlaxoWellcome amalgamation. The philosophy of clinical pharmacology was more like the ICI model: in-house work on volunteers from the workforce. We set up three new centres and there was no shortage of money. Zantac (ranitidine) was the first billion-dollar drug.¹⁷ We put a clinical pharmacology unit at Northwick Park, Harrow, in place, long before Parexel (a US clinical research organization) was on the horizon. And the important thing here, I think, was that it was the first time I had tried to set up a panel of patients – and this was with troglitazone in mind for the potential treatment of type 2 diabetes. Just on that one drug: I will say we were able to detect weight gain after repeat dosing in volunteers, and small changes in blood pressure.¹⁸ We could predict very early on that it was likely to be a problem.

So, other drugs that were of interest at Glaxo, of course, were the 5HT (serotonin) agonists and antagonists, and perhaps I could talk here a little about our interactions with the regulatory agencies, in reference to sumatriptan and ondansetron.¹⁹ Those are the two drugs I had most to do with when I was there. I didn't take sumatriptan into human the first time – that had been done before I joined – but we were interested in investigating the peculiar chest symptoms: difficulty in breathing, pressure on the chest, and whether it was vasoconstriction.²⁰

So that is a very rapid summary of 23 years in the pharmaceutical industry, in three major pharmaceutical companies. I'd be happy to talk about other interesting characters that I came across. Perhaps I will just pick out one

¹⁶ Cleary and Taylor (1986). See also Vagelos and Galambos (2004).

¹⁷ See Christie and Tansey (eds) (2002): 175–6, 131; Berstad *et al.* (1980); Brittain and Daly (1981).

¹⁸ See Parker (2002).

¹⁹ See Fowler *et al.* (1991); Peroutka (1990); Baber *et al.* (1992); Chaffee and Tankanow (1991); Christie and Tansey (eds) (2007): 51–2, 59–60, 64.

²⁰ See Mueller *et al.* (1996).

outstanding personality whom people might know, to finish with: hands up those who remember Jeff Thorp. He was probably the one real genius at ICI while I was there. Jeff really invented clofibrate and Clozic.²¹ He was an engineer from South Africa who had a BSc and nothing else. He was an absolute delight to talk to and he shared his knowledge liberally. I'll stop there, chairman, and be happy to reminisce about any other characters that people remember from those days.

Flower: That's a very good introduction, Nigel. Just as a matter of interest, since we're concerned with the development of clinical pharmacology, you mention that when you first went to ICI, your outfit was called clinical research. Was there a point at which it transitioned into clinical pharmacology – and if so, how did that happen?

Baber: Yes. I think this was really due to John Nicholls. John clearly saw that there was a need to try to understand the physiology of disease in parallel with the pharmacology of drugs. He set up two small departments: clinical pharmacology, under John Harry – I wasn't in that department at the time; and what he called clinical physiology under Ron Stark, whom some of you may well know, and that was quite successful. But it was really John Nicholls who commuted the term of clinical research into clinical pharmacology, and that has stuck since.²²

Flower: And what about the size of your department in those days?

Baber: In terms of medics, about six or seven. In terms of support staff, PhDs, clinical research associates (CRAs) and nurses, it was probably 20–25. And that's something perhaps one ought just to mention as we go on with our discussions. I guess we are all medics in the room, but there is an awful lot of clinical pharmacology in industry which owes much of its success to non-medical people: pharmacokineticists and clinical toxicologists and statisticians, so they are important to us as clinical pharmacologists in industry.²³

²¹ See Thorp and Waring (1962); Thorp (1963); see also Fitzgerald (2003).

²² See, for example, Nicholls (1972).

²³ Professor Baber wrote: 'Designing and executing a phase I study in healthy normal volunteers as patients was a multi-disciplinary team activity. It required input from: 1) the pharmacologists who discovered the investigational medical product (IMP); 2) the statisticians; 3) pharmacokineticists to develop an assay for the IMP and its metabolites and calculate pharmacokinetic parameters; 4) research nurses and clinical research scientists to conduct and monitor the trial, under the jurisdiction of the clinical pharmacologist.' Note on draft transcript, 8 July 2008.

<p>Phase I trials</p> <p>Initial studies to determine the tolerability, metabolism and pharmacological actions of a drug in humans; the adverse effects associated with increasing doses; and to gain early evidence of effectiveness. May include healthy participants and/or patients (c. 20–80 people).</p>
<p>Phase II trials</p> <p>Controlled clinical studies conducted to evaluate the effectiveness of a drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term adverse effects and risks (c. 100–300 people).</p>
<p>Phase III trials</p> <p>Expanded controlled and uncontrolled trials to evaluate the overall benefit to harm balance of the drug and provide a basis for labelling (c. 1000–3000 people).</p>
<p>Phase IV trials</p> <p>Post-marketing studies to delineate additional information, including the drug's adverse effects, benefits and optimal use.</p>

Figure 2: A summary of the organization of clinical trials.
Adapted from: www.clinicaltrials.gov/ct2/info/glossary (visited 1 May 2008).

Flower: In your talk, I was interested in how you contrasted the styles of the different companies in terms of their attitude to clinical pharmacology, and this leads me neatly on to the next topic, which is a consideration of whether there really is such a thing as ‘the pharmaceutical industry’ as an entity, or whether it is really just a collection of individual companies, each with its own style, procedures and clinical ethos.

I don't know whether anyone would like to comment on this: I think John Griffin may have something to say about that.

Professor John Griffin: I was pre-warned that I might be asked to make this sort of contribution. I've had three hats in the last 40 years. I was head of clinical research for 3M; I then, after a period of time, became head of the UK drug regulatory authority, which was in those days called the Medicines Division; and I then became director of the Association of the British Pharmaceutical Industry (ABPI). In the 1970s, just after the introduction of the 1968 Medicines Act, which came into force on 1 September 1971, having taken nearly four

years to implement, the ABPI consisted of 150 companies or thereabouts, and the common bond was that they all supplied prescription medicines to the NHS.²⁴ That was the bond that held them all together. This meant that, by and large, their profits and prices were regulated through the Pharmaceutical Price Regulation Scheme (PPRS). The companies were very different, disparate. There were native British companies which conducted basic research, clinical trials, manufacture and marketing in the UK, and exported goods from the UK. Examples of this are Glaxo, Beechams, Wellcome, ICI and Fisons. There were also major multinational companies that also conducted a full range of activities within the UK. However, other research-based multinational companies only conducted limited activities in the UK; for example, limited phase III or IV studies and marketing. Maybe they didn't even manufacture. Also within ABPI's ambit were manufacturing companies for generic medicines, other companies that specialized in the manufacture of specialized formulations, and those that were involved in research in delivery systems rather than in new chemical entities. It is important to realize that the PPRS didn't involve all companies in the same way. Companies with a large capital investment in the UK were allowed profits, which were based on the return on capital. Companies with a small investment were allowed profits that were based on a percentage of sales to the NHS. Generic sales were outside the control of the PPRS; it was a very disparate group. The only thing that bonded them all together was, in fact, the PPRS and the fact that they were selling to the NHS.

The introduction of the Medicines Act of 1968 also introduced a collection of disparate activities within ABPI companies. For example, when the Medicines Act came into operation, there were 39 000 products that were granted Product licences of right. About 6000 of these were outside the remit of the European directives that required a review. For example, there were blood products, homoeopathic products, etc. So there was an enormous breadth of work that was required to review these products. In addition, under the Medicines Act 1968 there was the need to process clinical trial certificate applications.²⁵ That meant that companies intending to conduct clinical studies in the UK had to obtain permission to do so. Phase I studies were outside the remit of the Medicines Act, so human pharmacology on normal, healthy volunteers was not

²⁴ The Medicines Act received the Royal Assent in 1968, based on proposals set out in the 1967 White Paper (Scottish Office *et al.* (1967)). For further details see Great Britain (1968); Griffin and O'Grady (2006): 457–88.

²⁵ Great Britain (1968): section 31.

controlled by the Medicines Act, but phase II and III studies were. In 1971, 170 clinical trial certificates were granted.²⁶

The Medicines Division was grossly under-resourced. There were enormous delays in handling clinical trial certificates, and by 1981 there were only 74 clinical trial certificates processed per year.²⁷ So something radical had to be done, otherwise clinical pharmacology in the UK was going to suffer enormously. A clinical trial exemption scheme (CTX) was introduced, and this stimulated the conduct of clinical trials in the UK so that by 1985 there were approximately 240 clinical trial exemptions issued for clinical trials in the UK.²⁸ The maximum was 263 in the year before that. So there was a tremendous stimulus.²⁹

The other problem that affected the UK was the fact that when the Medicines Act was implemented in the early 1970s, it was taking about eight months to process an application for a new chemical entity. By 1984 it was taking 23 months.

Abridged applications were another problem. I dealt with the problem of clinical trial certificates and something having to be done then. In 1982 we had an investigation by Sir Derek Rayner, later Lord Rayner, who suggested that abridged applications should all be dealt with within two months. We had 6 000 applications for abridged applications, variations and generics per year. That meant that if all the medical staff were directed to dealing with this, they would have to deal with two applications such as this per day, in addition to dealing with clinical trial certificates, clinical trial exemptions, product licences for new chemical entities, adverse drug reactions and the review of 19 000 product licences of right still outstanding; an impossible task and grossly under-resourced. The next phase, of course, was the even worse scenario that had developed by 1986, which set up the investigation by Evans and Cunliffe

²⁶ Griffin (1989): 13.

²⁷ Griffin (1989): 13.

²⁸ The clinical trial exemption scheme exempted pharmaceutical companies from the need to have a clinical trial certificate in order to develop rapid clinical trials for chemicals of interest. See House of Commons (1981). Professor John Griffin wrote: 'Devised by John Long, Assistant Secretary to the Department of Health and Social Security, and myself. See Griffin and Long (1981).' Note on draft transcript, 8 November 2007. For details see also Mann (1984): 631–2.

²⁹ Speirs and Griffin (1983); Speirs *et al.* (1984).

into the operation of the Medicines Division.³⁰ The result was that the Medicines Division became a first step agency, and then other factors came in and it later became the Medicines Control Agency (MCA) in 1989. It has now progressed even further in changing its name to become the Medicines and Healthcare products Regulatory Agency (MHRA), but it has the same problems we had in 1980.³¹ So, we've always had a problem of under-resourcing the regulatory authority, and this has had an effect on the conduct of clinical studies and clinical pharmacology in the UK.

Professor David Grahame-Smith: Observing the working of the Act at the time, one of the things that people wondered about outside 'the business' was whether abridged applications and exemptions from clinical trial certificates would, in a sense, be decreasing the effectiveness of regulations – something that worried me, because plainly it was possible for things to slip through a less rigorous system; but I don't think it happened. John Griffin probably knows better, but I don't think it actually happened, which was a blessing.

Professor Joe Collier: I find the position taken about clinical pharmacology in this country by John Griffin a trifle bizarre. It was certainly not in keeping with my own view but rather more reflected that of industry. It certainly had little to do with what I think academic clinical pharmacologists were doing. John Griffin said that if clinical trials numbers weren't to be increased, clinical pharmacology in the UK would suffer enormously. This suggests to me that in Griffin's view, and maybe that of others, a primary role of clinical pharmacologists was to do clinical trials. I don't think I've ever done an industry-funded traditional clinical trial actually, because I've spent my whole time doing interpretation and transitional studies and many other of my colleagues have done the same. If what Professor Griffin implied were true, and that all clinical pharmacologists do is to service the industry by doing clinical trials, it would account for the failing of clinical pharmacology as a discipline.

Flower: John, do you want to get back on that point?

Griffin: I think the pressure for looking at the clinical trial certificates and the way it was operated came equally from industry and from academia. The number of applications for clinical trial certificates that were processed fell, literally, by 50

³⁰ Evans and Cunliffe (1987). See also Keen (1991); Griffin and Shah (2006): 480.

³¹ See House of Commons, Health Committee (2005): 104: 'We do not believe that the MHRA has sufficient resources for effective post-marketing surveillance.' On the formation of the MHRA, see page 60.

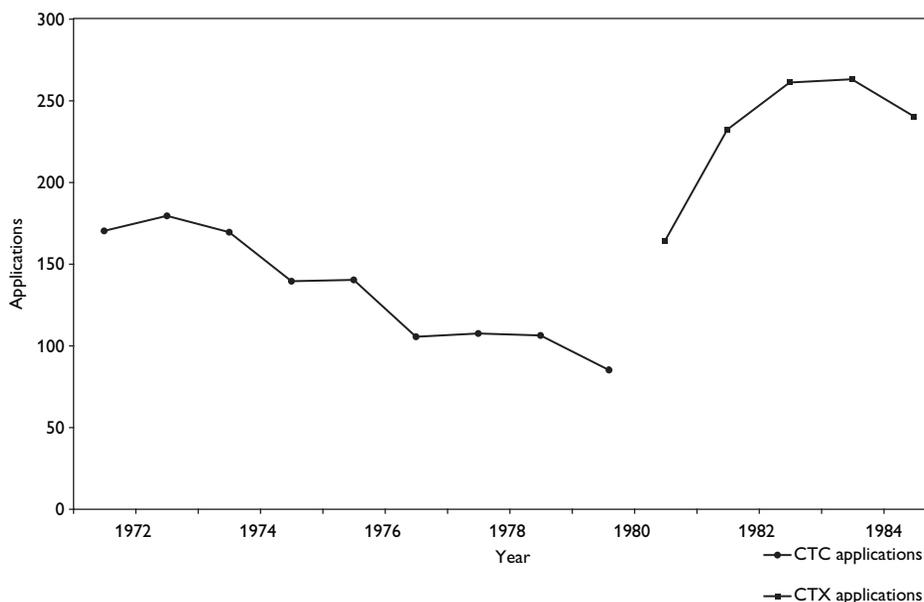


Figure 3: Clinical trial certificates (CTC) and clinical trial exemptions (CTX), 1972–1985. Adapted from Speirs and Griffin (1983) and Speirs *et al.* (1984).

per cent in ten years.³² And if that doesn't have an adverse effect on the conduct of clinical trials and clinical pharmacology in the UK, I don't know what does.

Professor Tim Mant: I think mention has to be made not just of pharma and academia, but also of contract research organizations (CROs). May I say a little bit of what happened to me? I did a degree in pharmacology – one of the reasons I did clinical pharmacology was that I heard the man in front of me (Michael Rawlins) speak on variability in human drug response, and it was inspiring.³³ I had wonderful professors at Guy's Hospital; Roy Spector, John Trounce and then Howard Rogers, who unfortunately died very young. I worked at the

³² See Figure 3, above. Professor John Griffin wrote: 'I did not say that the role of clinical pharmacologists was solely to conduct clinical trials, although that is certainly within their competence. I agree that clinical pharmacology has not developed as we all hoped it would. This is in no small measure due to the anti-industry stance of some.' E-mail to Mrs Lois Reynolds, 19 October 2008.

³³ Professor Michael Rawlins' inaugural lecture, delivered at the University of Newcastle upon Tyne on 22 January 1974. See Rawlins (1974). Professor Mant wrote: 'Also delivered in London in 1976, which is where I heard it.' E-mail to Mrs Lois Reynolds, 19 September 2008.

Hammersmith Hospital with Colin Dollery for a short time, and then went to the poisons unit at Guy's. That was practical clinical pharmacology, seeing people after overdose, and interesting. The academic department of clinical pharmacology at Guy's was involved in conducting drug studies for the pharmaceutical industry. We always had a Wellcome registrar and, I think, a Glaxo or Ciba registrar. So, the industry was helping to fund the health service in many ways. I remember clearly Howard Rogers telling me that if you want to work on new drugs, you have to work with the industry, who are the only people who have the finance to develop drugs. Certainly, when I saw the standards required to conduct trials to US FDA guidelines, I was very impressed. I think it is rather sad that phase I trials have drifted further and further from academia. The establishment seemed to have felt that industry research was somehow tainted. I don't know why. I felt academia considered industry-sponsored research as somehow inferior, and to be kept at arm's length. We at Guy's Drug Research Unit started with one full-time employee when I first started doing phase I work. The rest were all employed by the university or by the hospital. We now employ over 180 people. I think one of the sad things is that walls are being set up between academia, the NHS and the industry. We should all be working together in this, and I'm hoping that with the way the government is supporting translational medicine at the moment we will see better partnerships between industry, academia and the NHS. That's my hope.

Baber: I want to support something that Tim said, and also to come back to your original question: is there such a thing as the pharmaceutical industry, as opposed to individual companies? When I went to Merck, having worked with academic departments, I was aware of a divide, real or otherwise, that we were second-rate if we worked in the pharmaceutical industry. And one of the ways I tried to tackle this, with three of my colleagues, was to set up the Association of Human Pharmacologists in the Pharmaceutical Industry in 1985. The originators of this were John Harry at ICI, myself from Merck, John Posner at Wellcome, and Roy Drucker, who used to work at Sterling Winthrop. This has grown enormously now, and Tim will be able to say far more about its present form. Originally it was simply a discussion group – not meant to be political in any shape or form. There were no publications and no minutes. We just met on different premises to talk about common problems, shared by us all, such as doing kinetic and dynamic studies. We were very snooty to begin with and excluded CROs and this was evidently wrong, but at that stage most major companies had got their own trials units. We opened the invitation also to non-medics right from the inception. We believed it was very important that we had nurses and CRAs who were doing hands-on work. So, at that stage, a

number of us who were relatively senior in the industry were worried about this potential divide between industry and academia. I want to say that I can feel much sympathy for what Tim is saying, even though I am now somewhat withdrawn from the situation.

Flower: So, Arthur Fowle, I'll put that question directly to you. Did you feel when you were at the Wellcome Foundation that you were part of a different organization?

Dr Arthur Fowle: Yes, indeed, I did. I think the last two contributions would have been, should have been, displaced. They shouldn't really have followed Joe Collier, with whom I've got 100 per cent sympathy. I became head of clinical pharmacology at the Wellcome Foundation in 1968, and at the beginning it wasn't really about clinical trials. I think if we got back to pursuing the origins of clinical pharmacology, it would be fair to say that when I went to the Wellcome Foundation, it dawned on me only after I'd been there for a few years that I was a clinical pharmacologist. I didn't go there as one. I went to the Wellcome Foundation in November 1965 and went because it was very uncongenial as a senior registrar on an academic unit elsewhere in London. The head of medicine at the Wellcome Foundation, David Long, had a brilliant idea and I hope he gets some recognition for it. He thought that a good idea would be to be surrounded by medical advisors, whom he arranged to hold appointment on an honorary basis in academic units around the country; largely in London, of course. The advisors only gave opinions and advice to him when it was necessary. That seemed to turn out to be about once a month at a meeting in the building next door here (183 Euston Road, London, then housing the headquarters of the Wellcome Foundation), and for the rest of the time Long's staff went about doing clinical research in various units around London. I followed the same system. First I had remained senior registrar for a further year in the cardiac unit at the Middlesex Hospital, London, until I became locum consultant, then got a part-time consultantship in the NHS. I was followed by a team which we eventually built up, and where there was a certain irreverence about us all, which was due to the fact that we had mostly come from the Hammersmith Hospital. And when I got in charge at Wellcome, I actually inculcated more or less the atmosphere of the lower medical corridor.³⁴ The kind of work I did was to look at pharmacodynamics, and that seemed to be successful.³⁵ Our outlook

³⁴ Dr Arthur Fowle wrote: 'This was a well-known part of the Hammersmith Hospital where staff of the medical unit worked.' Note on draft transcript, 19 November 2007. See Booth (1985).

³⁵ See Fowle *et al.* (1971).

on success was to write papers for *Clinical Science* or to address the Medical Research Society. That was what gave us pleasure and nobody stopped us doing it. It was only after a while, after Colin Dollery published a lot on cardiovascular system pharmacodynamics, we began to realize, ‘Well, perhaps we are clinical pharmacologists.’³⁶ I was then made head of a clinical pharmacology department in 1968. Before that, we did things because they seemed to be worthwhile. It was successful because David Long saw to it that he only employed people with the membership of the Royal College of Physicians, which made it rather easy for dealing with the board of the Wellcome Foundation as to the level of our remuneration. This was also really quite a good political move. So, we were all very much the same kind of people, and doing similar things. I have to admit that, then, I had never heard of clinical pharmacokinetics. It was a revelation to me when we began to study pharmacokinetics. And at the time of the digoxin debacle,³⁷ which was after I’d been in the business quite a long time, it occurred to me that many of the great and the good in clinical medicine also had not heard of pharmacokinetics, and even if they had, they didn’t believe in it. In fact, I was hauled over the coals by some very eminent people with whom I’d worked at the National Heart Hospital for interfering with their use of digoxin, because it hadn’t occurred to them that when a drug was administered pharmacokinetics really mattered; you could not take absorption and dissolution for granted.³⁸ The problems we had with digoxin were met rather unsympathetically by the great and the good in cardiology. Even at that time pharmacokinetics hadn’t made a very big mark, and I own, what was to me a revelation, was one of John Wagner’s early papers, which obviously made it an exciting subject to study.³⁹ His conclusion from the pharmacokinetics of tetracycline was that you should use many more doses of tetracycline than I knew was clinically necessary.⁴⁰ So, it wasn’t always that pharmacokinetics gave the answer, but it certainly became a very interesting subject to study. At the Wellcome Foundation I was given the job of setting up the clinical pharmacology unit and recruiting more people like myself by Dr David Long, head of the medical division. And I’ll hand over to Tony Peck in a minute, who was very successfully looking after the psychopharmacology side of events. But at the beginning, like Colin Dollery,

³⁶ See Dollery (2006).

