

PRENATAL CORTICOSTEROIDS FOR REDUCING MORBIDITY AND MORTALITY AFTER PRETERM BIRTH

The transcript of a Witness Seminar held by the Wellcome Trust Centre for the History of Medicine at UCL, London, on 15 June 2004

Edited by L A Reynolds and E M Tansey

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CONTENTS

Illustrations and credits	v
Witness Seminars: Meetings and publications; Acknowledgements E M Tansey and L A Reynolds	vii
Introduction Barbara Stocking	xxi
Transcript Edited by L A Reynolds and E M Tansey	1
Appendix 1 Letter from Professor Sir Graham (Mont) Liggins to Sir Iain Chalmers (6 April 2004)	85
Appendix 2 Prenatal glucocorticoids in preterm birth: a paediatric view of the history of the original studies by Ross Howie (2 June 2004)	89
Appendix 3 Premature sheep and dark horses: Wellcome Trust support for Mont Liggins' work, 1968–76 by Tilli Tansey (25 October 2005)	97
Appendix 4 Prenatal corticosteroid therapy: early Auckland publications, 1972–94 by Ross Howie (January 2005)	101
Appendix 5 Protocol for the use of corticosteroids in the prevention of respiratory distress syndrome in premature infants. From the 1975 UK Study [Gamsu <i>et al.</i> (1989)]	103
References	109
Biographical notes	129
Index	139

ILLUSTRATIONS AND CREDITS

- Figure 1** Ross Howie and Mont Liggins, *c.* 1972. Reproduced by permission of Dr Ross Howie. 7
- Figure 2** Diagram of Liggins' work in sheep from which the serendipitous discovery of the effect of cortisol in accelerating fetal lung maturation was made. Liggins *et al.* (1973), Figure 19, 141. Reproduced from *Recent Progress in Hormone Research* by permission of Professor Sir Graham Liggins and the Endocrine Society. 10
- Figure 3** Investigators in the original Auckland trial (Liggins and Howie, 1972) and its 30-year follow-up (Dalziel *et al.*, 2005a and b). L to R: Stuart Dalziel (Research Fellow), Mont Liggins, Ross Howie and Jane Harding, July 2005. Reproduced by permission of Professor Jane Harding. 18
- Figure 4** Meta-analyses of corticosteroids in pregnancy, 1992–2004.(1) 7 trials from Crowley (1981) as used for the Cochrane logo, see Figure 6; (2) 12 trials, Crowley (1989); (3) 15 trials, Sinclair (1995); (4) cumulative meta-analysis of first 15 trials, Sinclair (1995); (5) 18 trials, Cochrane Library (2004). Reproduced by permission of Dr Patricia Crowley. 28
- Figure 5** Mary Ellen Avery and Richard Pattle at a CIBA Symposium in 1965. From Clements (1996): 222. Used with permission of the American Physiological Society. 31
- Figure 6** The story of the Cochrane Logo, 1992. Reproduced by permission of Sir Iain Chalmers. 55

Figure 7	Lamb lungs showing partial inflation after fetal infusion with cortisol at 118 days of gestation, birth at 120 days, photographed at autopsy. Reproduced by permission of Professor Sir Graham (Mont) Liggins.	86
Figure 8	Example of salbutamol treatment used in Gamsu <i>et al.</i> (1989). Reproduced by permission of Dr Clive Dash.	108
Table 1	Incidence of respiratory distress syndrome as percentages of live preterm births. Data taken from Crowley (1981): 148.	24
Table 2	Perinatal mortality rates as percentages of preterm births. Data taken from Crowley (1981): 148.	24
Table 3	Retrospective analysis of steroid and non-steroid use in preterm births, St David's Hospital, Cardiff, 1979–80. Reproduced by permission of Dr Roger Verrier Jones.	35
Table 4	Effect of prolonged rupture of membranes (PROM) on steroid- and non-steroid-treated preterm births, St David's Hospital, Cardiff, 1979–80. Reproduced by permission of Dr Roger Verrier Jones.	35
Table 5	Use of salbutamol in Group 1 patients for the management of premature labour for the trial of corticosteroids in the treatment of RDS. Reproduced by permission of Dr Clive Dash.	107

WITNESS SEMINARS: MEETINGS AND PUBLICATIONS¹

In 1990 the Wellcome Trust created a History of Twentieth Century Medicine Group, as part of 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 Wellcome Trust 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 40 such meetings, most of which have been published, as listed on pages xi–xix.

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 immediately 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.² 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, 2005–06**

Dr Tilli Tansey – Historian of Modern Medical Science, 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

Dr Robert Bud – Principal Curator of Medicine and Manager of Electronic Content, Science Museum, London

Dr Daphne Christie – Senior Research Assistant, WTCHM, and Organizing Secretary

Dr John Ford – Retired General Practitioner, Tunbridge Wells

Professor Mark Jackson – Centre for Medical History, Exeter

Professor Ian McDonald – WTCHM, former Professor of Neurology, Institute of Neurology, London

Dr Helga Satzinger – 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.

ACKNOWLEDGEMENTS

'Prenatal corticosteroids' was suggested to us as a suitable topic for a Witness Seminar by Sir Iain Chalmers, after Dr Mark Walport had raised the possibility with him earlier the same day. We are very grateful to Sir Iain for his help in planning the meeting. We are particularly grateful to Ms Barbara Stocking for writing such a useful Introduction to these published proceedings, and to Dr Edmund Hey for his excellent chairing of the occasion. Our additional thanks go to Professors Sir Graham Liggins, Ross Howie, and Jane Harding for their help with the organization of the meeting and during its preparation for publication; Professor Denis Hawkins, who read through earlier drafts of the transcript, and offered helpful comments and advice. We thank Professors Sir Graham Liggins, Ross Howie, Jane Harding, Sir Iain Chalmers and Dr Patricia Crowley for additional help with illustrations and Mrs Valerie Wildridge from the King's Fund Information and Library Service for details of the NHS Executive Letter. For permission to reproduce images we thank Professor John West and the American Physiological Society, and the Endocrine Society.