³⁷ See Staff reporter (1972).

³⁸ See Johnson *et al.* (1973); Johnson *et al.* (1974).

³⁹ Wagner (1967a).

⁴⁰ Wagner (1967b).

whose background was largely in cardiovascular research, most people in the early days of clinical pharmacology had a background in cardiology. That was probably because when cardiology blossomed at the time of Paul Wood's pre-eminence,⁴¹ it was the branch of medicine which was given most to clinical investigation. There was more money associated with starting off a clinical cardiac unit with a catheter lab; it cost a lot of money. And it was not surprising that most of the work that we did in the beginning was cardiovascular. That suited the Wellcome Foundation, because it itself was strong in cardiovascular research. In fact the non-cardiovascular research was also due to the business outlook of the Wellcome Foundation. It was very strong in immunological compounds. It had a huge and highly respected capacity for making immunizations against various things. And also there was an Empire Preference when I first joined there, which helped the company sell drugs in various parts of the world where tropical medicines were much in demand.⁴² Gradually we moved away from that as clinical pharmacology became the subject that we all now recognize. But it certainly wasn't recognized when I started in 1965. I have to say that I knew about a clinical pharmacology book, which I regarded as a good book, and along the lines of Samson Wright's *Applied Physiology*, which I thought was just about the best book I ever read as a medical student, but it didn't actually turn me into an applied physiologist any more than the first clinical pharmacology textbook turned me into a clinical pharmacologist.⁴³ It didn't start like that, good though those books were. It required something different for a subject to really blossom, as I think Joe Collier was indicating, into largely the study of pharmacodynamics in the first instance, even including what we came to call phase I studies and the first testing of drugs in humans. And because ethics wasn't controlled by ethics committees in those days, it so happened that I took ten drugs myself for the first time in the course of drugs coming into the medical department.⁴⁴ Another thing which would cause a gasp now but didn't cause a gasp in those days was that I didn't pay any of

⁴¹ See Silverman and Somerville (2000).

⁴² See Church and Tansey (2007): 227–32.

⁴³ Laurence (1963); Wright (1934).

⁴⁴ For details of the development of research ethics committees, see Professor Desmond Laurence's note on 'The initiation of research ethics committees in the UK', which has been deposited along with other records of Reynolds and Tansey (eds.) (2008b) in archives and manuscripts, Wellcome Library, London, in GC/253.

the volunteers. We had 1500 people on site when we decided to move down to Beckenham from the place next door here (183 Euston Road) and everybody was keen to take part. It never occurred to us to offer to pay anybody, everybody was very pleased to take part.

Flower: You seem to be saying that some people are born clinical pharmacologists, some people become clinical pharmacologists, and some have clinical pharmacology thrust upon them!

Fowle: Yes, indeed. I wonder whether the discipline is a ‘busted flush’ or whether it doesn’t exist any more.⁴⁵

Flower: I’d like to ask a couple of other people about their views on the ways that clinical pharmacology started in their neck of the woods. Peter, do you think there is such a thing as a pharmaceutical industry – or simply a collection of individual entities?

Dr Peter Lewis: I joined industry from Colin Dollery’s department at the Hammersmith in 1983. I went to France to work for an international company, Merrell Dow at the time, it’s now gone through a number of transformations, and I can’t remember quite what it is called any more.⁴⁶

On the subject of whether companies are all the same or different, I was very struck by what Nigel Baber was saying, as I had exactly the same experience. I went to work for a US company, although the research centre I was responsible for was located in France. They shared Merck’s attitude to clinical pharmacology: nothing in-house: ‘Go somewhere and get it done.’ I found that quite frustrating because I’d been doing quite a lot of phase I work and I naturally thought I could do some in-house. Of course one couldn’t do clinical studies in healthy volunteers in France at the time because it was forbidden by law, but we had a little lab over the border in Germany, not far from Strasbourg, and there was a phase I effort there, carried out by our German colleagues on a very

⁴⁵ Dr Arthur Fowle wrote: ‘In about 40 years clinical pharmacology has become an essential part of general medicine. Recognition of the subject has entirely succeeded in its purpose. Specialist teachers of the subject should therefore become less essential and “consultant” status for specialist clinical pharmacologists correspondingly harder to justify. At the meeting today I have heard of one teaching department (St George’s, University of London) proud never to have conducted a clinical trial or perhaps taught the art of them (see page 16). I regard the clinical trial as the only sure proof of clinical efficacy, even when it is not the highest intellectual medical endeavour. Perhaps industry will become the natural home for the specialty.’ E-mail to Dr Daphne Christie, 7 January 2008.

⁴⁶ Merrell Dow became part of Sanofi Aventis in 2004. See Irwin (1994).

small scale, a few studies a year. When I arrived in Strasbourg, I discovered this in-house clinical pharmacology unit in Freiburg, and so I was naturally very interested to go and see them. And I found – I was absolutely horrified by what they were up to – that they were doing phase I studies but in a very peculiar, Germanic fashion, in that the young volunteers who were being exposed to our compounds were being forced to do numerous psychometric tests, so it was impossible to find out whether there was any drug effect or not because they were so consumed with mental arithmetic. So, that was a bit of a frost. I had rather a lot of difficulty converting them to what I thought was a more reasonable way of doing things.

I think the US companies generally didn't like doing clinical pharmacology or human experimentation in-house, and there was a completely different ethos among the mainstream British companies, who were quite keen on employing clinical pharmacologists and on doing in-house research. Apropos of who the clinical pharmacologists were, I think that there were very few people who were ever actually recruited from clinical pharmacology departments in the UK into pharmaceutical companies. When I joined the industry in 1983 my experience was that most of the people whom I came across in industry had actually acquired their clinical pharmacology knowledge in-house while working for the pharmaceutical companies. There are quite a number of good examples. It was very difficult in my personal experience, and that of others, to prise anybody away from a clinical pharmacology academic unit in the UK to go and work in industry. There was a terrific barrier. Generally speaking, our medical people who came to work in clinical pharmacology were recruited into industry at a junior stage when they were senior registrar or registrar and then they were either sent on courses or educated up in the company itself, and that's how the industry got the majority of its clinical pharmacologists. That was my impression. I checked this on the telephone this morning with Tony Chandler, whom many of us here must have received gratifying phone calls from when he was running Talentmark and one of his activities as a headhunter was to try to poach people from academic work to work in pharmaceutical companies. And he shared with me this morning his experience: it was extremely difficult to get people out of academic units into the pharmaceutical industry.

My own case is, I think, illustrative. I was in Colin Dollery's department for quite a long time, and at his festschrift I was asked along to talk about the industry, because basically there wasn't anybody else who could do so, because

none of them had actually joined the industry.⁴⁷ They had a lot of contact with industry in different roles – a lot of them are here – but nobody had actually made the jump and left academia and joined the industry. So, I was very much the exception. In fact, for Colin's festschrift I did a headcount of the members of the British Pharmacological Society (BPS).⁴⁸ At the time there were 2300 members; about 25 per cent of them had an industry address – presumably they worked in industry. But of those, I was only able to identify 32 who were actually clinical pharmacologists. And that was an arbitrary definition on my part; they had a medical degree and they had some postgraduate training or contact in clinical pharmacology before they joined industry. It's a very small number. When you're talking about clinical pharmacologists in industry, I think it was largely home-grown, I mean the transformation of people inside the company, rather than academics joining the industry.

Flower: That's very interesting. I'm going to ask Tony Peck if he wants to comment on that and then I will go to Ray Hill. I'd like to try to pursue this for a few minutes longer because I think it is a very interesting topic.

DrAnthonyPeck: Well, I certainly joined the Wellcome group from a background of dissent. I was utterly dissatisfied with the outlook, at least for myself, in the health service and in academia, in 1969, when I returned from a year in the US. And there was Arthur Fowle, and in particular Douglas Munro-Faure, who really should have been here today, but alas, he said he's a bit too old to come along. He was the one who got my interest going in clinical pharmacology. I wanted to do human pharmacology, but I saw no chance for it at all in my old stable in the Middlesex. At Beckenham (the Wellcome Foundation research base), Munro-Faure gave me the problem: 'Here's a compound, benzylpiperazine, the basic pharmacologists say it might be an antidepressant. I think it's a pep pill. Sort it out.' Arthur had, by that stage, organized a soundproof room at the buildings at Beckenham, for four subjects, designed to be equivalent to the one in Baltimore that Horsley Gantt had built (the Pavlovian Laboratory, Johns Hopkins University, Baltimore, Maryland), Horsley Gantt being the last Westerner to work with Pavlov. Anyway, I inherited this question: 'How do you sort out whether something really is a pep pill or not?' Rather than reinvent the wheel, we had the philosophy of going along to groups who have got tests to tell you whether a drug was alerting. I went along to Bob Wilkinson at the Medical

⁴⁷ George (1996).

⁴⁸ The BPS was established in Oxford in 1931. See Reynolds and Tansey (eds) (2008b): 121; Cuthbert (2006); Bynum (1981).

Research Council (MRC) applied psychology unit at Cambridge, and he was enormously helpful, and gave me his audio vigilance tapes.⁴⁹ I copied them there and used them, and, of course, our benzylpiperazine was monumentally alerting.⁵⁰ We used a group of subjects that we had at Beckenham, who were mainly pretty informed people who understood what you were trying to do – they were all our scientific colleagues. Then after that – another feature of our unit was that when we couldn't do something ourselves we took it outside to units – we went out to Whitchurch Hospital in Cardiff, where Merdyn Evans had a group of post-amphetamine addicts, and we set up studies with design help from Hubert Campbell. Of course, they liked our compound better than amphetamine, and it did the same sorts of things to them. So my first lesson in the industry in the first year or two: if you can axe a drug fairly quickly before it goes into patients, that's a great service to the company. So we axed benzylpiperazine and we published the work.⁵¹ It has taken 30 years for that to be rediscovered in the literature and the substance is out there on the streets being abused.⁵² So that, sadly, was not a good point.

But then I went for 11 years before I got a new compound which was likely to be a product. Munro-Faure would often ask: 'Have you got a product, Tony?' And usually I said, 'No.' But then we got one. From 1975 onwards, the 'basic boys' developed lamotrigine, which eventually became Lamictal, and it's used in epilepsy.⁵³ And by that stage, of course, all we wanted was a better phenytoin and we would have settled for phenytoin with half-decent pharmacokinetics.⁵⁴ Pharmacokinetics bores me to tears, as I think it does many people, but to see those first plasma concentrations of Lamictal, lamotrigine, coming back from those first studies and seeing that it had first-order kinetics and linear handling, that was a very exciting time. Then, to work out the human pharmacodynamics and compare it with phenytoin in the lab, we went to Tony Nicholson and Dick Borland, and got their adaptive tracking stuff from the Royal Air Force Institute of Aviation Medicine (Farnborough, Hampshire) and set up those tests and could see that it wasn't as impairing as phenytoin and diazepam. So we were

⁴⁹ See Reynolds and Tansey (eds) (2003).

⁵⁰ See Campbell *et al.* (1972); Campbell *et al.* (1973).

⁵¹ See note 50, above.

⁵² Brennan *et al.* (2007); Butler and Sheridan (2007).

⁵³ Peck (1991); Cohen *et al.* (1985).

⁵⁴ Hvidberg and Dam (1976).

into epilepsy trials. Then of course, it had to leave the Wellcome Foundation because we were by then looking for surrogate endpoints in epilepsy patients – because we couldn't test for these on healthy volunteers. Down the road at the Maudsley Hospital, London, was Colin Binnie with photosensitive epilepsy, and Alan Richens, of course, over in Cardiff, and Chalfont.⁵⁵ So we were exploring their expertise in surrogate endpoints before anybody had ever mentioned surrogate endpoints. And that was really very satisfying, and we carried on and got, we think, a better phenytoin.⁵⁶ The lesson to me was the importance of axing compounds early on if they're not going to be any use. Additionally, it is terribly important in clinical pharmacology not to try to reinvent the wheel when there are units out there that can help you with methodology that will be useful, like Nicholson and Borland, and Wilkinson – the work had all been done before and we used it.

Dr Robert Smith: I want to talk about pharmacokinetics because we've alluded to it a few times, occasionally in a dismissive air, if I might say so. I was in clinical pharmacology in Sheffield and went on sabbatical to the US, particularly to learn more about pharmacokinetics with John Wagner, for nearly two years.⁵⁷ Of course, he had other postgraduates who were going through his unit. Even before I came back to Sheffield I started looking around for suitable British people who were trained. As it happened, three of them were already in the US and I encouraged Geoff Tucker to join the unit in Sheffield and there he remains. But I think pharmacokinetics has made a great difference to this specialty, especially in industry. Once you've got that information, you can begin to plan your development programme far more sensibly and avoid a lot of pits that you may otherwise fall into.

Flower: I'm going to ask Ray Hill to talk now. We're still trying to pursue this thread of discussion about whether there is a separate industry or many individual entities, as well as listening to reminiscences about the early days of clinical pharmacology.

Professor Ray Hill: Yes, I think that there are different styles between US and UK companies, or there were before all the companies started merging. I suspect that many of those differences have now gone. But I think that my

⁵⁵ The Chalfont Centre for Epilepsy, Buckinghamshire, is run by the National Society for Epileptics. Binnie *et al.* (1986); Jawad *et al.* (1986). See also Peck (1991).

⁵⁶ Steiner *et al.* (1999).

⁵⁷ John Wagner was professor of pharmacy at the University of Michigan (1968–82). See also page 17.

own memories come obviously from the side of the basic scientist who, I think, has always found clinical pharmacologist colleagues to be absolutely invaluable at the transition stage from discovery into development. I can remember my first experience, actually talking to Tony Peck when I was a graduate student and was working with colleagues in pharmacology on molecules that gave rise to lamotrigine some five years later, and saying what we would like to do if we ever got a molecule that had the right properties. I think one of the problems is synchronicity. You put a phase I unit in place for that drug when you discover it, but you can't always guarantee that the discovery scientist will produce the drug in the right timeframe. And events in Merck gave a very good example of putting a phase I unit into Terlings Park (Merck Neuroscience Research Centre, Harlow, Essex), where the phase I unit had almost closed before the first development compounds came through some ten years later. It's very important, I think, to have a dialogue between the clinical pharmacologist and the preclinical pharmacologist to make sure that things that you've seen preclinically don't get rediscovered when you get into the human. And then if you do see something unexpected, you can go back and talk to the people who have done the animal work. And certainly in developing the triptan rizatriptan at Merck, I think the dialogue between the clinicians and the preclinical scientists on the same site really saved us a lot of time and stopped us going round in circles.

Grahame-Smith: Could I ask the clinical pharmacologists in industry a question that from time to time has disturbed me? How often have they felt threatened, constrained or irksomely influenced by the 'marketing men' who want to get on, when in fact the clinical pharmacologists, the clinical scientists, know that there is still a lot of work to do with the compound in humans before they can take the next step? Just how often – I have certainly seen it happen – in the wide experience of people here has that happened? It's a very, very important matter.

Flower: Both Bob and Nigel have their hands up immediately so you have obviously touched a raw nerve there.

Smith: I think, first of all, it depends on your own personal attitude when someone is trying to pressurize you. You also need a very good boss. When I joined Glaxo I had David Jack, and nobody would push him around.⁵⁸ The marketing people would keep away from him. Before that I was in Roche and I was responsible for new drug development internationally as medical director in Basel. There was a long history of marketing people beginning to influence,

⁵⁸ See Jones (2001): 326–30.

if they could, the development programme. And, needless to say, I fought hard to reduce the number of compounds in development. You'd be amazed that when I arrived I had 134 products in some stage of development in the medical division, which is impossible. I recommended that we got them down to 23 and we compromised on 34. That was not a popular move, although it was very popular among the staff who had to handle the workload. I only stayed four years with Roche.

Baber: The short answer is that I never felt pressured by the marketing people in any of the three companies I worked with. I actually enjoyed the interaction because, particularly as time went on, they recruited brighter and brighter guys and girls into the marketing department, PhDs and so on. You could have a real rough and tumble discussion with them. One occasion when I could have been under pressure – Bob Smith will remember this – was when we were getting very worried about these funny pressure symptoms with sumatriptan. The drug was well into patients by then and clearly had the potential to be a very big blockbuster. I thought, 'I'm going to have to go and tell a certain Dr Richard Sykes (research and development director) about this.' So I went to see him, and I said: 'Look, you've got to know something. This could kill this drug, or at least result in some very severe warnings.' He was fine about it. He wanted to know the facts, exactly what it meant, and what the implications were. No, all right, he was not a marketing man, but he was in charge of the research and development directorates. So, I had no concerns or pressures which were ever unduly brought to bear on me in my career.

Lewis: I actually had the reverse experience. I was always trying to save drugs that the marketing people were not in the least interested in and tried to kill off. I remember my best triumph in that,⁵⁹ we had an antibiotic – teicoplanin – which was a very narrow-spectrum agent, only effective on Gram-positive organisms.⁶⁰ This was the time when everybody had a 'gorillamycin' that killed everything. So something with a narrow spectrum was thought useless. I pleaded in vain that aztreonam was doing well, and that was a narrow-spectrum drug for Gram-negatives.⁶¹ But there was a big argument about teicoplanin and they thought it was absolute rubbish and tried to kill it off. I remember a phone call

⁵⁹ At Merrell Dow in 1983.

⁶⁰ See Lewis *et al.* (1988); Babul and Pasko (1988).

⁶¹ See Reynolds and Tansey (eds) (2008a): 54.

in the middle of the night from the big boss in the US saying that they were just about to start a large feedlot experiment on a Texas farm, feeding this stuff to steers as a growth enhancer, and was I sure that the drug was actually likely to be a pharmaceutical, because if it was, he was going to have to kill off this experiment. They were, however, going to lose \$2 million, because the farmer would have already prepared all the steers. So it was one of those moments.

Flower: Did you go back to sleep again?

Lewis: Well, it took some years for me to get my equilibrium back, but it actually turned out to be the most successful drug I've been associated with in the industry. Not saying an awful lot, but anyway, it's still going and, you know, it did well. But the company was risk-averse at that time; they had had some nasty experiences, and the last thing they wanted was anything that was going to go wrong. The marketing department only wanted blockbusters. That's one of the terrible things; nobody wants 'niche products' and it has gotten worse and worse and worse. If you can't show that this compound is likely to be a billion-dollar agent, nobody's interested. So it's very difficult for people in pharmaceutical industry research to keep working on things that might turn out to be interesting, because they tend to get killed off at a very early stage.

Dr Julian Shelley: The pressure I experienced was actually from the preclinical side.⁶² We had project teams that comprised members from pharmacology, biochemistry, toxicology, pharmaceutical development and medicine. When we got into phase I and early phase II studies, the pressures to continue with the drug actually came from the preclinical representatives of the project team, because the marketing people were not members of the project group at that stage. So, my pressures were actually from pharmacology mainly.

Peck: Very briefly, I had to pressurize the marketing people in the Wellcome Foundation because in 1975 the entire anti-epileptic market was worth something like £29 million and they had no interest whatever in a new anticonvulsant. It was only when the problems of phenytoin really started to appear, that the zero order, saturation pharmacokinetics and the toxicity problems ensued, and suddenly they saw valproate taking off, that it was possible to get any interest at all.⁶³

⁶² At C H Boehringer Sohn, between 1975 and 1990.

⁶³ See Richens and Dunlop (1975); Richens (1979); Jeavons and Clark (1974); Hassan *et al.* (1976).

Flower: It's the prostacyclin story again, isn't it?⁶⁴ Andrew Herxheimer, do you have any concerns about the relationship between the marketing side of the pharmaceutical industry and the scientists and clinicians who develop and test drugs?

Dr Andrew Herxheimer: I think that the power relationships within companies are crucial to that. If the senior managers are on the marketing side, then what they say goes. On the other hand, if the people who have clinical experience and their feet in clinical reality can resist that, then things can be balanced. So I think from that point of view, it would be quite interesting to hear about the culture of different companies: how leadership gets allocated to different kinds of people, and how they behave when they are leaders. Some leaders just change when they become leaders and include everybody in an even sort of way, but I don't think that's so likely with marketing people. But that is just my gut feeling. I have no data. We want to hear about experience.