As with all our meetings, we depend a great deal on our colleagues at the Wellcome Trust to ensure their smooth running: the Audiovisual Department, the Medical Photographic Library and Mrs Tracy Tillotson of the Wellcome Library; Mr Akio Morishima, who has supervised the design and production of this volume; our indexer, Ms Cath Topliff; our readers, Ms Lucy Moore, Ms Fiona Plowman and Mr Simon Reynolds; and Ms Nickie Colson for additional research assistance. Mrs Jaqui Carter is our transcriber, and Mrs Wendy Kutner and Dr Daphne Christie assist us in running the meetings. Finally we thank the Wellcome Trust for supporting this programme.

Tilli Tansey

Lois Reynolds

Wellcome Trust Centre for the History of Medicine at UCL

HISTORY OF TWENTIETH CENTURY MEDICINE WITNESS SEMINARS, 1993–2006

- 1993** **Monoclonal antibodies**
Organizers: Dr E M Tansey and Dr Peter Catterall
- 1994** **The early history of renal transplantation**
Organizer: Dr Stephen Lock
- Pneumoconiosis of coal workers**
Organizer: Dr E M Tansey
- 1995** **Self and non-self: A history of autoimmunity**
Organizers: Sir Christopher Booth and Dr E M Tansey
- Ashes to ashes: The history of smoking and health**
Organizers: Dr Stephen Lock and Dr E M Tansey
- Oral contraceptives**
Organizers: Dr Lara Marks and Dr E M Tansey
- Endogenous opiates**
Organizer: Dr E M Tansey
- 1996** **Committee on Safety of Drugs**
Organizers: Dr Stephen Lock and Dr E M Tansey
- Making the body more transparent: The impact of nuclear
magnetic resonance and magnetic resonance imaging**
Organizer: Sir Christopher Booth
- 1997** **Research in general practice**
Organizers: Dr Ian Tait and Dr E M Tansey
- Drugs in psychiatric practice**
Organizers: Dr David Healy and Dr E M Tansey
- The MRC Common Cold Unit**
Organizers: Dr David Tyrrell and Dr E M Tansey
- The first heart transplant in the UK**
Organizer: Professor Tom Treasure

- 1998 Haemophilia: Recent history of clinical management**
Organizers: Professor Christine Lee and Dr E M Tansey
- Obstetric ultrasound: Historical perspectives**
Organizers: Dr Malcolm Nicolson, Mr John Fleming and Dr E M Tansey
- Post penicillin antibiotics**
Organizers: Dr Robert Bud and Dr E M Tansey
- Clinical research in Britain, 1950–1980**
Organizers: Dr David Gordon and Dr E M Tansey
- 1999 Intestinal absorption**
Organizers: Sir Christopher Booth and Dr E M Tansey
- The MRC Epidemiology Unit (South Wales)**
Organizers: Dr Andy Ness and Dr E M Tansey
- Neonatal intensive care**
Organizers: Professor Osmund Reynolds and Dr E M Tansey
- British contributions to medicine in Africa after the Second World War**
Organizers: Dr Mary Dobson, Dr Maureen Malowany, Dr Gordon Cook and Dr E M Tansey
- 2000 Childhood asthma, and beyond**
Organizers: Dr Chris O’Callaghan and Dr Daphne Christie
- Peptic ulcer: Rise and fall**
Organizers: Sir Christopher Booth, Professor Roy Pounder and Dr E M Tansey
- Maternal care**
Organizers: Dr Irvine Loudon and Dr Daphne Christie
- 2001 Leukaemia**
Organizers: Professor Sir David Weatherall, Professor John Goldman, Sir Christopher Booth and Dr Daphne Christie
- The MRC Applied Psychology Unit**
Organizers: Dr Geoff Bunn and Dr Daphne Christie
- Genetic testing**
Organizers: Professor Doris Zallen and Dr Daphne Christie

- Foot and mouth disease: The 1967 outbreak and its aftermath**
Organizers: Dr Abigail Woods, Dr Daphne Christie and Dr David Aickin
- 2002 **Environmental toxicology: The legacy of *Silent Spring***
Organizers: Dr Robert Flanagan and Dr Daphne Christie
- Cystic fibrosis**
Organizers: Dr James Littlewood and Dr Daphne Christie
- Innovation in pain management**
Organizers: Professor David Clark and Dr Daphne Christie
- 2003 **Thrombolysis**
Organizers: Mr Robert Arnott and Dr Daphne Christie
- Beyond the asylum: Anti-psychiatry and care in the community**
Organizers: Dr Mark Jackson and Dr Daphne Christie
- The Rhesus factor and disease prevention**
Organizers: Professor Doris Zallen and Dr Daphne Christie
- Platelets in thrombosis and other disorders**
Organizers: Professor Gustav Born and Dr Daphne Christie
- 2004 **Short-course chemotherapy for tuberculosis**
Organizers: Dr Owen McCarthy and Dr Daphne Christie
- Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth**
Organizers: Sir Iain Chalmers and Dr Daphne Christie
- Public health in the 1980s and 1990s: Decline and rise?**
Organizers: Professor Virginia Berridge, Dr Niki Ellis and Dr Daphne Christie
- 2005 **The history of cholesterol, atherosclerosis and coronary disease, 1950–2000**
Organizers: Professor Michael Oliver and Dr Daphne Christie
- Development of physics applied to medicine in the UK, 1945–90**
Organizers: Professor John Clifton and Dr Daphne Christie

2006 The early development of total hip replacement

Advisers: Dr Krishna Kunzru and Dr Francis Neary

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

Advisers: Professor Paul Andrews and Dr Anthony Woods

Medical ethics education in Britain, 1963–93

Adviser: Dr Michael Barr

Superbugs and superdrugs: The history of MRSA

Adviser: Professor Gordon Stewart

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

In: 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

In: 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

In: 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

In: 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

In: 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?

In: 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

In: 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

In: 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

In: 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

In: 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

In: 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

In: 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

In: 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

In: 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 854840 84 2

Leukaemia

In: 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

In: 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

In: 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

In: 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*

In: 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

In: 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

In: 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

In: 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

In: 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

In: 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

In: 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. This volume. ISBN 0 85484 102 4

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

In: 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. In press. ISBN 0 85484 106 7

Fifty Years of Cholesterol, Atherosclerosis and Coronary Disease, 1950–2000

In: 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. In press.

The Development of Physics Applied to Medicine in the UK, 1945–90

In: 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. In press.