Fowle: I want to point out that you've had a range of replies to the question: 'What was the pressure?' I wouldn't say it was always pressure, but there was always an interesting discussion that went both ways. I made a discovery very early on that nitrates applied to the skin caused venous dilatation. This was not recognized physiology when I discovered it; it was thought that nitrates went into the system and worked centrally, but they clearly didn't. There was vasodilatation and we were trying to get the Wellcome Foundation interested in it. And as Peter Lewis said, you can't always get them to take an interest. I do share their problem, and I'd just like to point it out to you. I thought it was a little unfair of marketing, but the argument they would use to me was: 'If we try to make this drug, we have to divert our resources from something which is making a great deal more money, and that's not a very good idea for something as minor as a local vasodilator.' They took a punt as to how big a market it would have been. Possibly they got it right, but it was an argument that was very difficult to resist, and I did feel slightly aggrieved that they wouldn't accept that. Neither would they accept a very nice device we got, a sort of dipstick to make a very rapid diagnosis of urinary tract infection, which also would have been very handy clinically. But I accept their argument that to make it would

⁶⁴ Professor Rod Flower wrote: 'This refers to a power struggle between the scientists and the marketing division at the Wellcome Foundation which followed the discovery of prostacyclin. It was said that there was no market for a drug of this type by the marketing division, but nevertheless it was finally licensed and sold. It still brings a regular income.' E-mail to Mrs Lois Reynolds, 14 July 2008. On the discovery of prostacyclin, see also Reynolds and Tansey (eds) (2005): 52–3.

divert resources from something that was making a great deal more unit profit. I throw that in for the sake of fairness.

Professor Sir Charles George: Two points: having looked at the fate of people who are senior registrars or lecturers in academic departments, I think David Grahame-Smith exported more of his trainees into the pharmaceutical industry than anybody else's unit in the UK.

The second is, given the fact that we've heard that quite a lot of people in industry learned their clinical pharmacology while being employed by the industry, we shouldn't forget that two things happened: first of all, the diploma of pharmaceutical medicine (DipPharmMed), for which there was a syllabus that included aspects of clinical pharmacology, and then subsequently the creation of the Faculty of Pharmaceutical Medicine, which I think has done a lot to raise awareness of clinical pharmacological principles within the industry.⁶⁵

Professor Owen Wade: May I ask you, or the people here, about the other way around: people coming from industry into academic work? Robin Shanks came to me at Queen's University, Belfast from ICI, and I'm sure this was certainly a very valuable thing for my department. And between 1975 and 1977 Martin Kendall went from my department in Birmingham to industry for a bit and then came back. This was, I thought, very valuable.⁶⁶

Baber: Just a brief comment on my own case. I had the privilege to work with Alasdair Breckenridge and Mike Orme while I was at ICI. For that whole nine years, I had a position at Liverpool University with the department of clinical pharmacology and spent one, sometimes two, days a week over there. So, I probably fall very much into that camp of learning much of my clinical pharmacology, if not most of it, while I was actually employed in the industry. It was a great privilege to have that opportunity, working with that company. But I think there were a number of clinical pharmacologists in industry who probably did have academic appointments, but who did not move completely back into academia.

⁶⁵ The Faculty of Pharmaceutical Medicine of the Royal College of Physicians was formed in 1989, see www.fpm.org.uk. (visited 9 July 2008). For details on the DipPharmMed see www.fpm.org.uk/examinations/dippharmed (visited 5 June 2008).

⁶⁶ One of the best known examples of such movement is the career of Sir James Black. After lecturing at the universities of St Andrews, Malaya and Glasgow, Black worked in industry for ICI and Smith, Kline and French. He then became professor of pharmacology at UCL. From 1978 he moved back to industry as director of therapeutic research for the Wellcome Research Laboratories, then returned again to academia in 1984, joining King's College London as emeritus professor of analytical pharmacology.

Lewis: Apropos of that point, when I joined industry from the Hammersmith, I asked Colin Dollery what would happen if I didn't like it. And he said, 'If you're not back within two years, forget it.'

Flower: John, would you like to comment on this? And while you're at it, I wonder if you could add a few remarks about the ABPI, which you touched upon briefly a few minutes ago?

Griffin: I'd like to pick up on the point that Nigel made about having days seconded out into academic departments. When I was working in the pharmaceutical industry, I was privileged to have two days a week working with Paul Turner at Bart's, and that was extremely valuable.⁶⁷ That was something that continued on a one-day-a-week basis when I moved into the Medicines Division of the Department of Health and Social Security (DHSS) in 1971. This is something that was encouraged and I'm not sure that it's still being encouraged. I think it would be very useful for young doctors doing clinical pharmacology within the industry and in the regulatory authority to have the opportunity that we had.

As far as ABPI is concerned: since I left ABPI they've started sponsoring clinical pharmacology within the industry and/or academia. I don't know whether anybody would like to comment more on that, because that happened after I left, but I think it's a very useful initiative.

Baber: Yes, this was an idea which was, if I may say, designed by Morris Brown and myself on the back of an envelope one day.⁶⁸ This is when I was at Glaxo. It may be possible to get funding, I suggested, from the postgraduate deans or whoever it was at the time, to finance half of a clinical pharmacology post, say at registrar level, and industry would fund the other half. I talked to many of my colleagues in industry and they thought it was a good idea, that there was probably more money available at that time from industry for doing this sort of thing. We were able to put the industry part of it in place, and that was done eventually through the ABPI. What we hadn't planned, really, was to track the careers of the holders of these joint posts. This seemed to be a very welcome opportunity for further amalgamation of function between industry and academia. The idea was that the person wouldn't be pressurised to follow a career in either industry or academia: they would make the choice of what they wanted to do. I doubt if that sort of thing is going to be possible now with the

⁶⁷ Barts and the London School of Medicine and Dentistry, University of London since 1995.

⁶⁸ See Baber and Brown (1996).

current arrangements and training, but it was a good initiative at the time. I'd be interested if anybody has comments on that, those who have actually had registrars going through this system.

Professor Denis McDevitt: I was just coming back to this point about people moving from industry into academia. Earlier we were discussing ICI 50172 (practolol) that many of us had interaction with.⁶⁹ My recollection is that the two people in ICI who were dealing with it were Mike Barrett, subsequently professor of pharmacology at Leeds University, and Desmond Fitzgerald who, for a period anyway, became the professor of clinical pharmacology at McMaster University, Ontario, Canada.

Professor Brian Prichard: We had two senior appointments of the sort that have just been discussed at consultant level. Dr Richard Waldon had a joint appointment with Sandoz Basel; this was set up with Dr Walter Aellig, well known as a regular contributor to the Clinical Section of the British Pharmacological Society.⁷⁰ Dr Walden had a Sandoz office at UCL to enable him to fulfil his industrial commitment, although most of his time – about 70 per cent – was spent working in the department of clinical pharmacology at UCL. This arrangement went on for many years. Another similar appointment was that of Dr Chris Owens. Dr Owens was a senior lecturer in clinical pharmacology and an honorary consultant physician at University College Hospital (UCH), in which capacity he participated in running a general medical firm. This appointment was set up with Dr Denis Burley, medical director of Ciba Horsham. Dr Owens spent on average two days a week, 40 per cent of his time, there in Horsham as a senior medical advisor, with the remainder at UCL.

Professor John Reid: May I just go back to the Department of Health/ABPI training scheme? I have different memories from Nigel of that being set up. I certainly attended a meeting with the council of the ABPI plus representatives of the Clinical Section of the BPS. We've had four people through that scheme. Some of them have done very well, some of them have not gone anywhere. Aberdeen has a long running programme – we still have someone now who is in his third year of a specialist registrar training post. He is funded jointly by Merck and the local postgraduate deanery through the scheme. I think overall it's been successful, as our links with both Pfizer and Merck coincided with the existing collaboration we'd had in early drug development with these companies. In our

⁶⁹ On practolol see page 4.

⁷⁰ For example, Aellig (1976).

case it was used to create an extra academic training slot rather than creating a cohort of people to go into industry.

Sir Iain Chalmers: I don't know if one is allowed to do this at one of Tilli Tansey's Witness Seminars, but this issue of movement between industry and academia is something in which she's had a fairly intense interest as a historian herself. I would be very interested, if it's allowed, for Tilli to reflect on the discussion that we've been hearing.

Tansey: Thank you, Iain. I'm very interested, as you pointed out, in this question, and I think it is very company-specific. I'm particularly interested in what has been said about the differences between UK and US companies. In this country we have a very long history of interaction between academia and industry, and it started very much with Henry Wellcome, with the Burroughs Wellcome Company.⁷¹ It was Henry Wellcome who first set up industrial research labs in this country that employed people like Henry Dale, George Barger and John Gaddum. They all started their research careers in the Wellcome Laboratories and then moved either into the MRC or into academia. That established a long tradition in this country that it was perfectly kosher to work in industry and to move then into research institutes or into universities. And of course Henry Dale himself became the first member from the pharmaceutical industry to be elected an FRS in 1914. And there was no prejudice – I have looked through minute books of the Physiological Society and Pharmacological Society – there was never any prejudice against electing people coming from industry. Now, in the US it was very different. The American Society for Pharmacology and Experimental Therapeutics did not allow members from industry. If a pharmacologist was in an industrial position, they could not become a member of that professional body. And if a member of the professional body joined the industry, then they had to resign from the society.⁷² That lasted until 1942 and that may account for some of the differences that have been raised today about in-house research in British companies and European companies, as opposed to the US tradition we've been hearing about. So, I do think it's rather different. I also think those barriers have actually become less free. I think the barriers have become much firmer in the more recent past. And I think there are training issues that have come up that

⁷¹ See Church and Tansey (2007): 475–95. Dr Derrick Jackson, who was unable to attend the meeting, is among several others who have made this point and has provided an account of his career in academia and industry, which has been deposited along with other records of this meeting in archives and manuscripts, Wellcome Library, London, in GC/253.

⁷² See Parascandola (1990).

are very important. But in the 1950s and 1960s from what I've been told by people like Tony Peck and Arthur Fowle and Douglas Munro-Faure about some of these exchanges, it was much more fluid, with people moving backwards and forwards. I think, however, it has changed in the past 20 years.

Sir Alasdair Breckenridge: When Michael Orme and I were in Liverpool, I guess we had about eight or nine of these ABPI-sponsored trainees. I would say I would regard about three or four of these as being successful. These three or four were people who came into the scheme with the aim of finishing up in industry. This was their aim, and they achieved this and they have done very well. Those people who had wanted to stay in academia or were open-minded about their future, very often resented their time in industry when they felt that they were being used as a pair of hands, very often in phase I units, diverting them from what they really wanted to do. For those who were interested in academia, when we tried to synchronize their work in the department and their work in industry so that there was a seamless passage from one to the other, this proved incredibly difficult, very often for very good reasons. Either the compound they were working on had been discarded, or there were production delays. So, I've got a very mixed view of the scheme and, as I've said already, I would regard it as very good for people who would want to go into industry, but not for those who wanted to progress in academia.

Smith: Nigel and I just exchanged thoughts. I don't accept Sir Alasdair's analysis. Particularly in the last 30 years in the US, I think there's very good interchange between academic departments and the industry. There were people going backwards and forwards. If you go to the national meetings, this is self-evident.

Tansey: I'm interested in hearing that. One of the things I'm very struck by looking through, say, the *British Journal of Pharmacology* in the 1950s and 1960s, is the amount of collaboration between people and interchange between drug companies. I'll be very interested to learn if that's something that has changed in the past 30–40 years. In the 1950s and 1960s, one can read papers where there are three or four authors from different drug companies all working on a compound together, particularly in tropical medicine.⁷³

⁷³ Dr Len Goodwin wrote: 'At that time, relations between scientists in the pharmaceutical industry were easy and friendly, and we (Wellcome) co-operated in a study of a whole series of antimony compounds.' Goodwin (1995): 340. For an example of Wellcome/Glaxo collaboration, see Goodwin and Page (1943). For earlier evidence of industry collaboration, between Allen & Hanburys and British Drug Houses on insulin production in the 1920s, see Church and Tansey (2007): 299–309.

Baber: Just a quick comment. Again, it's very Merck-specific, because that's a company I worked for. They supported financially a PhD for a person working with me, not a medic, and also with a topic of interest to the company but with a good academic background for his PhD. After I left Merck they appointed a professor of clinical pharmacology recruited in the US to head up the department, so there was an easy passage of academics into Merck.

Professor Cameron Swift: A very quick comment, again on the joint-training issue. It seems to me that we have anecdotal information with small n -numbers to feed back on the success or otherwise of these schemes. We've had a couple in my own unit at King's. One, in fact, came to us with a career interest in clinical pharmacology, and found the time at Harlow with GlaxoSmithKline (GSK), particularly the exposure to high-quality industry drug development programmes, absolutely invaluable. The experience broadened his outlook, and he has achieved his objective of a senior post in academic clinical pharmacology. The other proved unsuccessful, in that he didn't actually complete the course, and ended up in industry without full training as a clinical pharmacologist. I think a variety of accidental routes have emerged. It would be very useful, if possible, to try to get an analysis of just what has happened with a larger n -number, because our perception is of the potential for the scheme to be incredibly successful, for the right individuals. It's good and should be encouraged.

Reid: Simon Maxwell and David Webb are actually gathering this information at this time. I recall, within the last 12 months, being contacted about it.⁷⁴

Dr Jeffrey Aronson: I was going to make a quick comment about the ABPI training scheme. For the anecdotal part, in Oxford we have only had one such individual. I think I'm right in saying that he came to us with no intention of going into work for a pharmaceutical company. He had a six-year course and one year was an attachment to a drug company, GSK. He went off and came back as though he had been on the road to Damascus. He left a year early and is now very successfully working with GSK. I think that was a success story. My view of the scheme that Nigel and Morris instituted, under the aegis of the Royal College of Physicians with the ABPI and the NHS Executive, is that the intention, as far as I see it, should have been to train clinical pharmacologists in academic departments. This would provide academic departments with high-quality individuals for their purposes, but also enable those who wanted to, and that needn't be all of them, to find a place in a pharmaceutical company,

⁷⁴ Heaton *et al.* (2008).

because academic jobs are not readily available, certainly less so nowadays than they were. I think that the one story that we had was a success in that case. Now the scheme has not completely fallen into disuse, but it has not been formally pursued, and we are, as John Reid said, trying to find out what has happened to all the trainees that have been through the scheme. David Webb and Simon Maxwell in Edinburgh are surveying what's gone on. We hope that we'll have some information about that to follow up.⁷⁵

I wanted also to make a comment about the question about diffuseness of the different companies, because I confess that I suggested the question, 'Are there differences between companies and is there such a thing as "the pharmaceutical industry" that we all talk about'. And I think my prejudice that there is no such thing has been largely confirmed by the discussion today. We've heard a lot of disparate views on how things are conducted in different companies, but I think it is more diverse even than that, because we've only heard in the main about 'Big Pharma', as we call it. We've heard about Glaxo, the Wellcome Foundation, GlaxoWellcome, GlaxoSmithKline, Pfizer, Roche, AstraZeneca and ICI. We haven't heard about the small drug companies because we don't have people here who have been largely in these companies.⁷⁶ We've had a word from Tim Mant about clinical research organizations. We haven't heard about biotech companies, genetics companies or companies that mix pharma with genetics. I think there's huge diversity and I'm not clear at all that we can think about a single industry in one word, that we should regard as a single entity, and I think – I'd be interested to know what people think – but I think it's a mistake and the public has this view that the industry is one homogeneous mass, and it is not the case. There are different companies and they all behave differently. I do think that my prejudice in that has largely been confirmed by what we've heard today.

⁷⁵ Heaton *et al.* (2008).

⁷⁶ Professor Laurence wrote: 'After the major success of propranolol Sir James Black proposed to ICI that he develop a second class of histamine H₂ receptor blocker (cimetidine) that might revolutionize the treatment of the peptic ulcer (another potential money-spinner). ICI declined to implement his proposal, the consequence of which was that Jim left ICI in 1964 and went to Smith Kline and French. He was completely successful there and was eventually awarded the Nobel Prize for these two successes. Once I put to Dr Garnet Davey, ICI research and development director, that ICI could have had cimetidine "and you let the chance go". He replied that if Black was unhappy it was best that he should move. He said he had no reason for regret. I was dumbstruck. It was then that I realized that a giant private enterprise company could be as inflexible as any government department.' Letter to Mrs Lois Reynolds, 10 August 2008.

Mant: To emphasize how correct you are, I'm very fortunate in that I work with big pharma, small pharma, biotech companies, academia, charities, and across the industry, and there are dramatic differences. Often though, it is a leading person who has come from academia and is now the medical director or the scientific advisor to a biotech company, which is sort of almost three men and a dog, and they are often superb. Other people are not so good. As a CRO it is fascinating because sometimes you have to provide all of the clinical pharmacology backup; other times it is a learning experience from an innovative expert. So, complete diversity.

Collier: I couldn't disagree with you more, Jeff. It seems to me, that while there are differences from one company to another in certain respects, and there clearly have to be, from the outside there's so much that binds them, they can certainly be seen as 'the industry'. They have certain features that are absolutely standard: their information requirements; their legal requirements; their profit motive; their basic arrangements of determining trials, and so on. So, there's so much about them that's actually common, you can certainly say: 'That is what the pharmaceutical industry would do, and that's probably what the individual company would ultimately do', or you can guess what they would do, and they'll do it. I think it has always been so. However, in terms of how clinical pharmacologists function within any one company, clearly it is different, and maybe that's why you're saying it's different. But from my observations from outside, they are very similar.

Flower: I'd like to change topics now, to discuss, in a bit more detail, the interface that developed between academic departments and the pharmaceutical industry. Before we began this session, I asked Nigel Baber if he'd very kindly prepare a few words on the latter.

Baber: Again, this is going to be personal recollections. I'm certainly not the right person to give a historical perspective from thalidomide to the present day – there are others in this room far better qualified to do that than I. I guess you've asked me to do this because I've spent eight years at the MHRA, previously the MCA. But I would say that I did not work in the clinical trials unit, which is the department which dealt particularly with clinical pharmacology and the post-CTX system.⁷⁷ The industry I have described I could perhaps call the 'golden days in clinical pharmacology in industry', in some ways. It was the days of the CTX when we didn't require regulatory approval but we could move quickly

⁷⁷ See note 28.

into volunteers after local ethics committee approval. It was the *raison d'être* why US companies wanted clinical pharmacology to be done in their European subsidiaries. Of course, a question must arise from that – and I think Professor Grahame-Smith touched on it: were we as safe as we could have been without regulatory scrutiny? Our guardians were the ethics committees, who had to act both as ethics committees and scientific committees.⁷⁸ I like to think we were as safe as now: we had some very tough times getting our protocols through ethics committees at the companies for which I worked, when we had company volunteer studies, i.e. ICI and Glaxo. For Merck, of course, it was the ethics committee associated with the academic centre where we were working. So, that's been the big change for me, the obvious change, this pre- to post-European clinical trials directive.⁷⁹ Even with my time at Glaxo it was still the pre-European clinical trials directive. My impression from talking to the managers and people working in the clinical trials unit at the MHRA before I left – where, as I said, I was not responsible for this part of the business – is that the problems are not so much with industry and their protocols, with regard to getting permission to do phase I studies, but with academia. I'm sure that Alasdair will comment on this as well. I think that might be a very interesting source of debate: were the ethics committees in the past adequate to give protection to volunteers? We lost speed, time, and I must say interest as well, since the European clinical trials directive, because many clinical pharmacologists now in industry don't do hands-on work. Again, I'd be interested in Tim Mant's comments. When I was in these three organizations, all clinical pharmacologists wrote protocols, administered drugs and ran studies. And, I suspect, many clinical pharmacologists in the big companies now – I do stress the big ones – are very remote. They sign off but rarely write protocols; they are organizers and managers. It is a pity there aren't any younger clinical pharmacologists from industry here today to find out whether that is true or not. So, I think the divide between the CTX system and the European clinical trials directive has made a tremendous change in the interface of industry with the regulatory authorities.

Two quick anecdotes about personal interactions with the regulatory authorities: in all my time in industry, I was never asked to appear before the regulatory authorities. The CTX system worked very, very well indeed. I completed the technical part of the CTX application, then it was sent to the regulatory department of the company who did the administrative bit. I once had to appear

⁷⁸ See Glossary, page 107; Reynolds and Tansey (eds) (2007): 195.

⁷⁹ European Parliament (2001).

before the Dutch authorities when we were about to launch a combination of bendrofluazide.⁸⁰ The authorities wanted me and my colleagues to defend the dose that we'd selected for this fixed combination. The chairman was Dr Graham Dukes, and it was a very tough couple of hours. The other time was with sumatriptan, as I mentioned before, when we had these peculiar chest symptoms.⁸¹ I actually asked for a meeting with the MCA. I thought we ought to go down and talk to them. Pat Humphrey came with me, as did the head of toxicology, Michael Jackson, so we could give them a full picture of findings, our interpretations of them and what we intended to do.⁸² And they said, 'Thank you very much, that's very interesting. We will wait to see further data'. So my personal interactions of industry with the regulatory authorities over that long period of time were always minimal, and quite benign.