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Copies of volumes 21–26 can be ordered from www.amazon.co.uk; www.amazon.com; and all good booksellers for £6/\$10 plus postage.

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: P D'Arcy Hart, 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.

INTRODUCTION

The reader may wonder why someone who is currently Director of Oxfam GB is writing this introduction. There are two reasons. For many years I was engaged in healthcare and believed passionately that we needed to be clear what *is* good evidence about clinical care and then to make sure the knowledge is used in practice. Early on, it also became clear to me that information alone was rarely sufficient for people to change their practice: the whole wonderful complexity of wider culture and beliefs, individuals and their place in social systems comes into play. Despite many studies showing consistently that disseminating evidence is not enough, there were and still are, many people who ignore this evidence itself and are then surprised that change does not happen.

My second reason for writing this introduction is my own experience. In the mid-1980s I went into premature labour, eventually giving birth at 29 weeks' gestation. For the time I was lucky. Because I was a member of the National Perinatal Epidemiology Unit advisory committee, I was aware of evidence on corticosteroids, lucky too in having an obstetrician who knew the evidence. Both of us took it as a matter of course that I should receive corticosteroids. Despite the prematurity, I delivered a baby who never needed artificial ventilation and who is, as I write, a healthy 19-year-old. This itself illustrates another point, just how important it is that patients should, if they want it, have access to good information and should feel able to be involved in decisions about their own care. My experience was an excellent example of patient–doctor partnership. Fortunately, in recent years, patient involvement has stopped being frowned upon and clinicians from all professions are learning how valuable it can be to have the patient as a partner.

The use of corticosteroids for women at risk of giving birth prematurely in order to reduce respiratory distress in their newborn babies is a fascinating case study of change. The corticosteroids Witness Seminar is an intriguing account, firstly of how the discovery was made, particularly the crossover links from animal to human studies. Yes, there was a discussion in a tearoom, which led to the discovery (pages 5, 20). It may seem serendipitous but one does feel that, with the number of people interested in the various facets, it was an idea whose time had come and sooner or later the connections would be made. Then there are the accounts of those early trials and the difficulties in getting people to change practice. This part of the story illustrates the importance of good randomized controlled trials, with patient numbers and protocols that are robust enough to

withstand challenge. For the challenge certainly did come, for those who knew some evidence from very poorly researched trials and from those who, through their own personal experience, had a powerful inclination not to believe the proper trials. The witness evidence illustrates dramatically how one powerful experience (a death or near miss perhaps unrelated to the issue at stake) can influence a leading figure and, because of the personal authority of such individuals, prevent change from happening for a long time (see page 64).

Prenatal corticosteroids are now accepted practice and are included in all the guidelines, but it is worrying that so many babies would have died, and so many parents and babies suffered because the evidence was not put into practice for so long. The good news is that there has been a paradigm shift, I believe, in the acceptance of evidence-based healthcare. There has also been a dramatic change in understanding about what is good evidence, not least through the work of the Cochrane Collaboration. Beware though any complacency; remember change is so much a matter of culture, beliefs and individual experience.

Barbara Stocking
Oxfam GB

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Edited by L A Reynolds and E M Tansey

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Participants

Dr Mary Ellen (Mel) Avery

Professor Sir Christopher Booth

Dr Peter Brocklehurst

Sir Iain Chalmers

Dr Patricia Crowley

Professor John Gabbay

Professor Harold Gamsu[†]

Dr Dino Giussani

Mrs Gill Gyte

Dr Stephen Hanney

Professor Jane Harding

Dr John Hayward

Dr Edmund Hey (Chair)

Mr Ian Jones

Professor Richard Lilford

Professor Miranda Mugford

Mrs Brenda Mullinger

Professor Ann Oakley

Dr Sam Richmond

Dr Roger Verrier Jones

Professor Dafydd Walters

Mr John Williams

Among those attending the meeting: Dr Sheila Duncan, Professor Abby Fowden, Dr Anita Magowska, Professor Alison Macfarlane, Dr David Paintin, Professor Maureen Young

Apologies include: Professor Richard Beard, Professor Sir Robert Boyd, Professor Geoffrey Chamberlain, Dr Clive Dash, Dr Pamela Davies, Professor Sir Liam Donaldson, Professor Peter Dunn, Dr Jonathan Grant, Sir John Muir Gray, Professor Aidan Halligan, Professor Mark Hanson, Associate Professor Ross Howie, Professor Frank Hytten, Professor Marc Keirse, Professor Sir Graham Liggins, Dr Jerold Lucey, Professor Sally MacIntyre, Dr Jonathan Mant, Professor Jim Neilson, Dr Cliff Roberton, Ms Barbara Stocking, Dr Peter Stutchfield, Dr Mark Walport, Professor Jonathan Wigglesworth, Dr Peter Williams

[†]Died 31 August 2004

Dr Edmund Hey: I was always taught to check my references before I stand up to speak. Most of us haven't had a chance to check any of our references, but it may be that after today's meeting, some of us will go scurrying away to do just that.

I was provoked into checking up what Wellcome History of Medicine people had to say about Sir Peter Medawar and his statement that most scientific papers are a fraud.¹ I would encourage you to read what he actually wrote, because it isn't quite how it gets quoted nowadays. It was an unscripted talk, which I find quite amazing, on the Third Programme [Radio 3] – yes, it was called the Third Programme – back in 1963. Since we are in reminiscing mood, I had just started my first job as a Medical Research Council (MRC) physiologist/clinician/animal-worker, working with Kenneth Cross. I heard Medawar's talk on the day [it was given] and it had an absolutely profound effect on me. I thought I might read a bit of it, but then I found another talk in which he was actually interviewed defending this, just three years later. I think we will come back to this at the end of the day.

The issue is what he meant about research being fraudulent. I will just read a couple of sentences. The interviewer [Dr John Watkins] says, 'Arising out of your paper, "Is the scientific paper a fraud?"', which was written under the influence of Karl Popper's ideas on scientific method, your answer was "Yes, it *is* a fraud" in the sense that it systematically conceals or distorts the way in which the ideas were thought out or developed. Have any of your scientific papers been, in this sense, fraudulent?' And Peter Medawar replied:

A good many of my scientific papers have been moderately fraudulent. Let me put it this way:...I have never pretended that the research I reported in the scientific paper was done in the inductive style – that is to say by the vacuous collection of facts which then tumbled somehow or other into place. I think I have adopted a compromise. I have not practised what I have preached, but then I am not the first person to fail to do so.