Breckenridge: To follow up the points that Nigel made: there is no question that the European clinical trials directive was welcomed by the industry; it was formalizing a procedure that it had followed anyway, and it presented few problems. He's absolutely right: the problems that there have been have been with academia, both in terms of the cost of the applications and in terms of sponsorship. Coming on to the question of ethics committees, I think it is very important to make the point that TGN1412 was an absolutely crucial issue for the European clinical trials directive, and for ethics committees.⁸³ Many people are now questioning what the scientific roles of ethics committees are and whether or not they are qualified to make the decisions asked of them. I think one of the shakeouts is going to be the role of ethics committees in the light of the European clinical trials directive.⁸⁴ This is an area that I am very uneasy about at the present time.

Grahame-Smith: Could I give a slightly different angle? In 1988 I met with Keith Mant and David Morgan at Beecham's, when Beecham's were in the process of developing Seroxat (paroxetine) and they, it became apparent, wanted some external 5HT know-how; serotonin know-how. We talked, and

⁸⁰ See Agrawal *et al.* (1979).

⁸¹ See note 20.

⁸² Professor Baber wrote: 'Pat Humphrey was the lead pharmacologist at Glaxo (Glaxo Group Research) on the serotonin programmes. He is largely credited with the discovery of sumatriptan'. Note on draft transcript, 8 July 2008. See Humphrey *et al.* (1991).

⁸³ On TGN1412 see pages 59–60 and Glossary, page 107.

⁸⁴ On changes to the role of ethics committees in light of EU Directive 2001/20/EC, see MHRA (2004).

a unit was established that they supported, within, or attached to, the MRC unit of clinical pharmacology. This was mainly concerned with serotonin, both its basic pharmacology and its clinical pharmacology, in terms of its clinical psychopharmacology, which was examined in the department of psychiatry, all in Oxford. And so a unit of about 14 scientists, including technicians and so on, was founded just below the MRC unit of clinical pharmacology in the Radcliffe Infirmary, Oxford, and ran for ten years alongside the university department of clinical pharmacology.⁸⁵ Now, it's not for me to say whether it was successful or not, because the science moved along from what I would call a straight kind of receptor pharmacology to neuro adaptive responses, and the neurobiology of neuro adaptive responses, which became very murky indeed, and is still pretty murky and very interesting, but a different sort of science to that to which we were really used. I thought it was a very good combination of pharmaceutical industry's strategic interest and an academic unit with both clinical and basic expertise, which was able to move things along. Now one of the things we haven't really mentioned in terms of research in industry is that views change when scientific management changes. In other words, if a senior scientist is brought in at some level, to manage things, the views change as to what is useful and what is not useful, and what you want to go with, or what you don't want to go with. That can alter relationships within the company and external relationships as well, something which is one of those human things, that we all know about, but can actually have a big effect upon research and development.

Flower: A very interesting point. Phil Routledge, I am going to ask you whether you had any comments about your clinical trials unit in Cardiff?

Professor Phil Routledge: Yes. Alan Richens set it up – I think in about 1982 – and it ran until his retirement about ten years ago. It was very important; I met a lot of people in this room for the first time through that unit, and learned a lot about the industry. Also it obviously generated income, which was used to do research which was perhaps not in the pharmaceutical company's particular interest, but which was of academic interest, sometimes leading to useful pharmacology. I always remember it as being a very positive experience, and I think that it did encourage us to understand the pharmaceutical industry and to work better with them. I think that is always an important thing, especially in medicines management, we forget that the drugs we are using are from the industry and without them we wouldn't have those tools.

⁸⁵ See Reynolds and Tansey (eds) (2008a).

I would just like to comment on the ABPI scheme, because as clinical secretary of the BPS I was also involved in the early negotiations in setting it up and I believe it has been extremely useful. We actually have one candidate at present in Cardiff who is sponsored by AstraZeneca, and I think again it does help us to understand the role of the industry and hopefully for industry to understand better the role of academia, in us working together.

Professor Michael Orme: I just want to go back, since we've just mentioned clinical trials, as someone who has never actually worked in the pharmaceutical industry, because actually I have worked alongside them in a number of studies. Clinical trials to me have always been fairly fundamental, but it is not the only thing in clinical pharmacology. So, it surprised me slightly earlier on when Joe Collier said – I think he said – 'I have never done a clinical trial' or words to that effect.⁸⁶ As someone who has had a lot to do with training clinical pharmacologists, both in the UK and Europe, I regard clinical trials as something that clinical pharmacologists should have done and had practical experience. And perhaps Joe now feels differently.

Flower: Do you feel differently, Joe?

Collier: I have done trials in patients, directed by me, under my own protocol, resolving things that I wanted to know. I have not kow-towed to protocols thrust upon me by money-making arrangements, and which are not particularly interesting to me. So I have done small clinical trials on my own terms. Of course, I learned about clinical trials from my reading, but I have not got the sort of experience that people in this room have, in terms of managing vast clinical trials.

Swift: Just a quick point. I have a self-destructive (or perhaps self-interested) interest in the general area of ageing and in the need for industry to obtain data for drug development relevant to that. In the early stages when that became necessary, regulation was very non-prescriptive as to what particularly the equivalent of phase I studies in older subjects should contain. Equally, within academic clinical pharmacology and our own research interests, there was considerable flexibility of approach. The point I am trying to make is that for quite a bit of that work it was perfectly possible to have, at a pretty fundamental level, an exploratory dialogue between those in industry who for development needed to acquire pre-licensing data and ourselves who wanted to know more about the ageing process; how it affected drug handling and drug response.

⁸⁶ See page 13.

Then we could agree protocols that were capable of peer-reviewed publication, contributing to the field at a basic level, and also met the requirements of industry for drug development. It seems to me that that kind of symbiosis was useful and constructive across the divide on both sides.

Prichard: Large-scale trials are clearly very important in the evaluation of new drugs and defining their efficacy. I think actually one of the most interesting studies that I got involved with was with four different doses of propranolol and placebo, in a dose–response study, just asking the patient to record their attacks of anginal pain. We got a lovely relationship, everything as good as gazing at the guinea-pig ileum, which is something I did for three solid months.

Griffin: The comment I would like to make in summing up whether there is a single industry or a diverse collection of companies is: yes. The industry acts as a unit, in response to those things that are thrust upon it from outside, whether they be regulation or whether they be PPRS. But each individual company has its own ethic, its own needs and its own scope of activities. And outwith that area they are, or they can be, very diverse. So there are common reactions and diverse needs.

Flower: Well I think that's a very fair summary, and I think that's a good point to draw the pre-tea discussion to a close.

So, we shall begin the second part of the afternoon. There is one topic which we should have addressed before tea, but didn't get around to, and I'd like to rectify that by asking Andrew Herxheimer to address the subject of whether pharmaceutical companies are benign or malign.

Herxheimer: Thank you – I say neither benign nor malign. The industry has a critical problem: declining productivity in drug innovation, and it must solve it or adapt to it. But for the last ten years it has responded mainly by increasing investment in marketing, lobbying and public relations. There was the introduction of heavy direct-consumer advertising of prescription drugs in the US in 1997, and ever since the industry has pressed to introduce something like it elsewhere. And then there has been massive investment to secure forceful and systematic involvement in professional, government and public affairs. That's created a new health climate, especially in the US, resulting in over-medication, and that poses three threats to public health. One is iatrogenesis, personal illness – I was thinking of asking Cameron Swift if there's a systematic review of clinical trials in older patients of withdrawing their medicines, because that's where the problem is most visible, perhaps. But it's also social and cultural: it's

the spread of health anxiety. The second threat is unsustainable demand, which will lead to breakdown of health services, and to divisive inequity and access to health services. Thirdly, over-medication strengthens a drug establishment that perpetuates under-medication elsewhere in the world. Under-medication is the main problem for 2 billion people who can't get the essential drugs they need. Improved access to medicines could save 10 million lives a year. Now, what's this got to do with clinical pharmacology? Well, clinical pharmacologists in industry and in government are caught up in all this. They must serve their employers; they can't step out of line or they will be out of a job. So, it's a pretty grim situation, and the reason why they are neither benign nor malign is that pharmaceutical companies are socially blind.

Fowle: I'm not erudite enough to take on the philosophical side of what Andrew has just said, but I would like to point out that I worked as locum for several GPs when I was younger. And some of them used to say to me; 'No patient must leave this surgery without being given a prescription.' That had nothing to do with clinical pharmacology. And also, I formed a view that many of the GPs who flourished near teaching hospitals were not so good as those who flourished further away, because GPs in my early days were expected, if they lived near a teaching hospital, to send their patients to hospital because the patients demanded it. The GPs didn't have sufficient authority, or whatever they needed, to persuade patients otherwise. So not all of these bad things about prescribing arose because of professionals at the top of the profession, but for purely cultural reasons. And I suppose the remuneration of GPs had something to do with it.

George: While agreeing with Andrew that there is over-medication, I think that we should be aware of the fact that pharmaceutical physicians have an agreed code of conduct and very strong ethics guidance as to what they should not do within their company if there is pressure on them.⁸⁷ And that seems to be very potent as an antidote to what you just said, Andrew.

Chalmers: I think that the Faculty of Pharmaceutical Medicine is, as far as I know, alone among medical organizations in this country to have made some very clear ethical guidelines as to how pharmaceutical physicians should behave. Because one of my interests is publication bias, I'm particularly impressed by the statements they have made about the need to publish research that is done on humans. My question is: where on the board of companies is that ethical

⁸⁷ Bickerstaffe *et al.* (2006).

dimension? It seems to me that there ought to be, as a matter of course, a medically qualified person on the boards of all pharmaceutical companies, because otherwise some of the problems that Andrew has described won't really have any ethical reference point in the way that the Faculty of Pharmaceutical Medicine has provided through its ethics committee.

Flower: Joe, did you want to come in on this?

Collier: Yes, I could do that. I just wanted to respond a bit about whether the influence of the industry was benign or malign. Years ago I attempted to define what academic clinical pharmacologists did, and there seem to me to be four key strands: the first is that we teach, primarily medical students and young doctors, about medicines and their best use; the second is we advise, and that's pretty broad, but we might advise our trusts, colleagues, ministers, MPs, health departments, media, consumers, select committees or whatever, so advice is very important; third, as most of us are doctors, we also prescribe; and finally our fourth role is to do research.⁸⁸ Now, when it comes to the first three of those – teaching, advising and prescribing – the amount of misinformation that I receive from the industry, or the amount of distortion I get from the industry, makes them malign, because I can't necessarily trust them. Trust is a real problem. When it comes to research, they are clearly benign in some respects, because by the very nature of one's work with them, they prompt change and provide new products, they can respond to your interests and so on. So in this last role, provided one can control oneself and them, then I think the relationship is a benign one. But in the other three the industry causes no end of confusion and difficulty. If the industry was better behaved, a lot of the things I do would be unnecessary. So I would say, in three out of the four roles of my life as a clinical pharmacologist, the influence of the industry is on the side of malign.

Flower: Does anyone else want to get back on that question before I ask Joe to talk about the development of regulation in the post-thalidomide era?

Collier: I've been asked to give a bit about the background to the Medicines Act of 1968. As I'm sure all of you know it was the outcome – as in many, many other countries (apart from the US, which already had legislation in place) – of the thalidomide disaster.⁸⁹ I think everybody was piqued, infuriated,

⁸⁸ See Collier and Herxheimer (1991).

⁸⁹ See Tansey and Reynolds (eds) (1997): 106.

annoyed by the claim of absolute safety made by the drug company, ‘safe in mother and child’ or something like that, which was clearly wrong and a claim for which they had no evidence.⁹⁰ These and other outrageous and misleading claims meant that we needed to introduce tight controls. The Medicines Act was passed in 1968 in the UK and became law in 1971. Since then, much of the Act has been subsumed into the legislation as it relates to the European Union. It is now difficult to discover what the Medicines Act itself still covers and what is a specific remnant of the Medicines Act and what effect now relates to the European Union. I’m not going to try to distinguish between those, but there are differences; for example, in the UK the legal position on the availability of a medicine is based on the Medicines Act and states that a drug medicine can be sold as a pharmacy (P) medicine, as a prescription-only medicine (POM) or as general sales list (GSL) medicine. This differs from the rest of the EU where there are only two categories (POM and over-the-counter). As might be expected, much of what became European Union legislation came from the Medicines Act, while other sections will have been derived from other countries.⁹¹ The first thing that I want to say is that the Medicines Act is primarily directed at controlling pharmaceutical industry practices. It controls the manufacture, marketing, supply and promotion of its products. It also, to an extent, controls pharmacists and pharmacies. By contrast, it has relatively little direct effect on doctors and how they prescribe. People often forget that the Medicines Act is not aimed at the actual activity of doctors in their prescribing, although it has become part of what people think. It is no surprise, therefore, that it directs most of its attention to industry and similarly is very sensitive to industry’s needs.

Let me talk about the history of the Medicines Act. When any agency is introducing legislation, there are lobbying groups who work to ensure that their interests are reflected in the new law, and the Medicines Act is a very good example of what is known as ‘legal capture’. The industry – a powerful body – was very influential in determining the contents of the Medicines Act. And so, for instance, when one looks at the criteria to be used for licensing a new medicine there is no definition in the Medicines Act of relative efficacy in clinical practice. There’s no requirement to determine relative efficacy as such in

⁹⁰ Dr Walter Kennedy, who was then medical advisor to Distillers, the first company to put thalidomide onto the market in the UK, wrote a glowing report on the drug after visiting its German manufacturer, Chemie Grunthal. See Tansey and Reynolds (eds) (1997): 116.

⁹¹ See Griffin and Shah (2006): 489–534.

the same way as you might want to look at relative safety.⁹² There's no concept of the notion of 'need' – for many, the question 'do we need this medicine?' would seem very appropriate. There is no concept of price; indeed price must not be taken into account. Finally, there's no concept of the notion of convenience. And, of course, tied in with all this, there was the very powerful notion of secrecy, which is set out so forcefully in Section 118.⁹³ Much of this secrecy still lingers, which means that if doctors would wish to know how decisions were made, they couldn't easily find out. Now it is improving, but for years it has been very difficult to get explanations for decisions made during licensing.

Another weakness of the Act is that by and large it excludes the involvement and interests of prescribers and patients. It is not absolute, but the notion of patients being involved in any part of the considerations of the Act has only come in recently. It was certainly not part of the Act as such. The idea of prescribers being closely involved is equally omitted from the system. So much so that on the whole – in my experience and that of others – doctors, prescribers and others don't feel as though they know quite how the Act determines the ways in which drugs are controlled and licensed, and with this most prescribers and others involved in the use of medicines do not feel as if they own it. I don't know what the situation is in this group here, but I have had two copies of the Medicines Act for about 30 years, one of which I keep on my desk at work, one at home. I expect no one else here has got a copy apart from those working directly in legislation, it's perfectly obvious. I know Tilli Tansey has one, but for a different reason; I'm talking about active clinical pharmacologists. Now, of course, those in industry might have their own copies. When I go to meetings, it is very common for people not to know things about the Medicines Act, and even grand people know nothing, or very little, about it. So, recently there was

⁹² Professor Laurence wrote: 'Bradford Hill (the great statistician, founder of modern clinical trials and a delightful man) took a perverse pleasure in reminding the medical members of the bizarre requirement that comparative efficacy could not be taken into account, for he was himself a master of comparative efficacy. I have no doubt that this requirement was included to please pharmaceutical companies that understandably dislike their own products to be inferior or redundant'. Letter to Mrs Lois Reynolds, 10 August 2008.

⁹³ Great Britain (1968): Chapter 67, Section 118: 'Restrictions on disclosure of information. (1) If any person discloses to any other person – (a) any information with respect to any manufacturing process or trade secret obtained by him in premises which he has entered by virtue of section 111 of this Act, or (b) any information obtained by or furnished to him in pursuance of this Act, he shall, unless the disclosure was made in the performance of his duty, be guilty of an offence. (2) Any person guilty of an offence under this section shall be liable – (a) on summary conviction, to a fine not exceeding £400; (b) on conviction on indictment, to a fine or to imprisonment for a term not exceeding two years or to both.'

a very important paper from the British Medical Association about prescribing, and they got it completely wrong. They completely misquoted the Medicines Act, saying that medicines need a licence before they can be prescribed in the UK.⁹⁴ This is just not so. Now, it's because no one cares about the details of the Act, it is because it's 'over there' and it's left to other people, because there is no ownership, that there's no reason to work for its change.

Finally, I want to address how the Medicines Act has worked over the years in that, by and large, it's been reactive rather than proactive. And it has had to respond to others saying: 'That's wrong'. It could be ministers saying it's wrong due to pressures from other MPs; it could be select committees saying it's wrong; it could be the National Audit Office saying it's wrong or whoever. So the Act itself can be interpreted in various ways, but the implementation of the Act has allowed things to seem to go rather wrong, to become rather secretive, to be not particularly interested in patients. So, my own view is that while things are changing, but very slowly, the Medicines Act has failed patients to an extent, and doctors to an extent – by not involving them, not seeing them as important, and not having terms of reference which take up their interests – and the same for prescribers. If you just compare the wording of the Medicines Act and the terms of reference, let's say, of any single drugs and therapeutics committee, they are very different. Drugs and therapeutics committees have relevant considerations to medical practice, and, of course, the Medicines Act doesn't.

Flower: Since we are in the business of collecting personal reminiscences, is there anyone here who would like to talk about their experience on the Dunlop Committee? It was a long time ago. Owen?

Wade: I thought you'd start in 1963, which was when the Committee on Safety of Medicines (CSM) was created. Our first meeting was in a horrible building which is the Ministry of Health building down by the Elephant and Castle, London.⁹⁵ George Godber, Chief Medical Officer 1960–73, assured us that the Committee on Safety of Drugs (CSD) would be in business for about three years, and then there'd be the Medicines Act.⁹⁶ We were in business for seven

⁹⁴ British Medical Association, Board of Science (2007): 'Medicines must have a licence, termed a "marketing authorization", to be prescribed or sold in the UK, which is granted if they meet standards of safety, quality and efficacy.' (page 1). See www.bma.org.uk/ap.nsf/Content/evidencebasedprescribing?OpenDocument&Highlight=2,evidence,based,prescribing (visited 23 June 2008).

⁹⁵ See Tansey and Reynolds (eds) (1997): 122.

⁹⁶ Brindle (2008).

years. I don't know what you'd like me to say about the CSD. The person who dominated it was Derrick Dunlop. I was a very junior member, a tiny chap really, and for the first few months of our meetings I kept my mouth shut, because Derrick Dunlop – when we first met, in 1963 – didn't explain to us what the remit of the meeting – the CSD – was, and what the limits, what our activities were to be, and what powers we had. I learnt all this slowly and was then able to make some contributions, but it was a little bit difficult at the beginning. The first meeting was in 1963, and we were not supposed to be in action until 1 January 1964.⁹⁷ But at that first meeting we were told about the adverse reactions part of the outfit, of which I was a member. We were warned about nasty adverse reactions happening with monoamine oxidase inhibitors. And we collected up the information about this and sent out the first of the yellow letters.⁹⁸ And we were amazed. Two things, I think, surprised us: one was the tremendously adverse criticism, which we received from – let me put my glasses on, who was it? It was William Sargant.⁹⁹ He thought that these drugs were wonderful and took great exception to us criticizing them, and I think he thought we were actually banning their use completely, which, of course, was untrue. I think the other surprising thing for all of us was, when we started – I'm talking now about the Adverse Reactions Subcommittee, because that's what I knew most about – we had expected most reports to come from the hospital service. They didn't. Well, not surprisingly, most medicines in our country are prescribed by general practitioners, and 70–80 per cent of the reports we got about adverse reactions, and the yellow cards we got, came from general practice. Chairman, I think there's a lot more I could talk about but you've got a lot ahead of you.

Professor Sir Michael Rawlins: Can you ask Owen to tell us about why they are 'yellow' cards?

Wade: Well, there's a bit of argument about this, but it just so happened that my department in Belfast had some rather cheap yellow paper, which we used internally. And it just happened that when we got the draft of the message that was going to be sent out to general practitioners about these monoamine

⁹⁷ Professor Owen Wade's own records of the first meeting of the CSD will be deposited in archives and manuscripts, Wellcome Library, London, along with the records of Tansey and Reynolds (eds) (2008b) in GC/253. The National Archives hold 67 registered files (CSD and CSM series) for the CSD and CSM at MH 171 for the period 1963–76.

⁹⁸ See Tansey and Reynolds (eds) (1997): 119, 123–4. See also Committee on Safety of Drugs (1964).

⁹⁹ See Tansey and Reynolds (eds) (1997): 124.

oxidase inhibitors, I read it. It was typical of civil service statements. I knew the way it was written would be hated by doctors, so I wrote out what I thought they ought to say on the cheap yellow paper. When Lesley Witts, who in those days was the chairman of the Adverse Reactions Subcommittee, read out, first of all, the one we were presented with from the secretariat, and then mine, everybody chose mine. And, it just happened to be on yellow paper, but the boys liked that. So that was why we got yellow paper.¹⁰⁰

Flower: Owen, before you go, Joe said he felt that the Committee – at least in its present incarnation – didn't really address the needs of patients or doctors. What was your experience on that committee?