¹ Pyke (1990): 228–33, originally published in *The Listener* 70 (12 September 1963). Freely available online at www.dpi.inpe.br/cursos/ser212/artigos/medawar_paper_fraud.pdf (visited 2 August 2005). See also 'What is a Witness Seminar?', introduction by Tilli Tansey to Tansey *et al.* (eds) (1997): i–v, freely available online at www.ucl.ac.uk/histmed following the links to Publications/Wellcome Witnesses.

What he goes on to puzzle about is what it is that is the creative inspirational act at the beginning of that. He comes to the conclusion that he just hadn't the faintest idea. He says:

All that we know about it is that, whatever precedes the entry of an idea into the mind, isn't known consciously. It is something subconscious. There is a piecing together and a putting together of something in the mind, but the process by which we do it is totally unknown.²

I am not sure that's true. Sir Peter Medawar was a Nobel Prizewinner. He knew more about this than most. He made many very brilliant discoveries himself. But I will come back at the end of the afternoon and ask whether it is not fairly clear how Mont Liggins came to make the discovery he did. The papers he wrote describe the process very succinctly. If we can agree about this we are then left to spend most of today realizing that great ideas are 1 per cent inspiration and 99 per cent perspiration. I suspect we are going to wonder why we went on to perspire quite as heavily as we did over this particular inspiration, and why it is that some of us are still mopping our brow and realizing that we still haven't got things sorted.

I think that we should start by asking Mel Avery, who has come all the way from Boston – although I think she's been on the Rhine until a few days ago – to set the scene, because 30, 40 years ago clinicians and physiologists and animal research workers were much closer together than they often are nowadays. Certainly in the UK it's very uncommon for you to meet a person who spends some days in the lab and some days on the farm or in the animal laboratory. But you can tell us your story, because years ago much of what we understand now about the lung came from the combination of those interests, didn't it?

Dr Mary Ellen (Mel) Avery: I bring you a personal view of the discovery of aspects of maturation of the lung in the preterm infant by antenatal glucocorticoids. The story really began with Professor G C (Mont) Liggins, an obstetrician in Auckland. I am happy to acknowledge that he has been a most generous supporter and friend and we were in close touch during the 1960s and 1970s, when this story evolved.

² 'My Life in Science', a transcript of an interview with Sir Peter Medawar conducted by David Wilson and Dr John Watkins, was broadcast on the BBC Third Programme [now Radio 3] on 25 April 1966. Published in Pyke (1990): 1–14. Quotes from pages 5–6 of the 1991 paperback edition.

I was asked to give a personal point of view and I will tell you how I got into the act. The studies of sheep were initiated largely, I think, in this country, England, with Sir Joseph Barcroft and Don Barron also working with Maureen Young.³ I was finishing a fellowship supported by the National Institutes of Health (NIH) from 1957 to 1959 and then a fellowship from the Markle Foundation. So I was set free. I decided to go to the UK, because I had been associated with Clement Smith and knew that he felt great fondness for English research and animal research in particular, and, of course, within a month that was followed by time with Leonard Strang at University College Hospital.⁴

My research fellows at Johns Hopkins set out to map the course of events in the developing lung of the fetal lamb, the animal of choice. I have often wondered why, and I think it's because babies and lambs are about the same size at birth and the equipment you had for one worked for the other. I don't know if that is quite true or not, but those are my thoughts on the matter.

I became interested in other things, but the group in the lab continued and the names that come into mind include Florence Moog, a brilliant anatomist and embryologist who was studying the intestine of mice in St Louis.⁵ We were both members of the same study section at NIH, so this was a coffee break conversation: 'What do you do?' 'What do I do?' She tells me she can accelerate the maturation of the intestine of suckling mice measured by the appearance of alkaline phosphatase in the duodenum after administration of glucocorticoid to the mother.

That was 1962. Then we said we have to know about the normal appearance of various enzymes and so on in the developing lamb. That's when all the people in the laboratory – which then numbered 15 or 20 – produced a paper about the timing of various enzymes and other events in the normal lamb lungs.⁶ I went to New Zealand in 1968 as a guest of the Society of Obstetricians and

³ See, for example, Barcroft (1946); Meschia *et al.* (1965); Young (1992). Professor Maureen Young wrote: 'Mel Avery certainly heard about the animal work in England from me, but I told her after the meeting on 15 June 2004 that she was not correct in presuming that I had used the lovely preparations so soon in my career! I had been mostly associated with human babies before 1960.' Letter to Mrs Lois Reynolds, 9 August 2005.

⁴ Smith (1945); Strang (1977). For Professor Sir Robert Boyd's appreciation of Strang's work on the adaptation of the fetal lung to air breathing, see Christie and Tansey (eds) (2001): 16, fn.

⁵ Moog (1953).

⁶ Buckingham and Avery (1962).

the Paediatric Society.⁷ Mont Liggins was there and after I said that lambs were perfectly normal by 147 days' gestation, Mont said, 'What if I told you we can identify accelerated maturation in the lambs' lungs at 115 days?' That's too big [a difference] to be an error. Were New Zealand lambs that different from the lambs in the USA? I didn't believe that, neither did he. It appeared that, in fact, glucocorticoids could accelerate lung maturation of lambs.⁸

The story of the glucocorticoids moved ahead when Liggins and Howie proposed a randomized controlled trial [of glucocortico-steroids], and it was obvious that the effect was reproducible. I would also like to pay tribute to Sue Buckingham, a fellow at the Columbia Presbyterian Medical School, probably well known to you. She presented a paper on the effects on mice at the Federation of American Societies for Experimental Biology meeting.⁹ She made the point in 1968 and I thought it was frivolous. Then we had a series of observations, not well put together at that time, but confirmed over and over, that glucocorticoids accelerated maturation, not only of Moog's mice intestine, but also of the fetal lung. By then I had finished my fellowship – Sue, alas, died shortly after that meeting, which was a great tragedy, for her contribution was valuable.