Wade: Well, I think the Adverse Reactions Subcommittee from 1963 to 1971 was very much in touch with doctors, who were the people who sent the reports. Certainly, I had to go to see doctors sometimes in order to find out a little bit more about what they were reporting. The other two committees: Professor Hunter of Dundee ran the Clinical Trials Subcommittee and Professor Frazer of Birmingham the Toxicity Subcommittee at the beginning. I'm sorry; I just can't speak competently about those other two subcommittees.¹⁰¹

Professor Duncan Vere: Briefly; I came into that business a bit later than Owen, but certainly on the Adverse Reactions Subcommittee.¹⁰² I can only agree with what Joe Collier has said. It struck me from those earlier days that the whole procedure was in a sort of legal straitjacket. There was always a barrister sitting there and he would be asked about interpretation of the Act and so on. There were some strange legal rules. I won't go into all that at the moment, but the main problem that I had was the utterly unbiological thinking that was involved in some of those aspects of the straitjacket. This was true of the CSM and to some extent the Committee on Dental and Surgical Materials (CDSM), where there was endless debate about what a device was and what a drug was,

¹⁰⁰ For other versions of the origin of the yellow card for reporting suspected adverse reactions, see Tansey and Reynolds (eds) (1997): 111, 117–19, 121, 124 and 127.

¹⁰¹ Professor Owen Wade wrote: 'These two subcommittees clearly were thinking deeply about the safety of patients and the need to get information to doctors about the drugs being licensed, but were not as close to doctors as the Adverse Reactions Subcommittee, Professor Witts, Dr Bill Inman and I, were. We did not have any barrister present and were a very happy subcommittee under the chairmanship of Leslie Witts of Oxford and later under me. Perhaps things changed a lot after the Medicines Act came into action'. Note on draft transcript, 20 November 2007. For fuller comment see Wade (1996): 110–14; Inman (1999).

¹⁰² Professor Owen Wade wrote: 'This became the Adverse Reactions Committee in 1971, after the Medicines Act'. Note on draft transcript, 10 November 2007.

and when you had devices that were impregnated with drugs, you know, it all became desperately difficult. But it still had to be within this strange framework of legality. And there was a lot of fear about what happens with two things: either if somebody protests or is upset and there's danger of litigation from that angle; or if you haven't kept within the provisions of the Act. I think the provisions of the Act are very unbiological here, in fact, in their understanding, like lots of things that happen in law and in court.

Wade: I think the Dunlop Committee didn't have any legal power whatsoever, and the advice that we gave to the firms or other people didn't really have to be obeyed, but they did. I remember how amazed my US colleagues were when they found out we hadn't got any power at all, and it was all working with goodwill.¹⁰³ And, in fact, I think the old Committee on Safety of Drugs did do a good job. Remember, nobody had ever done anything like it before, and it was quite exciting. Certainly I found it extremely interesting.

Flower: Has anyone else got any other reminiscences about that era or comments they would like to make?

Griffin: Joe and Owen are quite right. The Committee on Safety of Drugs had no legal force behind it, other than a moral force. And it didn't take account in its justification of putting a new chemical entity on to the market, evidence of efficacy. Efficacy was built into the Medicines Act in 1968. Now, there is a flaw in the Medicines Act in that you cannot take comparative efficacy into account. You can take into account comparative safety or lack of safety by virtue of lack of efficacy, but you cannot take into account comparative efficacy. And this is still perpetuated in the various EU directives: you cannot take into account relative efficacy.¹⁰⁴

I became very unpopular with an article I wrote in the *British Journal of Clinical Pharmacology* in 1981, in which I reviewed the new chemical entities that reached the market from 1971 to 1981. There were 204 new chemical entities. Of those new chemical entities, there were three new therapeutic concepts. I defined a new therapeutic concept as something that enabled a doctor to do something which he hadn't been able to do before. And that covered 12 of the

¹⁰³ Professor Laurence wrote: 'The CSD had no legal authority. Its sanction was to make a public announcement that company "X" had marketed a drug against its advice. I doubt that any company would risk the consequences of that, I do not know that it was ever implemented'. Letter to Mrs Lois Reynolds, 10 August 2008.

¹⁰⁴ See pages 43–4.

204 new chemical entities. So, if you want to look at it, there were 21 non-steroidal anti-inflammatory drugs and 13 steroids.¹⁰⁵ Clearly you could have made an argument about need, if you'd had the power. The other thing that concerned me, and still concerns me, about the operation of the regulatory authority in this period, was the problem of dealing with adverse reactions. We had two working parties chaired by David Grahame-Smith, which made recommendations.¹⁰⁶ And I hate to say it, but none of them were implemented. And David, I think they should have been.

Flower: That's a good point to pull you in, David. What do you want to say to that? You could say, 'I told you so.'

Grahame-Smith: Well, yes. I've got a number of things to say because we've moved from the Committee on Safety of Drugs, after the Medicines Act was published, to the Committee on Safety of Medicines which was established in 1970, but started work in 1971, something like that.¹⁰⁷

Now, there was one summer afternoon, and I'd only just arrived in Oxford, and remember: (a) I didn't know anything about clinical pharmacology, really; and (b) I was professor of clinical pharmacology and was appointed to head the MRC unit of clinical pharmacology in Oxford. But just to liven proceedings up a bit: I knew all about serotonin and I knew a lot about digoxin. I knew a bit about the sharp end of practical therapeutics. But anyway, sitting in my office on a nice summer's afternoon, in came Richard Doll. And he said, 'Would you like to sit on the Committee on Safety of Medicines?' To which my reply was, 'What's that?' So he said, 'Well, you know what it is, don't be silly'. And so I said I'd be interested. So, the weeks went by, as these things go, you know. Looking back, I met a number of people and I was introduced to a number of people, and I realize now it was the establishment at work. Do you know what I mean? The word was being dropped here and there, and 'Is he a good chap?' and all that sort of thing. So anyway, I went to the first meeting of the Clinical Trials Committee, as it was called, and Desmond Laurence was chairing it. I'm sorry Desmond isn't here because he was a great man chairing that committee.¹⁰⁸ I

¹⁰⁵ Griffin and Diggle (1981).

¹⁰⁶ See Grahame-Smith (1983, 1986).

¹⁰⁷ The CSM held its first meeting on 25 June 1970 and took over the work of the CSD on 1 September 1971. See Griffin and Shah (2006): 473–4; see also Tansey and Reynolds (eds) (1997): 114, 131.

¹⁰⁸ Professor Laurence was unable to attend this meeting, but contributed to the first meeting on 6 February 2007 [Reynolds and Tansey (eds) (2008a)].

wasn't on the main committee then. And I sat down next to Austin Bradford Hill. Now, you know, there are some people who just take your breath away, and Austin Bradford Hill was one of those people. I had his book on medical statistics and didn't understand a word of it, because I'm not a numerate sort of person. So I sat next to Austin Bradford Hill and we were going through some data on something or other, and he handed me an envelope, showing me on its back just upright marks as it were, indicating the number of patients in each group that was being treated in this particular study. And he said to me, 'What do you think?' I was greatly heartened that this great man, who knew everything about medical statistics and so forth, was relying upon me just looking at these little marks on a bit of paper to decide whether this drug was effective or not.

Flower: We're dying to know what your answer was, by the way!

Grahame-Smith: Well, I can't remember what it was or what my answer was. Now, this was in Finsbury Square and I still have a pair of shoes that I bought at a shoe shop on my way to the meeting of the Committee on Safety of Medicines in 1975.¹⁰⁹ I regret that the Committee was moved to Market Towers (Vauxhall, London) because there weren't any shoe shops nearby. No, no shops at all, except for Covent Garden fruit and vegetable market, which had moved there, and of course, you could walk through that, couldn't you? Anyway, when I arrived there was the main committee. Now, Joe has been berating the Committee, 'the committees', 'the system', for not looking after patients and doctors. Well, I did read the Medicines Act, Joe, once upon a time – I can't remember all of it, of course – but I used to go back to it quite often to check up on things. And, as John Griffin says, safety of drugs is one of the main things, whether it's during development or when it's on the market, doesn't matter: safety is important. In the 1968 Act *efficacy* is very important.¹¹⁰ That's important to patients. Both those things are important to patients and they're important to doctors too: to know that drugs work. The system doesn't always get it right, but generally speaking it's been right.

And then there are pharmaceutical standards. In other words, do the pills contain what they're supposed to contain? Alasdair Breckenridge has been telling me that very often with counterfeit medicines they don't know, but by and large

¹⁰⁹ The Medicines Division moved to Finsbury Square House, 33/37a Finsbury Square, London in April 1971 from its original location in Queen Anne's Mansions, Queen Anne's Gate, London. It moved to Market Towers, 1 Nine Elms Lane, Vauxhall, London, in March 1980. See Griffin and Shah (2006): 464.

¹¹⁰ See pages 43–4 and 48.

they do. And, they are manufactured to standards which guarantee, generally speaking, that the drug gets into the body in a fairly predictable sort of way. So, to say that our drug regulatory system ignores patients' and doctors' needs is quite wrong. It may not be as refined as Joe Collier would like it, but it is certainly serious about these matters, and we operated under the law. Eventually I became chairman of the Subcommittee on Toxicity and Clinical Trials, and I'd better tell you about the evolution of that committee. 'Adverse reactions' was taken into the Toxicity and Clinical Trials Subcommittee because it was felt that we had the expertise around the table there to deal with the adverse reactions, which I think by and large was true. And so it became the Adverse Reactions, Safety and Efficacy committee.

Rawlins: And we decided that wasn't appropriate.

Grahame-Smith: Wait a minute. The acronym for that, Rawlins, is rather rude. So we called it the Safety and Efficacy, Adverse Reactions Subcommittee (SEAR) and avoided the rudeness of the other.

Rawlins: Much more fun, though, David.

Grahame-Smith: Much more fun. And no doubt would have created a lot of hot air, but we will leave it at that. Eric Scowen was the chairman when I arrived and poor old Graham Wilson was appointed after him, but died. And then Eric Scowen took over again, and then Abe Goldberg from 1980 to 1986, and then Bill Asscher from 1987 to 1992, and then Michael Rawlins, and then Alasdair Breckenridge. Whether it was still the Committee on Safety of Medicines then, I don't know. It was, wasn't it? Right, right, but not any longer. So it's now the Commission on Human Medicines (CHM) and Gordon Duff chairs that committee. John Griffin loomed large at the time, and I have to say, the professional civil service upon which such a committee – and that's the Committee on Safety of Medicines – relied was absolutely terrific.

There were huge amounts of detailed work requiring great diligence to make sure that things didn't pass by. I always remember that picture of Desmond Laurence and piles of paper, piled up taller than he was.¹¹¹ And this was just one afternoon's meeting. Absolutely ridiculous, but still, you learnt how to speed-read. That was one of the things it taught me. And I think that there were tremendous efforts all round. I remember Bill Inman, probably a thorn from time to time in John Griffin's skin, nevertheless did a tremendous job in raising awareness of

¹¹¹ See Figure 4, page 65.

adverse reactions with the yellow cards and later prescription-event monitoring. John, you say that I chaired working parties and all that sort of thing, and made recommendations that were never taken up: that was because they cost money. And the difficulty – and now even more so, if this giant NHS computer ever comes to pass – I’ll leave the silence after that just to sink home – if this giant computer ever comes to pass, the answer is: ‘record linkage’, where you put diagnosis, prescription, adverse reaction or event, and the thing clicks away in the night and then spews out a correlation. And then the human assesses whether there’s anything there or not.¹¹² Although record linkage took place in Scotland in a limited way, it never really invaded the south. The Department of Health really couldn’t afford it; I think that was the reason. I don’t think there was anything wrong with the concept, it was the actual putting into place of the system.

Many specialties were represented on the Committee – I’m talking about medical specialties. And it was a bit of a club; it was a good club. We got on well together, no, no, Joe, we did get on well together. You might not like that, Joe, it might be beyond your experience for all I know, but most of us like to get on with our colleagues, and we got on well together, by and large. We had our differences and arguments and so on, but the information was swapped between us all and we were highly informed. And I think that Mike and Alasdair would agree that, round the table, we were highly informed and consensus was usually, but not always, achieved. We did have, I remember, something that troubled me – I don’t know how much all of you know about animal toxicity tests and whether they tell you anything about a drug and so on and so forth. I think I would rather have it go into a few rats before it goes into me, rather than not, but the animal toxicity tests had become very laborious. So, we had a working party on animal toxicity, we did clean the thing up quite considerably from the point of view of the industry. It wasn’t industry that had asked us to do that, but toxicity testing had got a little bit out of hand. It is very difficult actually designing sets of animal toxicity tests to take care of everything from acute toxicity to long-term cancer problems. You can imagine, it’s not easy. Anyway, from my own point of view it was a tremendous education and you got to know nearly everything that was going on in drug development. Like Michael Rawlins knows everything that is going on about the drugs in the country and so does Alasdair Breckenridge. It’s a tremendous education. There were problems: Opren (benoxaprofen) was a problem.¹¹³

¹¹² See Skegg and Doll (1981).

¹¹³ Dahl and Ward (1982).

Rawlins: That was my first meeting.

Grahame-Smith: Yes, Opren was a problem and it was a pharmacokinetic problem in the elderly.¹¹⁴ Pharmacokinetics. It may be boring, but if you're old, beware, because you get high blood levels of benoxaprofen and it rots your liver, for some reason, and can kill you. And it did, unfortunately, kill a number of people.¹¹⁵

Flower: Can I just remind everyone that we are trying to capture reminiscences here?

Grahame-Smith: This is reminiscence, a sort of reminiscence anyway. Joe will agree that things evolve and we used to sit round the table at the Committee on Safety of Medicines and argue: 'We don't really need this drug – it's not worth the risk'. 'That's not your business' the lawyers used to say, 'Stick to: is it safe and is it efficacious?' Well, what we needed really was a body to consider whether we need this drug and what it costs. And, out of the woodwork a few years later, pops Rawlins and the National Institute for Health and Clinical Excellence (NICE). It's an evolution of the regulatory system that was in place, because the regulatory system was not doing that. Now, I know it trod on a lot of toes and so on and so forth, but now it's fully accepted as a process and there we are. So, that's all I have to say, really, about the Committee on Safety of Medicines. I'm sure that I've said some wrong things and there are other people who would like to say more.

Rawlins: Can I just add something about the yellow card scheme in the early 1980s, because it was chronic beyond belief the way it was looked after. I mean, this isn't John Griffin's fault, but the Department of Health and Social Security had only one computer and that was at Reading, and it produced the Giro payment cheques, except on Thursday afternoons when it had a little bit of

¹¹⁴ See James (1985).

¹¹⁵ Professor Cameron Swift wrote: 'It's of interest to reflect on the interface of drug regulation and clinical pharmacology with demographic change. The Opren events (among others) helped to drive the now established licensing requirements for pharmacokinetic and clinical trials information in older subjects, who are the largest group consumers of prescribed medication in developed societies. Indeed, the entire non-steroidal adverse drug reaction (ADR) story, as an example, embodies a strongly age-associated dimension. Twenty-five years on, we have some already dated international harmonization guidelines for drug licensing data in this population, ICH (1993). The story is perhaps still incomplete. Arbitrary and often inappropriate age exclusion criteria still emerge in clinical trials; pharmacokinetic and pharmacodynamic data, as well as prescribing, are often sub-optimal; and the international standard for ADR identification in trials (the Medical Dictionary for Regulatory Activities, MedDRA) still lacks some relevant categories (e.g. drug-induced *falls*). Is there yet more to be done?' E-mail to Dr Daphne Christie, 6 December 2007.

spare space. So, on Thursday afternoons it was able to interrogate the yellow cards. But the officers on the Medicines Division had to write out in triplicate precisely what analysis was needed and so on. And of course, you needed to go back to the original yellow cards themselves and do it all by hand, and really it was only a mechanism for pulling out the yellow cards of interest. And although David's working party may not have immediately materialized in something substantial, over the years there have been enormous changes and the place has got its own dedicated computer systems and computer languages and so on. And so it's a complete revolution to what it was. But I do remember those Thursday afternoons in Reading.

Flower: So that's why I never got my Giro cheque on Thursdays! Jeff has a comment.

Aronson: About the yellow cards. Owen has said there was debate about why they were yellow. For those who want to read about this, it was covered in a Witness Seminar that Tilli ran – one of the first – on the Committee on Safety of Drugs.

Tansey: Yes, on the Committee of Safety of Drugs, and we had four different accounts of why they are yellow.¹¹⁶

Aronson: That was an excellent Witness Seminar. I recommend it to everybody. Tilli, is it on the web? Can one get it?

Tansey: It is on the web.¹¹⁷

Dr Peter Fletcher: I'm really going to say a few words in response to David, because I think at the time, the committee, of which I was a secretary – not that I did much writing on it – was your first of the working parties.¹¹⁸ And that was looking at a problem that had arisen through the industry being unhappy about the length of time that assessments took to be made, and indeed the length of time that they were involved in actually doing the studies, as these seemed to be escalating year by year. Was there some way in which we could abbreviate the

¹¹⁶ See note 100.

¹¹⁷ See Tansey and Reynolds (eds) (1997): 103–35, freely downloadable at www.ucl.ac.uk/histmed/publications/wellcome_witnesses_c20th_med.

¹¹⁸ See Grahame-Smith (1983). The terms of reference for this working party were: 'To consider how best the Committee on Safety of Medicines should fulfil its statutory functions of promoting the collection and investigation of information relating to adverse reactions, for the purpose of enabling it to give advice on safety, quality or efficacy of medicinal products; and to make recommendations.'

amount of information that had to be scrutinized by John and myself and other people in the Medicines Division at that time? We came to the conclusion that the Medicines Act is deficient in not permitting there to be such a thing as a provisional licence. It would be nice if we could, in fact, allow certain drugs that had obvious benefits, but in which the safety profile was perhaps not as certain as we'd like it to be, to get onto the market so that the benefits were enjoyed without undue delay. This would have helped, in that delay obviously means money – it obviously means more intensive work – it means more patients, and perhaps even more animal studies. So, the first working party was set up to define some parameters by which we could have what we then came to know as post-marketing surveillance, or pharmacovigilance as it is now known. I think I'm right, that we hit upon a number drawn out of the air, that one in 10 000 – something the sort of number – that we began to get worried about adverse effects if they were thought to be there. So, we wanted to have cohort studies of 10 000 or about that sort of size or bigger if we could, and we would like to see fairly prolonged surveillance of those patients over that time. I think that, if I'm right in saying, was the outcome of the first Grahame-Smith working party.¹¹⁹

You've also mentioned the matter of animal toxicity, and that's quite right. That was also becoming, I think, a problem for the subcommittees as well as the whole licensing process. That was one thing which I think – I don't know whether it was with you, David, or not – I pointed out that in non-steroidal anti-inflammatory agents, which were demanding very long-term dog studies, every single dog study that had ever been done – and there'd been about 10 of them, I think, at that time – showed that dogs had gastrointestinal haemorrhage, at the same dosage level as that recommended for humans. And the committee would say: 'It doesn't matter because we know it doesn't matter.' So, we'd go on doing it. I think I pointed out that it was rather pointless to continue doing very expensive long-term dog studies, when in fact we knew that no notice was going to be taken of them. So, I think that is a little bit of the history of that time.

Vere: Very briefly on this problem of how the legalities operate. Obviously record linkage is terribly important and I can remember, before the Grahame-Smith working parties, this being pointed out. At that stage it was impossible for the funny computer that we had to communicate with the rest of Europe, because they were all incommunicable. I remember David Finney (a medical statistician) being apoplectic because he wanted to advise about the sort of machine that was needed and which could be purchased, and the answer clearly was, 'No,

¹¹⁹ See note 118.

no, it's the civil service that must decide;' and we got the wrong machine.¹²⁰ It wasn't able to talk to Norway or share data. That was just one thing. The other thing was toxicity testing that, in those days and times you had to go through the specified tests, which were agreed, even if they were irrelevant to the likely actions of a drug. And yet, if you knew what a drug might do, you couldn't, for example, look at the adrenal gland if that was a likely target organ if it wasn't on the agreed list of structures that must be examined or whatever biological system it might affect that could cause mischief in relation to the activity of a particular drug. Those are just two examples of the kinds of problems that used to arise.

Flower: In a minute I'm going to ask Mike and Alasdair to talk about later developments in this committee structure, but I just wanted to return to Owen for a minute. Owen, can you tell us something about the Committee on Review of Medicines (CRM)?