This is the story in which I had first-hand involvement, but I have never got over wanting to know what the long-term outcome of anything that's invasive would be. Others at Columbia were saying, 'Never should a premature baby be allowed to die without a course of glucocorticoids'. It was a sad commentary in retrospect. It didn't seem to make much difference one way or another, except in the context of accelerating maturation of the fetal lung and intestine. There are still those who are worried about long-term outcomes and I think we will hear more about that from some of the participants here. I, too, have been concerned that there has been a temptation to assume that if a little bit is good, more is better, and give more than one dose: 'Just let's try it, postnatally, maybe we don't need to give it prenatally, we will give it postnatally and we will give bigger doses, because you might get a bigger effect.'

Hey: I don't think we will take questions at this stage, because Mel has just set the scene. She's been very modest, our main American witness, and she will be

⁷ Dr Ross Howie wrote: 'The date was 1968 as I remember (the occasion was the opening of the new Christchurch Women's Hospital), but Mel Avery will confirm.' E-mail to Mrs Lois Reynolds, 22 August 2005. Confirmed by Mel Avery, note on draft transcript, 17 August 2005.

⁸ Liggins (1969).

⁹ Buckingham *et al.* (1968).

able to tell us a lot more later about the way in which things rolled out. We shall want to hear from her about when the collaborative [US NIH Collaborative Group] trial was done and how it was done, and why it was done the way it was.¹⁰ But that's a long way down the line this afternoon. What we should do now, before we have our first break for discussion and questions, is to hear from Jane Harding, who works in the room Ross [Howie] once worked in. I get the impression she almost had to sit on the papers that he had left behind, because he had left rather a lot, and it's surprising how much more is still coming out of those papers. So we haven't got Ross here in person, but you might just hear his voice.

Professor Jane Harding: It's a great honour for me to be here. I am sorry that Mont Liggins and Ross Howie are not well enough to attend. They would both wish to be here and although the programme suggests that I might speak on their behalf, I wouldn't dare. I will tell you a little of what they have told me and, later on perhaps, my own involvement in the continuation of this story 30 years later.



Figure 1: L to R: Ross Howie and Mont Liggins, c. 1972.

¹⁰ Collaborative Group on Antenatal Steroid Therapy (1981).

I will start by reading from a letter written by Mont Liggins to Iain Chalmers earlier this year and I quote:¹¹

When I returned to a position as a Senior Lecturer in Obstetrics and Gynaecology at the National Women's Hospital in 1959, I asked my friend Bill Liley, of fetal transfusion fame,¹² how to choose a topic. He said to look for a major problem that was potentially solvable. The major problem was easy: prematurity stood out above everything else. I naively thought that all I had to do was solve the ancient question of what controlled the onset of labour at term and the reason for premature onset would become apparent.

Mont then described how he worked on his idea that the onset of labour was controlled by the fetus not the mother, and how he spent a sabbatical period at the veterinary school at the University of California at Davis, to assess the role of cortisol¹³ in initiating parturition in sheep. I return to his letter:

Back in Auckland I needed a lab and money. The hospital gave me an abandoned shed; the Wellcome Trust gave me money.¹⁴ The first experiments were to test the idea that the effects of the pituitary were mediated by the fetal adrenal [gland]. Infusion of cortisol or ACTH [adrenocorticotrophic hormone] caused premature labour at any gestational age.

From that point in the story I invite you to listen to Mont's own words describing the application of these findings to the lung. The recording you will hear was made in April last year [2003], as part of a recording of an oral history project undertaken by the place at which I now work, the Liggins Institute. It is named after him, and we asked Mont to record his life story. He agreed that I could play a part of it to you, as it relates to this story.¹⁵

¹¹ Letter from Professor Sir Graham (Mont) Liggins to Sir Iain Chalmers, 6 April 2004. Reproduced in full in Appendix 1, pages 85–8.

¹² Liley (1964).

¹³ Cortisol is the naturally occurring glucocorticoid in humans and sheep.

¹⁴ The Wellcome Trust gave more than £40 000 in grants and supplements for research assistance to Professor Liggins over eight years from 1968 to 1976. See Appendix 3, pages 97–9.

¹⁵ Professor Sir Graham Liggins wrote: 'The tape is held by The Director, Liggins Institute.' Letter to Mrs Lois Reynolds, n.d., received 25 August 2005. An audiotape of Liggins' 1989 James Young Simpson Lecture given at the Silver Jubilee Congress of Obstetrics and Gynaecology, has been donated by Sir Iain Chalmers, which will be deposited along with the records and tapes from this meeting in GC/253, Archives and Manuscripts, Wellcome Library, London.

Mont Liggins [from a tape recording]: I had always been meticulous in doing a complete autopsy of all the lambs that I delivered, weighed organs – helped, I must say, by my secretary who used to come in and help me when she was in the office. And I remember one morning, there was a lamb lying in a cage with its mother. A lamb that had been infused as a fetus with cortisol. And to my surprise this lamb was still breathing, not very healthy breathing, but it was alive and breathing. It had no right to be. It was so premature that its lungs should have been just like liver, and quite uninflatable. And this struck me as surprising, and when we came to do the autopsy the lungs were partly inflated and this was absolutely surprising. So, weighing this up I postulated that the cortisol had accelerated the maturation of enzymes in the lung that caused accelerated maturation. Now, at that time my facilities were fully occupied in studying the question of parturition and I didn't have time to pursue this lung problem any further.¹⁶ But it so happened that Mary Ellen Avery, who was a big name in respiratory distress syndrome [RDS] and lung problems, and the discoverer of the fact that surfactant was necessary for the maintenance of lung expansion, was visiting New Zealand.¹⁷ So we were both going to a meeting in Christchurch where I described my findings in a series of lambs with expanded lungs.

She couldn't get back to the US fast enough to set up experiments in rabbits – giving cortisol to fetal rabbits – and produced the definitive paper on the effects of corticosteroids on lung maturation.¹⁸ So, as far as I was concerned, it rested at that point and I thought, 'Well, if it works in animals, why shouldn't it work in human babies?' As far as we knew, lungs in human babies had the same enzymes as animal lungs. Should we not do a clinical trial and put it to the test? So I was gossiping with Ross Howie, our paediatric colleague, and Ross is a very meticulous guy; and Ross and I, with most input from Ross, wrote the protocol for doing a controlled clinical trial of corticosteroids in preterm infants. That protocol I might say has been cited as one of the earliest and best controlled trial protocols.¹⁹

Harding: One of the things that I noted in this recording, and in my many discussions with the principal players, was how they always give the credit

¹⁶ See Appendix 1, pages 85–8.