Wade: I think this was part of the Medicines Act, wasn't it? There was the CSM, the CRM, there was the Veterinary Products Act, and then a Pharmaceutical Commission. I was chairman of the Committee on Review of Medicines. When I started, I made two changes, well, two developments really, because I'd had such a tough time on the Committee on Safety of Drugs with Derrick Dunlop at the very beginning. I made two recommendations: first, that new members got properly instructed by me when they first arrived, so that from the very beginning of their membership they could contribute properly. The second thing was that in MRC meetings we always had a system by which people led discussions and I introduced that system so there was always somebody whose responsibility it was to lead individual items as they came up.

The only other thing that I'd really like to talk about is in 1972, I think it was, I was challenged by Squibb. They had two drugs, Motival and Motipress. These were compounds that had fluphenazine in them but this wasn't clear from the names of the drugs, and fluphenazine was causing some adverse reactions. We recommended that the Minister should revoke the licence for these two drugs. And then Squibb appealed. We heard this appeal but didn't agree with it, so we told the Minister to go on revoking. They could have gone to the Medicines Commission and had another shot at it, but no no, they sued the CRM, in

¹²⁰ Professor John Griffin wrote: 'Proper monitoring could only be achieved with computerized record linkage schemes.' Griffin (2009). For details of Finney's further comments, see Tansey and Reynolds (eds) (1997): 113–14, 131–2.

particular me, for advising the Minister wrongly. And there was a long, drawn-out legal case. It was hell, I think, for the administrative officers of the outfit. I know I had to sign countless affidavits and the thing went on and on and on. Then eventually they gave up. But why did it go on so long? Because neither of these drugs was used very much in the UK, but they were in the US. And of course, as soon as the decision was made that their licence was to be revoked, then WHO would tell every country in the world about this, and their market in the US would go down. So, there was trouble there.

Collier: I had something to say about the Medicines Act which is rarely if ever talked about, and it is the way in which the committees meet, in which they're held. Because of the secrecy surrounding the Act I suspect that by giving you insights into the way meetings are run I'm breaching Section 118 now – so I may be in jail tomorrow, but let me tell you,¹²¹ in the regulatory system, in my experience, the chair always sits with people from the department, and is supported by them while the other members of the committee always sit on the other side of the table. I think that's the case in the CSM; it was certainly the case in the Medicines Commission when I served on it. This meant that the most powerful member of the advisory body – the chair – was on the opposite side to the members. That relationship, i.e. the chair being very close to officers, civil servants, whatever, I think threw some of the decision-making.¹²² Now I see Michael saying 'no', but if you ask the questions: 'How do committees make decisions?' 'How are the committees arranged?' If you look at the table and the arrangement and where the chairs are seated, I suspect that the seating arrangement, by its very nature, will have influenced decision-making. We don't know, but I suspect it will have. I am sure you'll get a response on this matter in a minute from my friend, my colleague on the left (Michael Rawlins).

Griffin: I'd just like to pick up on a point that Mike Rawlins made about the Medicines Division's facilities. He grossly understated it. In 1979 we moved to the Market Towers from Finsbury Square. In Finsbury Square we had manual typewriters. When I went to look at the building at Market Towers, it was all nicely equipped from a previous government department with word processors. The trades union insisted that all these word processors were going to be taken out, because it would affect our employment of secretaries. I created merry hell, as a result of which we got golf-ball typewriters. Now, that was the level

¹²¹ On section 118 of the Medicines Act, see note 93.

¹²² Professor Desmond Laurence wrote: 'True! True!' Note on draft transcript, 7 July 2008.

of technology that we had, and I made a comment earlier on that the Medical Division was under-resourced. It was grossly under-resourced.

George: The Committee on Review of Medicines was chaired initially by Owen Wade, as you heard. But then, of course, there was Bill Asscher and finally David Lawson. Earlier on today we heard about the 39 000 products with a licence of right. The work of that committee was completed on time, and the number of products on the market reduced to around 10 000. I think overall that was a great achievement. I know that a lot of companies didn't think it was worth a candle, actually, submitting for a product licence, or renewal of a product licence, but it was a very smooth process.

Breckenridge: There are two remarks I'd make to previous speakers: first to David, about the amount of data seen by advisory committees. You'll be interested to know, David, that the Commission on Human Medicines held a working party over the summer this year to decide how it could reduce the amount of information which was going to be sent to members. Of course, it didn't come to a conclusion and they'll have to convene another one. So, not much changes. The second remark is to Joe Collier, on the question of why the chairman sits opposite the members of the committee. There is a very good reason: in this way, he is the only person who can see the members of the committee, and so that when he says, 'Does everyone agree?' and he will say, 'Yes, everyone is nodding', where, of course, probably half of the people are not, but nobody else can see that.¹²³

Just for a few minutes I want to pick up the regulation of medicines post-thalidomide, and this is very appropriate because those of you who have read today's *Financial Times* (26 September 2007) and the *Financial Times* at the weekend (22/23 September) will know that it is 50 years ago this week since thalidomide was introduced into medicine. One of the nicest quotes I remember from Derrick Dunlop was that his committee only concerned themselves with efficacy in as far as it concerned safety. So, safety was always the predominant thing in his reckoning. But after that, after the CSD and the CSM were set up, one could be pretty sure that the decisions reached on efficacy were watertight and could be substantiated. The same couldn't be said for the decisions on safety, for the very good reason that the number of patients who had been included in clinical trials was small. So, an argument started in the

¹²³ Professor Desmond Laurence wrote: 'True, of course. But Joe Collier's innuendo is also true; chairs are chosen because they will comply'. Note on draft transcript, 7 July 2008.

1970s, which is still continuing to this day: how do you get a handle on the safety of marketed drugs? A new title has been given to this: ‘post-marketing surveillance’.¹²⁴ You’ve heard already about yellow cards, very useful in their way, but with severe limitations – very good for picking up signals. The emphasis today is on active methods of monitoring, and in that respect patient registers are important and also in testing hypotheses which have been raised by yellow cards. The General Practice Research Database (GPRD) is also very important and there are huge developments taking place in GPRD. This debate on post-marketing surveillance came to a head in 2004 with Vioxx.¹²⁵ Remember Vioxx (rofecoxib), the COX-2 (cyclo-oxygenase-2) inhibitor, which was withdrawn by the company because of cardiovascular safety at a time when regulators knew about the problem, but for various reasons, which we don’t need to go into, had not acted. The end result of this was that in European law, risk-management plans were included. In a risk-management plan there is a statement of the safety profile of the drug: what’s known about the safety; what’s not known about the safety; what needs to be done to get more information; and anything else that needs to be done. These are now part of the licence, so when this is granted the company must sign up that it will fulfil its obligations in a risk-management plan. As has been said earlier this afternoon, the record of pharmaceutical companies in completing post-marketing studies, that they said they would do, is really pretty poor. Data from the MHRA shows that one-third of these studies are completed satisfactorily; one-third are already in progress; and one-third have never been started. Until now in Europe, we haven’t had the legal ability to make companies complete these studies. A law was passed in the US last week renegotiating the Prescription Drug User Fee Act by which hopefully the same kinds of guarantees in the US that post-marketing studies need to be done will be obtained.¹²⁶

This brings us up to last year and TGN1412, which was a wake-up call for better regulation of first-in-human studies of high-risk compounds.¹²⁷ EU proposals for these regulations have been consulted on and the regulations are being laid

¹²⁴ Andrew *et al.* (1996).

¹²⁵ Mamdani *et al.* (2004); Sommet *et al.* (2008).

¹²⁶ HR 3580, the Food and Drug Administration Amendments Act was signed on 27 September 2007; for details see www.fda.gov/oc/pdufa/ (visited 26 June 2008).

¹²⁷ See Glossary, page 107.

at the present time.¹²⁸ This is of great importance in the history of medicines regulation. Probably it will not be the last event which will predicate medicines regulation, because all such regulation has been guided by adverse events. It has been said already that the regulations of medicines in the UK have been largely subsumed into European regulations under the Treaty of Rome. The former MCA and the Medical Devices Agency (MDA), which were funded in entirely different ways and worked under entirely different legal systems, were merged to form the MHRA in 2003. The story is told how the MHRA – a name that doesn't actually trip off the tongue – was so called. The name was to be decided at a meeting of officials of the Department of Health, including the Minister. There was a series of suggestions as to what the new agency should be called, and only one person voted for MHRA. The problem was that that one person was the Minister, so apparently this is how it got its name. We have streamlined the advisory committee structure that we've been talking about: the Medicines Commission and the CSM have fused to form the CHM, and in keeping with what's happening in Europe, we have formed expert advisory groups in different therapeutic areas. We are working very closely with our colleagues in Medical Devices, because, scientifically, medical devices and medicines are coming closer together in areas like tissue engineering.

Finally, as I was discussing with David Grahame-Smith over tea, one of the areas which is concerning us most at the present time in regulation is drug distribution. We've got a pretty good regulatory handle on drug discovery, and we've got a pretty good regulatory handle on drug development. But after that, after the licence is given, it is more difficult. The distribution of medicines is an area where there are a lot of problems, such as counterfeiting. You'll remember that just before the summer three major drugs which were counterfeits went into the NHS health care system and this is a matter of continuing concern.¹²⁹ I would see this as an area where regulation will have to get its act together in a tighter way than it has up to now.

Flower: About two months ago, the British Pharmacological Society was approached by a Chinese delegation who asked if they could visit with us during their trip to London and seek some advice. I was roped into the discussion because I was one of the only people around who was available at the time. We met them in the upstairs office of the society's headquarters in Angel Gate.

¹²⁸ See Duff (2006); European Medicines Agency (2007); Boyce (2007), especially page 21.

¹²⁹ The three drugs were Casodex, Zyprexa and Plavix. See MHRA (2007a, b and c).

When they arrived we found that their delegation comprised about ten doctors and scientists accompanied by a charming interpreter. As none of them spoke English, and everything had to be relayed through this interpreter, it took us about an hour or so to find out exactly what it was that they wanted to ask us. In the end it turned out that they were seeking an insight into how we managed quality control issues in the UK. Apparently, in China, there is an issue about pharmaceutical companies using different manufacturing methods to prepare drugs such that the final products are often radically different from each other in terms of purity. The immediate stimulus to this, I suspect, was that the Chinese Minister for Health was executed after a substantial slip up in drug regulation implementation in China led to several deaths.¹³⁰

Breckenridge: They signed a memorandum of understanding with the MHRA. And the person who signed it was the deputy commissioner of health, the boss having been dispatched on July 10th. And we said to one of the translators: ‘We hope this doesn’t become a paradigm for regulators who don’t quite come up to scratch.’

Rawlins: I was asked to talk a bit – reminisce a bit I suppose – about the CSM in the 1980s and 1990s. I joined the CSM, the main committee, in 1980 when Eric Scowen was still chairman. Eric was a remarkable chairman, he absolutely dominated the Committee. Most of the proceedings were a dialogue between him and the chairman of the subcommittee on Toxicity and Clinical Trials, i.e. David Grahame-Smith. He was quite clear that he wanted his way and was going to get it, and he did it by all sorts of underhanded means, many of which I have remembered and used myself. On my very first meeting, for some reason or other – John Griffin must have been asleep or away that week – we had before us a transfer of a licence from one manufacturer to another. We wouldn’t normally come near it. It was for Vicks, the stuff you rub on your chest. It was just about to go through on the nod and I said, ‘Chairman’ (very pompously) ‘what’s the evidence for efficacy there?’ And he gave me a sort of withering look and said, ‘Rawlins, we have a long tradition at this committee of granting licences to products the public have enjoyed for many years. So while you’re looking out of the window and not paying any attention, we’re going to give it a licence.’

¹³⁰ Zheng Xiaoyu, former head of State Food and Drug Administration was executed on 10 July 2007 for taking 6.5m yuan in bribes to approve substandard medicines. See www.ihf.com/articles/2007/07/10/news/china.php (visited 22 July 2008).

I became chairman of the CSM in 1993 and I was very fortunate with members; they were all extraordinarily able. There were a couple of them, very distinguished, who were unable to make decisions. I've noticed this in expert committees: there are one or two people who can't make decisions and you just have to live with that and rely on their other virtues. As Alasdair said, the reason why it's so important for the chairman to sit opposite – it's not a conspiracy – is so that you can see not only whether people are nodding, but also the body language of those who are uneasy with the way the dialogue is going. And so it's a practice that I strongly commend. As I said, the decision-making was very collegiate and it was generally by consensus. Conflicts, as always in these committees, revolved around what you might call modest issues. The big conflict when I was chairman was always the change in legal status from POM to P, and then to GSL. When you went from POM to P, the pharmacists on the committee thought this was wonderful, and many of the doctors disliked it intensely. When it went from P to GSL the pharmacists were outraged. During my time, I had a miserable time with the pharmacists who were quite clearly all on a three-line whip from the Royal Pharmaceutical Society to try to oppose this. And it took me 11 years to get 5ml sachets of Calpol available in the local garage, so that I could buy them when my grandkids were getting febrile illnesses.

The other thing I was going to mention was pressure. And there is pressure on committees and pressure on the chairman and senior members of the committee, and it comes from a variety of sources. Once when I was standing in for Bill Asscher as chairman I was subjected to political pressure from one of the secretaries of state for health. Suddenly I got a message; he wanted me to write a letter to all doctors that night to say that Serevent (salmeterol xinafoate inhalation powder, a β_2 -adrenoceptor agonist) was safe.¹³¹ Now, no chairman of the Committee on Safety of Medicines has ever written a letter to say something is safe. I was only acting for Bill Asscher who was away somewhere, and I knew he'd absolutely clobber me if this ever got round, so I had a lot of difficulties making sure that I couldn't do a letter, couldn't sign the letter, had to go back to Newcastle, and all that sort of stuff to avoid it. There are obviously media pressures, and at the time I was chairman of the CSM, I thought the media pressures were pretty fierce. Now I've had eight years at NICE, I know that the media pressures on the chairman of the CSM were as nothing and really were not a problem. There is some professional pressure; always very difficult to know whether it is truly from the profession or whether the pressure has been coming from other quarters, particularly the

¹³¹ Ullman *et al.* (1990); Johnson (1991).

pharmaceutical industry. And, of course, there was pressure on the Committee and on the chairman from the industry. Some of it was quite legitimate; in a democracy, if the regulated want to make remonstrations about the way they are being regulated, they have the right to do so. I don't disagree with that. Sometimes it was underhand. There were two occasions I now know where members of the Committee had entered into agreements with companies so that when their terms of office expired they would become consultants, but remained on the Committee for a year without declaring it. There was one attempt at me with bribery: a pretty pathetic one, actually. There was also an attempt at blackening my reputation when one company persuaded a Member of Parliament to ask a question about how much money I'd been paid over the previous year, quite clearly hoping I hadn't declared it in my income tax. As I couldn't remember, I went back home and was relieved to see I had declared £2 600 but the Parliamentary Answer was that I'd only been paid £2 400 over the course of the year, so I breathed a huge sigh of relief that I'd paid £200 too much; it didn't really matter. About a week later, I got a letter from the Inland Revenue questioning my tax return and my payments from the Department of Health. So I rang them up and said, 'What's going on here?' And they said, 'Well, we saw this parliamentary exchange and, you must understand, it was referred to us. We checked up your income tax and we realize you've overpaid, and we think it's rather hard on you, and we think you ought to have an opportunity to claim the £200 back.' There was one occasion of pure fraud, which Alasdair sorted out after I left, belonging to a company that's no longer in existence – Scotia Pharmaceuticals. Alasdair revoked all their licences, and I think he did a great job. But of course, that was plain fraud and one of the investigators was taken to the GMC and the other main investigator died and so was unable to be taken.¹³² So there are those pressures too.

But the one other thing I'd like to say is about patients. All the way through my period on the CSM, we did think about patients. We thought about them all the time, and Joe Collier is wrong to think that we didn't think about patients. We may have looked at the risk-balance ratio in a sort of patronizing way, and I'd accept that. We may not have had meetings in public – in that period no scientific committee had meetings in public – but to say we didn't think about patients is completely wrong. And the one person, above all, actually – surprisingly – who was always talking about patients, was the late Sue Wood. And although she was a very difficult woman in many ways, and she and I had huge arguments, which apparently reverberated around the building,

¹³² See Dyer (2003); Richmond (2003).

nevertheless she was always, always talking about the ‘poor ***** patients’, as she put it. ‘What are you going to do about them?’

Flower: I’m sorry we don’t have a bleeper to disguise those sorts of words.

Rawlins: Well, if you knew Sue Wood she used that particular word beginning with ‘f’ very often.

Breckenridge: I think Michael’s very right to make this point about patients, about our concern for them. He knows, and I’m sure the rest of you might know as well, that, since his time on CSM, the CHM and its expert advisory groups all have lay and patient representatives as well. They do make a substantial contribution, especially in the area of information.

Wade: Yes, yes, obviously all you youngsters here don’t remember, but in the early days we weren’t paid anything. I understand now you are paid.

Rawlins: Yes, I got £200 a day as chairman.

Wade: Really? Yes, good. Not in my time. I remember that there was some payment made at the end of the days of the Committee on Safety of Drugs, and I used to get this and used to give it to my department because, you know, I’d been away in London the whole day and they had a lot of work. So I thought the department ought to get this money, and that was splendid while it lasted, but then the income tax people rang me up and they said, ‘You were paid this bloody money, and you must pay income tax on it.’ So I said, ‘No, but I gave it away’. And then George Godber rescued me. He explained to them that I was financially incompetent, that I wasn’t getting the pay, it was for my department.

Vere: Very briefly and frivolously: we used to have those enormous bags full of papers, which were sent to our homes, that had to be kept sealed at all times except in secret when we were reading them. I can remember sitting on a tube train once with two of these vast bags, which I could barely carry, and one of them burst open in the tube. I only saw Sir Eric Scowen non-plussed and fazed once, and that was when we’d all brought our papers to the Committee and we discovered that neither the papers that had been provided for us nor the papers that had been brought by the company for their own staff related to the drug that was on the agenda to be discussed.

Aronson: Before I start to say something about the Medicines Commission, I have a reminiscence about Desmond Laurence. There is a wonderful photograph of Desmond staggering under the weight of at least half a dozen of those enormous

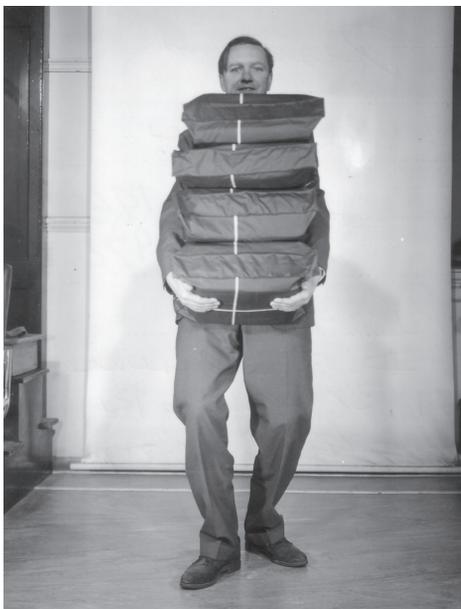


Figure 4: Professor Desmond Laurence and his monthly burden of documents for a meeting of the Committee on Safety of Medicines.

green bags that used to flood on to the desk. We published it in the issue of the *British Journal of Clinical Pharmacology* that we produced to celebrate the 30th anniversary of the journal. It is worth looking at the issue just for the picture of Desmond, which was wonderful.

Now, the Medicines Commission – I think Joe Collier will correct me if I've got the history wrong – was established under the Medicines Act of 1968, as the main committee advising Government. Under section 4 of the Act, the commission was empowered to set up committees to assist it in its work. And so a section 4 committee was begun: the Committee on Safety of Medicines. I guess at that time – I hope that somebody will tell us the story about this – the Medicines Control Agency (MCA) was set up to service the Committee on Safety of Medicines. Quite how the MCA – later transmogrified into the MHRA after it was amalgamated with the MDA – became so powerful in that area without having been constitutionally or statutorily set up is something that I'd like to hear about from, say, Alasdair or anybody who knows about that. The Medicines Commission was the main advisory committee which set up the CSM. I didn't join the Medicines Commission until 2001, and became vice-chairman in 2002 until it was disbanded in 2005. But, before I talk about

my perspective of that period, I wonder if there is anybody here who was a member of the commission, either when it began or subsequently, who has reminiscences about how it worked in those days?

Rawlins: John Griffin must know more. But I'm not sure if your interpretation of the law is quite right, Jeff. The Medicines Commission was set up as an advisory body, but section 4 of the Medicines Act also gave powers to ministers to set up additional committees and that was how the CSM and the CRM and the herbal medicines committee and things like that were set up. And there was always a lot of dispute as to which committee had supremacy: the Medicines Commission or the CSM. The chairmen of the two bodies used to vie with each other as to whose was more important. Right, Alasdair? Well, you and I had no disagreement about it.

Breckenridge: We could talk about this for a long time. It devolved into personalities and I don't think we want to talk about that.