¹⁷ Avery and Mead (1959); Kotas and Avery (1971); Motoyama *et al.* (1971). See also Avery *et al.* (1981).

¹⁸ deLemos *et al.* (1970); Avery (2000).

¹⁹ Liggins (2003); Liggins and Howie (1972). For the next well-controlled study following Liggins and Howie (1972), see Papageorgiou *et al.* (1979).

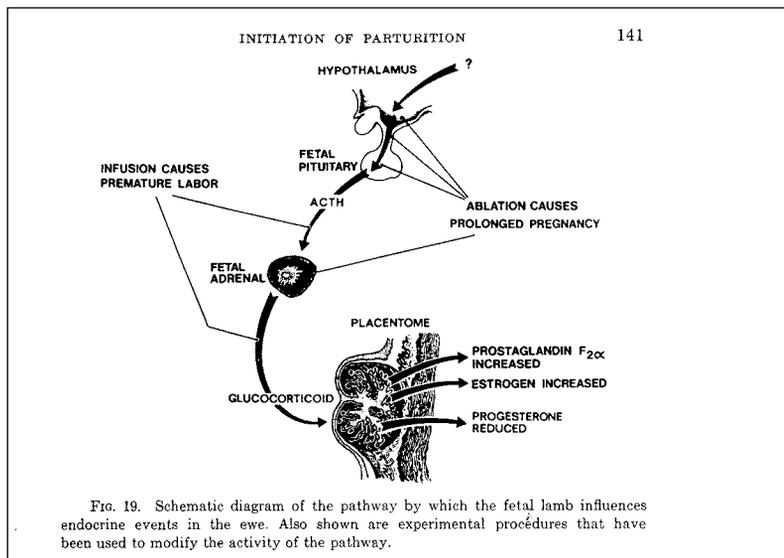


Figure 2: Diagram of Liggins' work in sheep from which the serendipitous discovery of the effect of cortisol in accelerating fetal lung maturation was made.

Originally published in Liggins et al. (1973), 141.

to everybody else. You heard on the tape that Mont gives all the credit for surfactant work to Mary Ellen Avery, and for the clinical trials to Ross Howie. Ross, on the other hand, assures me that it was all Mont's idea. In fact, it's my view that it was a quite remarkable partnership. At the time, Ross was a New Zealand MRC research fellow, the only paediatrician at the National Women's Hospital in Auckland and indeed in New Zealand, who was able to ventilate newborn babies. I would like to quote now from Ross Howie's words describing these events, although I have abbreviated them somewhat:

At the outset, it might be worth reminding others that the project was only a sideline of the main work of both Mont Liggins on the one hand and myself on the other. Mont has his much more widely ranging research into reproductive endocrinology for which he is justly renowned. My own main interest was in health rather than science, especially in helping develop newborn services in New Zealand, and I just happened to be around at the time. But I helped to design the trial, supervised the collection of data and did all the work in analysing them....I still remember the excitement I felt at my first evidence of it, when he handed me the lungs of twin lambs for pressure-volume studies. The lambs had been delivered very early...one had been infused with glucocorticoids and the other not. Lungs of the infused lamb were perfectly stable after

inflation: pink, fluffy and floated in water. In total contrast, the lungs of the other remained solid and liver-like, and sank.²⁰

There are a couple of things that interest me about these descriptions. One is the unique pairing of an experimental scientist who was also an obstetrician, with the only paediatrician in the country who was capable of looking after the premature babies. Another is that whatever the later perceptions became, it's clear that both the authors of the study were involved together from the beginning, in the animal laboratory, as well as in the clinical aspects.²¹ Finally, I am entranced with Ross's comments that this lamb trial was simply a sideline for both of them. It's an interesting warning against the narrow and predetermined endpoints of some research programmes, and highlights the importance of serendipity in progress.

Ross describes presenting the results of the completed study – not the initial part of the study that was published in 1972, but the completed study – at a symposium hosted by the Royal College of Obstetricians and Gynaecologists (RCOG) of the UK in 1977.²² He said to me, 'They didn't really want to hear'. He also reported that when he was asked for a recommendation as to what people should be doing, he said that the treatment looked very promising, but that it would be unsafe to initiate a new treatment on the basis of a single trial. He said that he knew what he should do, but that others should wait for ongoing trials. Other people here can talk about the progress of the treatment after that time. My own involvement began perhaps when I entered medical school in 1973. Both of the principal actors were my tutors. The use of antenatal steroids was routine at that time in our hospital and has remained so ever since.

²⁰ See Appendix 2, pages 89–95, quotes on page 89, 91.

²¹ Dr Ross Howie wrote: 'Jane Harding is too kind in saying that I was involved in Mont's animal work from the beginning. Our contacts were occasional. I do remember what may have been the start of his work, a visit to the Ruakura Agricultural Research Station, the leading institution of its kind in the country, about 120km south of Auckland, probably between 1962 and 1965. I have an idea this visit was facilitated by Sir William (Bill) Liley of fetal transfusion fame. Contacts in Ruakura would have helped Mont with his work, notably Bob Welch. But animal work was not my thing; in any case I had too much else to do.' E-mail to Mrs Lois Reynolds, 12 June 2005. For details of the Liley chart to measure amniotic fluid bilirubin levels plotted against gestational age, see Zallen *et al.* (eds) (2004): 11–12. See also Appendix 1, page 85–8.

²² Dr Clive Dash wrote: 'At the time when Ross Howie presented the results to the RCOG in 1977 [Howie and Liggins (1978)], the UK study was in its recruitment phase. Whether knowledge of the status of the UK study played any part in the cool response of the delegates at the meeting that Ross sensed, would be speculative.' E-mail to Dr Daphne Christie, 10 January 2005. For the protocol for the UK Study, see Appendix 5, pages 103–8.