McDevitt: I was a member of the Medicines Commission from the late 1980s to the late 1990s, and I think for the last five years was the vice-chairman of it. Initially, during my time, Rosalind Hurley was the chairman, and then subsequently David Lawson.¹³³ It basically heard appeals from companies that didn't like what the CSM was telling them when they'd gone through the process. Ultimately they could come to the Medicines Commission and put in a final appeal to us. These meetings were relatively infrequent, it has to be said. In addition to that, there was a whole series of other issues relating, not just to the CSM, but to the Veterinary and Dental Committee and the Medical Devices Agency. There were one or two other issues that came straight to the Commission. One that springs to mind was when the European Commission was introducing various rules and regulations that had to apply to Britain as well. I remember we had a long debate about homoeopathic medicines, I think it was, as to whether we were going to agree to this legislation being introduced within the UK. There was great concern and there was a debate in which we finally agreed that we would have legislation. Then in fact, the secretariat said, 'Could we write efficacy out of it?' I think that must have been part of the process because they said, '(a) we don't want to have to make the decisions, and (b) we wouldn't have the resources to have anything to do with this.' There were

¹³³ The first chairman of the Medicines Commission was Lord Rosenheim (Jan–Dec 1972). He was followed by Professor A Wilson (1972/3), Sir Ronald Bodley Scott (1973–5), Lord Butterfield (1976–81), Dame Rosalind Hurley (1982–93), Professor David Lawson (1994–2001) and Professor Parveen Kumar (2002–05).

a few contentious decisions that eventually came to the Medicines Commission from the CSM. But, I have to say, over a ten-year period, these were relatively few and far between.

I would also endorse the idea that there were all these people from a whole variety of backgrounds who played a very significant part in the role of these committees: clinical pharmacologists, doctors from other specialties, very senior people from the pharmaceutical industry, veterinary people, patient representatives, even as early as the 1980s. It was actually very interesting, when you got a topic that maybe one or two people knew a lot about and other people didn't know that much about, to see the knowledge base growing as the discussion took place, so effective decisions were eventually made. I must say, I found it a very interesting and rewarding experience.

Professor Donald Davies: The general theme here has been the contribution of clinical pharmacology to drug regulation. I wonder whether under current conditions the contribution of active researchers in clinical pharmacology to regulation is greatly reduced? When I was a member of the CSM we were allowed to have interests with drug companies provided we declared them, and we left the room if there was a specific interest under discussion. Now one cannot have any interest whatsoever if one wants to sit on a regulatory authority committee.¹³⁴ Joe will not agree, but I'm sure that that does bar people with the relevant knowledge and experience.¹³⁵

Flower: Joe, you wanted to make a comment about the Medicines Act, but you can also reply to the previous comment.

Collier: I would agree. The issue here, as I have the Medicines Act with me, is typical of the system. Jeff is right and Michael's wrong, but you should know better, Michael, let me read it to you. Section 2 – which is the second bit of the Medicines Act – says: ‘There shall be established a body to be called the

¹³⁴ Professor Laurence wrote: ‘In 1964 I was appointed to the CSD Clinical Trials Subcommittee. One night the medical correspondent of the *Observer* phoned me and said he had a report that the CSD had breached the (informal, voluntary) agreement with industry that no committee member would have professional financial links with a pharmaceutical company. This was “news”, he said. I said that the whole CSD enterprise was based on trust, and it would be a disaster if that was impaired at the outset. I agreed to try to find out. I was able to meet the chairman (Dunlop) and I told him the story. After a pause he said “Oh, my God: I forgot!” After a brief conversation I felt able to tell the *Observer* that I had spoken to Dunlop and I was satisfied that the agreement with industry was intact. The *Observer* did not publish’. Letter to Mrs Lois Reynolds, 10 August 2008.

¹³⁵ MHRA (2006).

Medicines Commission.’¹³⁶ Then it goes on: ‘And that is a statutory body’, meaning that it cannot just be disbanded. Then it goes on to section 4 and says: ‘The ministers (the health ministers or the agriculture ministers) having regard to any recommendations made by the Commission under section 3(2)’, which I’ve just read to you, ‘and after consultation with such organisations as the ministers concerned consider appropriate, may by order establish one or more committees under this section’, i.e. ‘section 4 committees’.¹³⁷ There is no mention of the name of the CSM there and it’s only as a result of the Medicines commission and the ministers asking: ‘Why don’t we have it?’ The reason – I suspect – why the word ‘commission’ is in the new body is that there is a statutory requirement to have it there, because you cannot disband it. So the commission per se would be seen as the first or senior committee. It is, indeed, the case that the CSM was more powerful, more influential, and I think functionally the better. In fact, my view has always been that the commission has been a dysfunctional committee, but that’s a maybe. I think the CSM really took over many of the roles of the Commission. I think it was a shame, in a way, but I always saw the legislation as giving the Medicines commission the role of the eyes and ears of the public.¹³⁸ But that’s too late now, we failed in that respect. But there we go. Michael, I don’t know if you want to read this again – but I am sure you are incorrect.

Fletcher: Before we end this, I’d like to go back to this question of efficacy and the position of the Committee on Safety of Medicines in this assessment. I have a little story about that, which I was involved in over a number of months, and Eric Scowen also was involved. It involved an OTC product called Enterovioform (clioquinol) which was an anti-diarrhoeal for travellers. We received a number of reports that, in fact, it wasn’t working very well, and so Eric had this put on

¹³⁶ Great Britain (1968) (c.67) S.1.

¹³⁷ Great Britain (1968) (c.67): S.4(1).

¹³⁸ Professor Desmond Laurence wrote: ‘The Medicines Commission was there to advise the Minister – it was the premier committee to act in the public interest in theory and in law. But, one day when John Butterfield was chairman, a familiar situation arose – the public interest versus the bureaucratic interest. The civil servants said “chairman, the commission does not have to do this” (I forget the topic, but it related to patient/public safety). I became frustrated and said “but what about compassion?”. The meeting was stunned, then the chairman let the cat out of the bag when he said: “Desmond, it is my duty to protect the civil servants”. The meeting stayed stunned. Of course everybody knows this, but nobody is supposed to actually say it, it is the “elephant in the room” that ensures that it is only after the civil servants and the ministers’ interests have been protected that the public gets a look in (I hardly exaggerate)’. Letter to Mrs Lois Reynolds, 10 August 2008.

the agenda and we decided that we would reduce the number of indications for which it could be used. And it was for, I think, one or two, I can't remember what they were now. Anyway, that went through and the number of indications was removed from the data sheet so that it was brought into line. Time went by and there were more complaints that, in fact, even in the ones that were left, it was still not particularly effective. So we reduced that down to, I think, about two, one of which I think was some tropical dysentery and so it was left with one indication. In fact a paper had come up to show that it wasn't any use in that either. So now what we had was a product that kept its product licence but lost all the indications.

Vere: Well, that's right. With Enterovioform, the most frequent problem was that it messed up thyroid function tests.¹³⁹

Aronson: Sub-acute myelo-optic neuropathy did it. Well, I thought I'd finish off with my experience of the Medicines Commission, which, as I say and as we've heard already, was disbanded in 2005. First of all, there were actually a lot of clinical pharmacologists on the Medicines Commission when I joined it. Now there are a lot of clinical pharmacologists on the Commission on Human Medicines for that matter. I think we had quite a lot of influence in these matters, and continue to do so. These major committees are chaired by senior clinical pharmacologists, and the clinical pharmacologists who were there apart from me were Joe Collier, Phillip Routledge, Jim Ritter and Cameron Swift. I can't think whether there were any others, but that's five in a committee of 15 or 20. So, we had quite a loud voice and a fair group presence on that committee. The other clinical pharmacologist who was on that committee when I joined was, of course, David Lawson, who was the chairman. I have to say that he was, if not the best, then one of the best chairmen I have ever served under. He was superb: he was relaxed and good-humoured, and I think that these are the most important attributes for any good chairman of a committee. He listened to everybody, and Alasdair's point about sitting on that side of the table is actually very important, because he was the one, as Alasdair has said, who could see when Joe was falling asleep, for example, and when people were nodding or shaking their heads. But he did listen and he didn't just listen; he elicited opinions and he made sure that everybody's opinion was heard. In the end his summing-up was masterful. I don't think anybody went out of those committee meetings thinking that a wrong decision had been made, or that they had somehow been neglected, even if the decision went against their views. His whole conduct of that committee

¹³⁹ See, for example, Mann (1986).

was magnificent, and I sat there thinking, ‘I wish I could do this’. I have always tried to model my own chairmanship – when I’ve had the chance – on his style, because I thought it was so effective, very difficult to achieve, and he seemed to do it very naturally. I’m sorry he’s not here today.

He had to leave that committee and Jim Petrie was appointed as his successor in 2002, but Jim unfortunately died before he could take up the post. So the then vice-chairman, Parveen Kumar, took the chair. Parveen, in typical fashion, said that we should have a ballot for who should be the next vice-chairman. She didn’t like the term ‘chair’ incidentally; she liked to be called ‘chairman’. I managed to bribe enough of my colleagues to be elected and I was the next vice-chairman. It was one of the best committees I think I’ve ever served on; it was hugely educative. Someone said that what we did was to hear appeals; well, that was just one thing. The range of topics that we covered on that Commission was huge and eclectic. It dealt with anything and everything about drugs that the CSM was not dealing with in addition to overseeing their reports – because, of course, as Joe has told us, the CSM reported to the Medicines Commission – and other matters such as veterinary affairs, because the human veterinary commission – I can’t remember the exact term – was part of the Medicines Commission.¹⁴⁰ I recall one debate about residues of benzylpenicillin in animal products, and the degree to which a particular level or a concentration of residue was permissible. The experts on horses on the committee were exceptionally helpful when it came to talking about veterinary medicine. There was also an expert on fish. We covered huge ranges of topics and were educated all the time. The quality of debate was enormously high and I remember it as one of the most enjoyable committees I have ever served on.

But Europeanization, as Alasdair has reminded us, led to the demise of the Medicines Commission when the CSM and the Medicines Commission were joined together as a single body in the CHM. I don’t know how this is working, but I thought the one function that might suffer as a result of that was the appeals function, because we often heard appeals from drug companies against decisions of the CSM. I don’t know how that works now and perhaps that’s for another day. I regret the demise of the Medicines Commission. I hope, and I’m sure, in fact, that the new system works well also, and that the matter of advising Government on drug matters has gone forward exceptionally well, particularly since there are so many clinical pharmacologists involved.

¹⁴⁰ The Veterinary Products Committee was established in 1970 to advise on safety, quality and efficacy in relation to the veterinary use of medicinal products and reported to the Medicines Commission.

Breckenridge: The commission has not died at all, its function has been subsumed into the Commission on Human Medicines, and, please, you mustn't say it has died.

Flower: I think we'd better wind it up here. I know that Tilli has got some housekeeping announcements that she wants to make.

Tansey: First of all, may I say thank you to everyone for coming here this afternoon and sharing your reminiscences with us. It's been a privilege to listen to you. We've touched on some serious historical issues, but we've also had some very entertaining stories, and it's been a very interesting afternoon. Tony Peck mentioned earlier that he was often asked, 'Have you got a product?' We do have a product this afternoon and that is a transcript of this meeting. It will be edited and hopefully published, probably in conjunction with the first meeting that we held earlier this year, and all the correspondence and transcripts will be put in the archives of the Wellcome Library.

It remains for me to thank Jeff Aronson, who has been incredibly helpful in organizing this meeting and its predecessor. He's put a lot of work into it and I and my team are very grateful to him for that. And also to thank Rod Flower for his excellent chairing. He got us to tea on time and five minutes late for the glass of wine. He did say he was hoping that he would get a medal of honour from the Wellcome Trust; well, I'm afraid you haven't quite made that, Rod, so I'm afraid you'll have to make do with the more traditional thanks and a round of applause.

Flower: Thanks very much everyone, you've been a wonderful group and it's going to be a great transcript. I'm sure you are going to look forward to reading it in times to come.

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FRCP FBPharmacolS FFPM (b. 1947) trained in the University of Glasgow (1964–73) and the Medical Research Council unit of clinical pharmacology, Oxford, under Professor David Grahame-Smith. He is currently reader in clinical pharmacology at the University of Oxford and honorary consultant physician in the Oxford Radcliffe Hospitals Trust. He was president of the British Pharmacological Society (2008/9); vice-chairman of the Medicines Commission (2002–05); and editor-in-chief of the *British Journal of Clinical Pharmacology* (2003–07). He has been chairman of the British Pharmacopoeia Commission's Expert Advisory Group on Nomenclature since 2006; a member of the Formulary Committees of the *British National Formulary* since 2006 and the *British National Formulary for Children* since 2003. For full curriculum vitae and list of publications see www.clinpharm.ox.ac.uk/JKA (visited 22 July 2008).

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FRCP FFPM FRSA (b. 1931) was professor of medicine at the University of Cardiff (1976–87);

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Professor Nigel Baber

FRCP FRCPE FFPM (b. 1945) worked in clinical pharmacology in the pharmaceutical industry from 1975 to 1998 at ICI Pharmaceuticals, Merck Sharp and Dohme, and Glaxo Group Research. He has been involved in the development of new medicines in the cardiovascular, respiratory, gastrointestinal and endocrine areas, and has maintained an active interest in the teaching and training of clinical pharmacologists. He also worked for the MHRA (1998–2006) and is currently clinical director in the clinical trials coordinating centre at the University of Hertfordshire.

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respiratory and general medicine at the London Chest Hospital and the Royal London Hospital since 1988, and professor of respiratory medicine at St Bartholomew's and the Royal London Medical College since 2002.

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Kt CBE RCP FRCPE FRSE FMedSci (b. 1937) following house jobs, was lecturer and senior lecturer at the Hammersmith Hospital, London and the Royal Postgraduate Medical School (1964–74); professor of clinical pharmacology, University of Liverpool (1974–2002); and has been chairman of the Medicines and Healthcare products Regulatory Agency since 2003. He was a member of the Committee on Safety of Medicines (1982–2003), serving as vice-chairman (1996–98) and chairman (1999–2003); he was also a member of the Medical Research Council (1992–96).

Professor Hubert Campbell

FRCP FSS (1920–2007) qualified in mathematics at the University of London. In 1963 he joined the Welsh National School of Medicine as a joint appointment with Archie Cochrane's Medical Research Council epidemiology unit, and became the foundation professor of medical statistics at the University of Cardiff in 1970.

Sir Iain Chalmers

Kt FRCP FRCPE FFPH FCOG(SA) (b. 1943) qualified at the Middlesex Hospital Medical School, University of London. He was registrar to the department of obstetrics and gynaecology and MRC fellow in the department of medical statistics at the Welsh National School of Medicine; director of the national perinatal epidemiology unit in Oxford and clinical lecturer in obstetrics and gynaecology, University of Oxford (1978–92); director of the UK Cochrane Centre in Oxford (1992–2002); and honorary consultant in public health medicine, Oxfordshire Health Authority (1997–2003). He has been editor of the award-winning James Lind Library since 2003.

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Professor Sir Colin Dollery

Kt FRCP FMedSci (b. 1931) qualified at Birmingham and trained at the Hammersmith Hospital, London, where he has been a consultant physician since 1962. He was a lecturer in medicine (1962–65); professor of clinical pharmacology (1965–87); professor of medicine (1987–91); and dean (1991–96) at the Royal Postgraduate Medical School, Hammersmith Hospital. He was pro-vice-chancellor for medicine (formerly medicine and dentistry), University of London (1992–96) and has been a senior consultant in research and development at GlaxoSmithKline (formerly Smithkline Beecham) since 1996.

Professor Sir Derrick Dunlop

Kt FRCP (1902–80) was professor of therapeutics at the University of Edinburgh (1936–62); physician to the Queen in Scotland (1961–65); extra physician (1965–80); and consulting physician, Royal Infirmary, Edinburgh. He was chairman of the Ministry of Health's Committee on Safety of Drugs (1963–69) and the first chairman of the Medicines Commission (1969–71).

Professor David Finney

CBE FRS (b. 1917) was lecturer in the design and analysis of scientific experiment at the University of Oxford (1945–54); reader (1954–63) then professor (1963–66) of statistics at the University of Aberdeen; and professor of statistics at the University of Edinburgh (1966–84); a member of the Subcommittee on Adverse Reactions of the Committee on Safety of Drugs/Committee on Safety of Medicines (1963–81).

Dr Peter Fletcher

FFPM(by distinction) (b. 1930) gained a PhD from St Mary's Hospital Medical School in 1965. He was MRC fellow, lecturer and senior lecturer in chemical pathology at St Mary's Hospital, London (1961–70); senior medical officer and principal medical officer for the DHSS in the Medicines

Division, Toxicology Division, and Scientific Services, National Health Service (1975–80); medical assessor to the Committee on Safety of Medicines, the Subcommittee on Toxicology and Clinical Trials and the Subcommittee on Chemistry, Pharmacy and Standards, as well as senior principal medical officer, chief scientific officer and under secretary. He was secretary to the Grahame-Smith working party, and a member of the European pharmacovigilance research group chaired by Sir Michael Rawlins. In 1987 he became international medical director of IMS International, director of Post-Marketing Surveillance International Ltd; and in 1995 he became an independent consultant to the pharmaceutical industry as the director of Pharma Services International.

Professor Roderick Flower
FMedSci FRS (b. 1945) trained as a physiologist at Sheffield University, subsequently receiving a PhD in experimental pharmacology from the University of London and a DSc in 1985. After 12 years working in industry at the Wellcome Foundation, he left to take the chair of pharmacology at the University of Bath in 1985. In 1990 he returned to London to establish a new unit at the William Harvey Research Institute, Bart's and the London. During this time he was

head, on a part-time basis, of the clinical pharmacology department, and was president of the British Pharmacological Society (2000–03).

Dr Arthur Fowle

FRCP (b. 1929) trained at King's College Hospital, London, intending to practise cardiology. He joined the Wellcome Research Laboratories, Beckenham, in 1965 as a clinical physiologist. Security of tenure was promised if he became a part-time consultant physician in the NHS. In the interval, clinical pharmacology was recognized as the discipline which he practised. He became head of the clinical pharmacology department in 1968 and part-time consultant general physician in the same year. He retired from the Wellcome in 1992.

Professor Sir Charles George

Kt FRCP FFPM FMedSci (b. 1941) studied medicine at the University of Birmingham and after junior posts in the West Midlands and Manchester trained in clinical pharmacology with Professor Colin Dollery and Dr Alasdair Breckenridge. He moved to the University of Southampton as a senior lecturer in 1974 and a year later became professor of clinical pharmacology there. He served two terms as dean of medicine (1986–90; 1993–8) and was chairman of the General Medical Council's

Education Committee before he became medical director of the British Heart Foundation (1999–2004); president of the British Medical Association (2004/5) and he has been chair of their board of Science and Education since 2005.

Professor Sir Abraham Goldberg
Kt FRCPGlas FRCPE FRCP
FFPM FRSE (1923–2007) held posts at the University of Glasgow (1956–99); was chairman of the Committee on Safety of Medicines (1980–86); foundation president of the Royal College of Medicine's Faculty of Pharmaceutical Medicine (1989–91); and editor of the *Scottish Medical Journal* (1962/3).

Professor David Grahame-Smith
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Professor John Griffin
FRCP FRCPATH FFPM (b. 1938) qualified from the Royal London Hospital. He was head of clinical

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Dr Andrew Herxheimer
FRCP (b. 1925) worked in preclinical and clinical pharmacology at St Thomas' Hospital Medical School, the London Hospital Medical College and at Charing Cross and Westminster Medical School until 1991. He was founding editor of

the *Drug and Therapeutics Bulletin* (1962–92), while working with Consumers International. In 1986 he became the first chairman of the International Society of Drug Bulletins. He was extraordinary professor of clinical pharmacology at the University of Groningen (1968–77); and has been part-time consultant at the Cochrane Centre in Oxford since 1992, and emeritus fellow since 1995. In 1996 he and Dr Ann McPherson started the DIPEX project. See www.dipex.org, www.adverseeffectsmethods.com, and cochrane.org; (sites visited 11 October 2007).

Sir Austin Bradford Hill

FRS (1897–1991), medical statistician, was professor of medical statistics at the London School of Hygiene and Tropical Medicine (1945–61). A series of 17 articles published by him in the *Lancet* in 1937 introduced the medical researcher to the use of statistics, later reprinted as Hill (1937). His first attempts to introduce the concept of randomization in controlled trials were for the Medical Research Council. See Wilkinson (1997).

Professor Ray Hill

DSc (Hon) FMedSci (b. 1945) gained BPharm and PhD degrees from the University of London. He was a lecturer in pharmacology at

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Dame Rosalinde Hurley
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Professor William H W Inman
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Professor Sir David Jack
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Dr Keith Jones
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Professor Parveen Kumar
FRCP CBE (b. 1942) qualified in medicine at St Bartholomew's Hospital Medical College, University of London. She was academic sub-dean and later director of postgraduate medical education at Barts and the London School of Medicine and Dentistry, University of London. She was non-executive director of the National Institute of Health and Clinical Excellence (NICE) (1999–2002); member of

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Professor Desmond Laurence FRCP (b. 1922) qualified in medicine from St Thomas' Hospital Medical School, London, in 1944 and was appointed lecturer in therapeutics there in 1950. He was senior lecturer in pharmacology and therapeutics at University College Hospital Medical school jointly with University College London (1954–61) and professor there (1961–89). He served on the Committee on Safety of Drugs, Committee on Safety of Medicines and the Medicines Commission (1963–88). In 1967 he was a member of the Royal College of Physicians committee on the supervision of the ethics of clinical investigations and institutions, and subsequently served on the college's committee on ethical issues in medicine. For 26 years he served on research ethics committees as chairman or member.

Dr Peter Lewis FRCP (b. 1944) was senior lecturer in clinical pharmacology at the Royal Postgraduate Medical School, Hammersmith Hospital, London, until 1983 when he joined the pharmaceutical industry, working

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Dr David Long was head of the experimental biology department, Wellcome Research Laboratories, Beckenham, Kent (1969–74); head of the biology division (1974–83) and director of biomedical research (1984/5).

Professor Tim Mant FRCP FFPM RCP (b. 1954) completed an honours degree in pharmacology, graduated in medicine from Guy's Hospital in 1979 and trained at various hospitals in London in internal medicine, clinical pharmacology and human toxicology. He is senior medical advisor to Quintiles, Guy's Drug Research Unit and visiting professor at King's College London School of Medicine, Guy's, King's and St Thomas' Hospitals, London. He specializes in the investigation of new chemical entities and biologics in humans.

Professor Denis McDevitt DSc FRCP FRSEd (b. 1937) trained at Queen's University, Belfast, and later at Vanderbilt

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Professor Michael Orme

FRCP FMedSci (b. 1940) trained as a clinical pharmacologist in the UK and Sweden and worked for most of his career in Liverpool. He was dean of the faculty of medicine in Liverpool (1991–96) and helped to found the European Association for Clinical Pharmacology and Therapeutics in the early 1990s and was its chairman (2003–07).

Dr Anthony Peck

FRCP FFPM (b. 1933) qualified at the Middlesex Hospital, London, and gained his PhD in 1967 from the University of London. In

1968 he was appointed assistant professor at the San Francisco Medical Center; was a clinical pharmacologist at the Wellcome Foundation (1969–94); part-time senior lecturer at the Middlesex Hospital (1969–98), later University College Hospital. He was also part-time senior medical assessor to the Medicines Control Agency (1994–2000).

Professor Brian Prichard

CBE FRCP FFPM FESC FACC FB Pharmacol S (b. 1932) started pre clinical studies at King's College London in 1950 and qualified at St George's Hospital Medical School, London, in 1957. He was appointed research assistant in clinical pharmacology to Professor D R Laurence at University College Hospital Medical School, London, in 1961, and became professor in clinical pharmacology at UCL in 1980. He is past president of the International Society for Cardiovascular Pharmacotherapy, past vice-dean of the faculty of clinical sciences at UCL, and was foundation secretary of the Clinical Section of the British Pharmacological Society (1970–75) and has been chairman of the Institute of Alcohol Studies since 1993, a councillor in the London Borough of Wandsworth for over 40 years and a medical officer to Boys' Brigade camps.

Professor Sir Michael Rawlins

Kt DL FRCP FRCPE FFPM
FBPharmacolS FMedSci
(b. 1941) qualified at St Thomas's Hospital, London, where he later was lecturer in medicine (1967–71); moving to the Hammersmith Hospital, London, as senior registrar (1971/2), a visiting research fellow at the Karolinska Institute, Stockholm, Sweden (1972/3) and was Ruth and Lionel Jacobson professor of clinical pharmacology at the University of Newcastle upon Tyne (1973–2006). He was a member of the National Committee on Pharmacology (1977–83); the Committee on Safety of Medicines (1980–98; chairman 1993–8); Committee on Toxicity, (1989–92), the Standing Group on Health Technology Assessment (1993–5). He has been chairman of the National Institute for Health and Clinical Excellence since 1999.

Derek Rayner, Baron Rayner of Crowborough

(b. 1926) was joint managing director (1973–91) and chairman (1984–91) of Marks and Spencer plc and advised the Prime Minister, Margaret Thatcher, on improving efficiency and eliminating waste in government (1979–1983).

Professor John Reid

OBE FRCP FRCP(Glas) FRS(E)
FMedSci (b. 1943) graduated in medicine from Oxford and trained in clinical pharmacology at the Royal Postgraduate Medical School (RPMS), Hammersmith Hospital, London. After a Medical Research Council travelling fellowship to the National Institutes of Health, Bethesda, Maryland, he returned to the RPMS as senior lecturer and later reader. In 1978 he was appointed Regius professor of materia medica and therapeutics at the University of Glasgow and in 1989 translated to the Regius chair of medicine and head of the department of medicine and therapeutics. He is past president of the Association of Physicians of Great Britain and Ireland and of both the British and European Societies of Hypertension.

Professor Alan Richens

FRCP FFPM FBPharmacol was clinical pharmacologist and reader at St Bartholomew's Hospital Medical College, London, and professor of pharmacology and therapeutics at the University of Wales college of medicine until his retirement in 2005.

Professor James Ritter

FRCP gained a degree in animal physiology and a DPhil in pharmacology before completing

clinical medicine at the Radcliffe Infirmary (Oxford). He trained in Oxford, London and the Johns Hopkins Hospital, Baltimore, MD, with specialist training in clinical pharmacology at the Hammersmith Hospital, London. He is head of the department of clinical pharmacology at Guy's King's and St Thomas' School of Medicine and an honorary consultant physician at Guy's and St Thomas' NHS Trust. He sat on the Subcommittee on Safety and Efficacy of the Committee on Safety of Medicines, has chaired local and multicentre research ethics committees, and chairs the Thames Specialty Training Committee in Clinical Pharmacology. He is one of the two editors of the *British Journal of Clinical Pharmacology* and has been the co-author for the 3rd and subsequent editions of Rang and Dale (1987).

Professor Philip Routledge

OBE FRCP FRCPE FBTS (b. 1948) qualified at Newcastle University has been professor of clinical pharmacology at the school of medicine, Cardiff University, since 1989 and consultant general physician at the Llandough Hospital, Cardiff since 1981. He has been head of Yellow Card Centre Wales since 1983; and chair of the All Wales Medicines Strategy Group since 2006.

Professor Sir Eric Scowen

Kt FRCP FRCS FRCPE FRCPath FRPharmS FRCGP (1910–2002) qualified at St Bartholomew's Hospital Medical School, London. He became reader in medicine at Bart's in 1938, where he remained throughout the war, serving as one of the Prime Minister's physicians. In 1955 he became director of the medical professorial unit at Bart's, and professor of medicine at the University of London (1961–75). He was chairman of the British Pharmacopoeia Commission (1963–69); member of the Committee on Safety of Drugs (CSD) (1963–71); chairman of the CSD's Subcommittee on Toxicity; twice chairman of the Committee on Safety of Medicines (1971–76; 1977–80); member of the Committee on the Review of Medicines (1975–78) and chairman of the Council of the School of Pharmacy (1970–80).

Dr Julian Shelley

FRCPE (b. 1932) was a medical specialist in Tanzania (1958–1964); director of clinical research at C H Boehringer Sohn, Germany (1971–90); and chairman of the board of examiners for the Diploma in Pharmaceutical Medicine (1987–1992).

Dr Robert (Bob) N Smith
FRCP FRCPE FFPM (b. 1934)
graduated at the University of Birmingham and, after army service, went to Sheffield University as research assistant with Professor Graham Wilson, becoming lecturer, and in 1971 senior lecturer in pharmacology and therapeutics and consultant physician. He spent two years at the University of Michigan working on pharmacokinetics. He joined the pharmaceutical industry in 1976, becoming director of clinical research and drug development with Hoffmann-la-Roche in Basel, Switzerland, then moving to Glaxo Group research in the UK in the same role for eight years. He guided the international development and early registration of many major products. He was director of medical affairs for five years before his retirement in 1994, founding editor of the *International Journal of Pharmaceutical Medicine* for 15 years, and member and chairman of the board of examiners of the Faculty of Pharmaceutical Medicine.

Professor Cameron Swift
PhD FRCP FRCPI (b. 1946) is emeritus professor of health care of the elderly at Kings College London School of Medicine, having served as head of department and honorary consultant physician at King's College Hospital (1986–2004),

where he established the Clinical Age Research Unit. He completed his specialist and research training in medicine and clinical pharmacology with Professors James Crooks and Ian Stevenson in Dundee, Scotland, where he was Medical Research Council Research Fellow (1977–80), working on a programme of investigation into the influence of ageing on drug handling and response. He subsequently edited (and contributed to) the first international text on clinical pharmacology in the elderly, (Swift ed., 1987). He served on the Subcommittee on Efficacy and Adverse Reactions of the Committee on Safety of Medicines (1987–92) and the Medicines Commission (2001–05). He was president of the British Geriatrics Society (2000–02) and a scientific advisor to the Association of Medical Research Charities (2002–07).

Sir Richard Sykes
Kt DSc FMedSci FRS (b. 1942) was head of the antibiotic research unit at Glaxo Group Research UK (1972–77); Squibb Institute for Medical Research (1977–86) where he was vice-president of infectious and metabolic diseases (1983–86); Glaxo Group Research, where he was deputy chief executive, 1986; chairman and chief executive (1987–93); Glaxo plc: Group R&D Director (1987–93); deputy

chairman and chief executive (1993–97), chairman (1997–2000), Glaxo Wellcome; chairman, GlaxoSmithKline (2000–02); director, British Pharma Group (1998–2001). He has been the rector of Imperial College, London since 2001.

Professor E M (Tilli) Tansey
HonFRCP FMedSci (b. 1953)
is convenor of the History of Twentieth Century Medicine Group and professor in the history of modern medical sciences at the Wellcome Trust Centre for the History of Medicine at UCL.

Professor Duncan Vere
FRCP FFPM (b. 1929) trained in medicine at the London Hospital Medical College and completed a postgraduate research fellowship there. He was medical officer at the RAF Institute of Aviation Medicine; senior lecturer in medicine and consultant physician at the London Hospital; reader and then professor of therapeutics at the London Hospital Medical School and was appointed head of the department of pharmacology and therapeutics there in 1969. He was a member of the Committee on Safety of Medicines, the Committee on Dental and Surgical Materials and the Medicines Commission (1970–1990), and a member of the Nuffield Enquiry

into Pharmacy, St Christopher's Hospice Research Committee.

Professor Owen Lyndon Wade
CBE FRCP HonFRCPI
(b. 1921) trained at Cambridge and UCH, and joined the Medical Research Council's pneumoconiosis research unit, (1948–51) under Charles Fletcher and Archie Cochrane. He worked with K W Donald in the early days of cardiac catheterization (1951–57) and spent a year as a Rockefeller fellow at Columbia University, New York, with Robert Loeb. He was appointed to the chair of pharmacology and therapeutics at Queen's University, Belfast (1957–71) and to the chair in clinical pharmacology at Birmingham University (1971–86), serving six years as the dean of the faculty of medicine and dentistry and three years as pro-vice-chancellor. He was a member of the Joint Formulary Committee responsible for the *British National Formulary* (1963–86) and chairman of the Joint Formulary Committee (1978–86). He was chairman of the Subcommittee on Adverse Reactions of the Committee on Safety of Drugs. He was also a founder member of the World Health Organization Drug Utilization Research Group. See Wade (1996): 110.

Professor Andrew Wilson

CBE FRCP FRCPGlas
(1909–74) was Weir assistant in materia medica, University of Glasgow (1933–37); lecturer in pharmacology and therapeutics, University of Sheffield and clinical assistant, Sheffield Royal Infirmary (1939–46); lecturer in applied pharmacology, UCL, and UCH Medical School (1946–48); reader in the University of London (1948–51); professor of pharmacology, University of Liverpool (1951–74); and chairman of the British National Formulary Committee.

Glossary

Association of the British Pharmaceutical Industry (ABPI)

The trade association of more than 75 companies producing prescription medicines in the UK, who research, develop, manufacture and supply more than 80 per cent of the medicines prescribed through the National Health Service (NHS). See www.abpi.org.uk (visited 13 May 2008).

AstraZeneca

A company formed by the merger of Astra AB of Sweden and the Zeneca Group plc in 1999. Zeneca was one of the three demerged businesses of Imperial Chemical Industries (ICI) in 1993. See www.astrazeneca.com/article/11163.aspx (visited 30 April 2008).

British Pharmacological Society

The British Pharmacological Society was established as a ‘daughter society’ of the Physiological Society in 1931 by Walter E Dixon FRS (1871–1931), J A Gunn (1882–1958) and Sir Henry Hallett Dale OM FRS (1875–1968). It met once a year until 1946 when launch of the *British Journal of Pharmacology* increased its activities and four times a year from 1968. The 50th

anniversary was celebrated by a short history [Bynum (1981)] and its 75th with a special supplement [*British Journal of Pharmacology* (2006) **147**: S1–307]. See Cuthbert (2006); Aronson (2006); Dollery (2006).

clinical trial exemption scheme

A scheme introduced in 1981 to exempt pharmaceutical companies from the need to have a clinical trials certificate, a process considered, at that time, to have delayed rapid clinical trials of chemicals of interest. See Griffin (1989): 13.

Cohen Committee

A subcommittee of the Standing Medical Advisory Committees for England and Wales and for Scotland, an expert committee established in 1962 under the chairmanship of Lord Cohen of Birkenhead. The need for advice arose from an earlier internal review that legislation should be extended to improve public safety in light of the 1961 thalidomide deformities and that the Minister needed an independent expert body for that function. The 1963 recommendations included the creation of an independent expert

body with power to secure adequate pharmacological and safety testing and clinical trials of new drugs before their release for general use; early detection of adverse effects; and to keep doctors informed of the experience of such drugs in clinical practice. See MoH (1963); Griffin (2006); Tansey and Reynolds (eds) (1997).

Commission on Human Medicines (CHM)

A body combining the functions of the Medicines Commission and the Committee on Safety of Medicines established in 2005.

Committee on the Review of Medicines (CRM)

Established in 1975 to advise the Licensing Authority on the review of the safety, quality and efficacy of products on the market before 1971 holding product licences, licences for proprietary medicines granted before 1976 and disbanded in 1991, having completed its work. See Griffin and Shah (2006): 474–5.

Committee on Safety of Drugs (CSD)

Established in 1963 arising from the Cohen Committee recommendations, although with no statutory powers, prior to framing of comprehensive legislation. Chaired by Professor Sir Derrick Dunlop, it started work in January 1964 with voluntary

agreement of the pharmaceutical industry that no new drugs would be marketed without its approval. Three subcommittees dealt with toxicity, clinical trials and therapeutic efficacy, and adverse reactions. The CSD's findings formed the basis of the 1968 Medicines Act. Sir Derrick Dunlop left the Committee in 1969 to become the first chairman of the Medicines Commission and was succeeded very briefly by Professor A C Frazer before his sudden death and Professor E F Scowen thereafter. Known colloquially as the Dunlop Committee. See Griffin (ed.) (1989); Griffin and Shah (2006); Tansey and Reynolds (eds) (1997).

Committee on Safety of Medicines (CSM)

The independent committee established by the Licensing Authority to advise on questions of safety, quality, efficacy of new medicines for human use in 1971. A number of subcommittees assisted the main committee, for example, the Subcommittee on Safety, Efficacy and Adverse Reactions (SEAR).

Dunlop Committee

See Committee on Safety of Drugs.

European Clinical Trials Directives

Four main directives involve pharmaceutical preparations:

65/65: arrangements for granting authorizations; 75/318: requirements for pre clinical testing, pharmaceutical quality and manufacture; 75/319: established the Committee for Proprietary Medicinal Products in 1975; and 83/570: amended earlier directives in 1985 concerning format and data requirements for applications for marketing authorizations.

International Studies of Infarct Survival (ISIS)

The International Study of Infarct Survival Collaborative Group conducted four large-scale clinical trials (ISIS 1–4) between 1987 and 1993 comparing various treatments for high blood pressure, and the prevention of angina and heart attacks. These international trials involved more than 120 000 patients in more than 1000 hospitals in 29 countries. See ISIS (1986, 1988, 1992, 1995); Reynolds and Tansey (eds.) (2005): 40–1, 78–9.

Investigational New Drug (IND)

The first stage of the US drug regulation system after a molecule changes its legal status under the Federal Food, Drug, and Cosmetic Act 1938 to become a new drug, subject to specific requirements of the US Food and Drug Administration (FDA). For example, an exemption granted to

the drug's sponsor (pharmaceutical or marketing company) from intrastate transportation and distribution regulations for the purpose of clinical trials. See www.fda.gov/cder/Regulatory/applications/ind_page_1.htm (visited 21 August 2008).

Licensing Authority

The body responsible under the Medicines Act, 1968, for controlling and monitoring the production of new medicines by product licences, product licences of right, manufacturers' licences, clinical trial certificates and clinical trial exemption certificates. It is made up of the Secretaries of State for Health and Social Services (Health only in England after 1989), for Agriculture, for Wales, for Scotland and for Northern Ireland; is advised by the Medicines Commission; and was initially administered by the Medicines Division. See www.opsi.gov.uk/RevisedStatutes/Acts/ukpga/1968/cukpga_19680067_en_1 (visited 21 August 2008).

Medicines Act 1968

The main UK legislation protecting the public from dangerous compounds, and ensuring the efficacy and safety of medicinal products, implemented in 1971.

**Medicines and Healthcare
Products Regulatory Agency
(MHRA)**

The new body resulting from the merger of the Medicines Control Agency and the Medical Devices Agency in 2003 that is the government agency responsible for ensuring that medicines and medical devices work and are acceptably safe. See www.mhra.gov.uk/Aboutus/index.htm (visited 21 August 2008).

Medicines Commission

The advisers to the UK Ministers of Health on the execution of the Medicines Act 1968.

Medicines Control Agency (MCA)

The reorganized Medicines Division, so named in 1989 under the directorship of Dr Keith Jones, with a staff of 300 at that time.

Medicines Division

The day-to-day administrative body for the Medicines Act 1968 in the UK Department of Health and Social Security. It coordinated the professional staff and medical assessor to the Medicines Commission; was managed jointly by an under secretary and a senior principal medical officer. In 1988 the Department was divided into the Department of Social Security and the Department of Health.

**Merck Sharp & Dohme Ltd
(Merck; MSD)**

The UK subsidiary of Merck & Co. Inc., of Whitehouse Station, New Jersey, established in 1891.

Northwick Park

A hospital in Harrow, Middlesex, initially housing the MRC Clinical Research Centre, opened in 1988. See Reynolds and Tansey (2000): 19.

**Pharmaceutical Price Regulation
Scheme (PPRS)**

A scheme to secure value for money for the NHS while providing pharmaceutical companies with incentives to invest in new and useful drugs; it is re-negotiated every five years between the Department of Health and the ABPI. See www.offt.gov.uk/advice_and_resources/resource_base/market-studies/price-regulation (visited 13 May 2008).

Poisons Unit, Guy's Hospital,

Established in 1963 to provide a poisons information service, it moved in 1967 to its own premises with a laboratory in south east London and was renamed the Medical Toxicology Unit. It is part of the Guy's and St Thomas' NHS Foundation Trust, providing a wide range of clinical toxicology services. See www.medtox.org/info/default.asp (visited 14 May 2008).

Rayner Reports

Reports by Sir Derek (later Lord) Rayner, adviser (1979–83) to Margaret Thatcher, Prime Minister, on the promotion of efficiency in Government. His scrutiny of specific activities in government departments, the main feature of which was a radical self-examination of a specific policy, activity or function under the close supervision of the Minister responsible and with contributions from Sir Derek and his small unit. See, for example, Montagu *et al.* (1981).

research ethics committee

A committee established to safeguard the welfare of participants in clinical trials. They became mandatory for every NHS health district in 1991 following publication of guidance by the Department of Health HSG(91)5. For detail on the remit of research ethics committees see Department of Health (2001), Alberti (1995).

Talentmark

A recruitment consultancy specializing in the pharmaceutical, biotechnology and life-science industries. See www.talentmark.com (visited June 4 2008).

TGN1412

A super agonistic anti-CD28 monoclonal antibody for the treatment of B cell leukaemia and autoimmune diseases developed

by the sponsor, TeGenero AG, Wurzburg, Germany, which caused multi-organ failure in six healthy human volunteers in March 2006 in a phase I study conducted by Parexel, a US clinical research and bio/pharmaceutical services company founded in 1982, at the Northwick Park Hospital, Harrow. See Department of Health (2006).

Wellcome Foundation

The umbrella organization formed in 1924 by Henry Wellcome to absorb his libraries, museums, research laboratories and the pharmaceutical company of Burroughs Wellcome & Co. Sir Henry Wellcome's will created the medical charity, the Wellcome Trust, which managed the Foundation until it was floated on the stock market and merged with Glaxo in 1995. For a company history until 1940, see Church and Tansey (2007).

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