By this time Mont had moved on to other studies. Ross was completing the four- and six-year follow-up of the original cohort, funded by the World Health Organization.²³ He always believed very strongly that long-term follow-up was essential for anything in neonatal care and set about this with his usual thorough approach. The follow-up studies were published in the early 1980s and the ongoing follow-up studies we will talk about later.²⁴

Hey: Would you like to explain why they chose the steroids they did, because a lot of people never seemed to have noticed. Most people think that if they are using betamethasone they must be using the product that Ross and Mont did. They think it was betamethasone, full stop.

Harding: I can tell you that story because I specifically asked both of them in recent weeks. To paraphrase a long story: Mont had been doing work in human pregnancy on the effects of steroids on the fetus. He had a reasonable idea of what dose of steroid was required to suppress oestrogen production and he presumed that that would be an adequate dose to do something to the fetus. He knew that he wanted something that would be reasonably long-lasting, so that it didn't have to be given too frequently to pregnant women and decided that something that would last for 24 hours – and therefore two doses would give you about a 48-hour effect – would be adequate, based on the animal studies. He therefore set about looking for a drug that would be clinically easy to manage, long-lasting, and which had an identical appearing placebo. This is not easy, because all the long-lasting preparations of glucocorticoids are opaque, they are milky substances, and a placebo wasn't easy to find. He wrote to a number of drug companies asking for help, and in the end Glaxo – originally the name of a dried milk powder sold by a New Zealand company, and it so happened that the medical director was a mate of Mont's – provided an opaque placebo.²⁵ Their long-acting preparation was the one he used, because that was the one that was

²³ MacArthur *et al.* (1981, 1982).

²⁴ See notes 105 and 197.

²⁵ Dr Clive Dash wrote: 'Because of the Glaxo link, it was well known in the UK which product had been used in New Zealand [Gamsu *et al.* (1989)]. The NZ product was an ester of betamethasone (acetate), the properties of which caused a slower absorption from the intramuscular site than the very soluble product (phosphate salt) available in the UK. It was estimated that more frequent injections of the soluble product would give a similar bioavailability. The placebo used in the UK was specially prepared for the study by Glaxo and consisted of the vehicle in which the phosphate salt was formulated. Both were opaque solutions in identical vials and labelled similarly except for patient numbers assigned randomly. Thus, the blind was preserved.' E-mail to Dr Daphne Christie, 10 January 2005.

available and they were provided with the placebo. So the placebo was cortisone acetate, which had much lower potency but looked the same, and the drug that he selected was the Glaxo drug because that was what was available and because the director was a mate who provided it for free. I might say that the study was unfunded. Mont said to me, 'We didn't need funding to do this trial'. And of course they didn't, because the drug was provided free, and both Mont and Ross were fully salaried and were able to put in all of their time.

Hey: Just remind us how many babies were eventually recruited.

Harding: Twelve hundred. The actual number was 1218.

Hey: Still the biggest trial.

Harding: Still the biggest trial. The original publication that everybody cites from 1972 was only the first 282.²⁶ But they continued to recruit long after that trial.

If I could just comment: the other thing that most people aren't aware of is that after the first 717 women were enrolled, when they did the first analysis and thought 'The stuff really does work': they doubled the dose. In the rest of the trial, the other 500-odd actually received twice the dose, to see whether more was better. They concluded that it was not, and published all of the data as a combined single trial.²⁷

Hey: May I just ask one other question? I get the impression that the gap between their having the recognition that it worked and starting the trial was pretty short. The trial started in December 1969, and it's there in print in July 1972.

Harding: That's correct.

Hey: Were the first patients actually randomized? Did they start right from the beginning?

Harding: They truly did start randomizing at the end of 1969 and it really was the beginning of the trial. In his usual way, Mont decided that the animal studies were conclusive and that they should move on to human trials. When

²⁶ Liggins and Howie (1972).

²⁷ Liggins (1976); Howie and Liggins (1978, 1982).

I asked him why it was so short a period, because it was only a few months between concluding the animal studies and starting the trial he was already convinced that it needed to be a randomized trial. Ross was also very much of the same mind and they devised the protocol together. It didn't take them long to get the drug. There were no ethics committees in 1969, but the hospital's Senior Medical Staff Committee approved all trials. It functioned as an ethics committee at that time, and this committee approved it without further discussion. Mont was very keen to get started, because the head of department was actually planning a different trial which would have precluded this one and Mont was going to get in first, which he did.

Professor Richard Lilford: It sounds, from the way you speak, as though Mont regarded this as a sideline and that there wasn't a need to pursue it himself.

Harding: In the end he did pursue it, but I think you are right. I think the interest elsewhere, particularly from Mel Avery's group and the San Francisco group [Roberta and Phil Ballard, Jo Kitterman, John Clements and Bill Tooley] on the effects of steroids on lung maturation, not so much rekindled as accelerated his interest in the topic. He recognized the importance of pursuing this and what a clinical impact it might have.²⁸ He took Ross along with him, because it was a sideline for Ross as well.

Professor Miranda Mugford: I am a health economist. I just wanted to ask what the clinical situation was with neonatal intensive care at that time in New Zealand? Was it at different states of development in different countries? Just the background to what was normally done with babies at an early stage of gestation when they were born. What was the funding situation for their care?

Harding: The funding situation was easy. We had a public health system so there was no direct charge to patients and that has always been the case for newborn intensive care in New Zealand. It's fair to say that the state of intensive care varied around the country. The National Women's Hospital was opened in 1964, I think, but I would need to check that, specifically to enhance both the care of women and their babies and to encourage research in this field.²⁹ It

²⁸ See, for example, Platzker *et al.* (1975).

had the only intensive care unit in the country where babies were ventilated. Ross started ventilating babies in the mid-1960s with a primitive Bird ventilator and started using continuous positive airway pressure (CPAP) in the 1970s.³⁰ That was before Gregory's publication on CPAP, again because of the link to San Francisco, both he and Ross knew the San Francisco group well and had seen the data before it was published and were convinced that this was a useful thing to do.³¹ So the CPAP was just beginning to be used at the time of the trial. Ventilation was initiated, but outcomes were still poor and in the paper from Ross, which I think everybody has a copy of, he describes the change in perinatal mortality over that time.³² I think he also describes in that paper, but certainly has described to me in person, that at the end of the trials he went to Geneva in 1975 to talk to the World Health Organization about the funding of the follow-up, and while he was away two large preterm babies died of uncomplicated RDS, because nobody else could care for them. He was extremely upset about that. So it was a unique position in a sense that this was the only place that it could have been done, in New Zealand certainly, and the only people who could do it.

Professor Ann Oakley: I am a sociologist. One of the lessons that one could take from this story is that the progress of scientific research and the testing of ideas in clinical trials is helped if there aren't any obstacles such as ethics

²⁹ Dr Ross Howie wrote: 'Both the hospital and the academic unit actually started before 1964. What those of my generation called the "new" National Women's Hospital indeed opened in that year (incidentally, it closed in 2004), but the relevant date is probably 1951 when the Postgraduate School of Obstetrics and Gynaecology (O&G) was set up. It all started in the rather dilapidated remnants of what had been built as the 39th US Army General Hospital during the Second World War in a city park. After the war the buildings were taken over by the then Auckland Hospital Board, which moved both its O&G Unit and geriatric wards there in 1946. This was possibly a unique pairing of services for both the beginning and end of life. The O&G Unit became the National Women's Hospital in about 1954.' E-mail to Mrs Lois Reynolds, 29 August 2005.

³⁰ Dr Ross Howie wrote: 'I started using CPAP in 1970 (Gregory *et al.*'s paper appeared in 1971). The idea was brought back to Auckland by Mont Liggins; I did not myself meet the San Francisco group until 1972. It [CPAP] was, incidentally, brilliant and possibly the greatest single advance ever made in the management of RDS, therapeutic surfactants notwithstanding. In retrospect the development was simple and logical, and I am sure I was not the only one in the field who kicked himself for not having thought of it.' E-mail to Mrs Lois Reynolds, 26 August 2005.

³¹ Gregory *et al.* (1971). See also Dunn *et al.* (1971); Dunn (1974). For one source of Gregory's inspiration, see Christie and Tansey (eds) (2001): 25. The new Cochrane Review will appear in Issue 2, 2006.

³² See Appendix 2, pages 89–95.

committees, and that is a point of view that is held in some circles. I thought of this because I know a little bit about the history of the National Women's Hospital in Auckland and it doesn't have a very good history itself in terms of ethics of trials.³³ So I just wondered what the original protocol for this trial said about seeking consent and giving information to the parents of these babies.

Harding: I have to tell you that I have never seen a detailed trial protocol. I have seen the paper that went to the Senior Medical Staff Committee and it does say that the women would be asked to consent to randomization. It would have been verbal consent.³⁴ And, like you and a number of other people, I wondered how real and how effective that process was at the time. We will talk further later, I am sure, but we have just completed the 30-year follow-up of these babies, and one of the things that we had some concerns about is how people would react to being approached 30 years later about a trial in which we weren't sure how informed the consent was.³⁵ We have been overwhelmingly impressed with how positive people were about the trial.³⁶ In the end, we traced 72 per cent of the original participants and a number of the children, now 30-year-olds, who obviously did not know they were part of this trial, and who went back to their mothers, and sometimes we traced the mothers rather than the children. There were a few women who did not recall being part of the trial. I think that's not surprising, given the circumstances. Remember that the tocolytic [a labour inhibitor] used during the first three years of the trial was intravenous ethanol, which was in use until about 1971.³⁷ However, the vast majority of women did

³³ Professor Ann Oakley wrote: 'From the late 1950s for some 20 years staff at the National Women's Hospital carried out an uncontrolled experiment examining the natural history of untreated cervical cancer. Some women with abnormal smears [vaginal vault] were left untreated, and outcomes in this group were compared with those in treated women. Smears were also taken from newborn babies. The experiment lacked a scientific research design since there was no proper control group, and there was no provision for informed consent. The scandal of the experiment was exposed by two journalists [Coney (1988)] and there was a public inquiry [Cartwright Report (1988)].' E-mail to Mrs Lois Reynolds, 22 August 2005. See www.nzma.org.nz/journal/117-1202/1084/ (visited 1 September 2005); see also Young (2005).

³⁴ See Appendix 1, page 87.

³⁵ Dalziel *et al.* (2005). Mrs Brenda Mullinger, who worked with Professor Harold Gamsu (died 31 August 2004) during the 1975 UK trial, wrote: 'Professor Gamsu was disappointed that we did not learn more from Professor Jane Harding of the data from the original Liggins and Howie trial in New Zealand, as promised in this part of the Witness Seminar.' Letter to Dr Daphne Christie, 6 January 2005.

³⁶ Dr Ross Howie wrote: 'This would have been greatly helped by the way Barton MacArthur and Anne Dezoete carried out the four- and six-year follow-up studies. They were superb not only in their testing but in the way they related to their subjects and the parents.' E-mail to Mrs Lois Reynolds, 26 August 2005.

recall that they were in the trial and recalled it very positively. A number of the subjects, the offspring, the children – now adults, I don't know why to call them because of that difficulty – came along because they said their mothers told them they had to come. The mothers were so grateful that they had been part of the trial, that their preterm baby had survived as a result of this trial, as they perceived it, and were very positive about it. That's a slightly long answer to your question. I think consent really did happen, it was verbal consent, and the reaction of the majority of people involved was very positive 30 years later. [Figure 3.]

Mrs Gill Gyte: I am interested also in the women who were in the control arm. Did you get a similar sort of response, 30 years later?

Harding: The vast majority of participants *still* do not know which group they were in. So in terms of the 30-year follow-up, most of the people that came along were convinced they had had steroids because their babies survived, and we have done our best not to unblind them, because we think a further follow-up is going to be fairly critical for reasons that we might talk about later.³⁸ So women simply know they were in a trial and have a surviving baby, because obviously we didn't trace the mothers of the babies who did not survive.³⁹

Professor Dafydd Walters: Could you remind us of the gestation, the shortest gestation period of this group of babies?

Harding: Given a moment, I could look it up, but from memory the youngest

³⁷ Dr Clive Dash wrote: 'The UK study was being planned at the time of the move from ethanol as a tocolytic to various newly introduced β -agonists. We decided to use salbutamol, if a tocolytic was clinically necessary, so as to standardize one of the management modalities – and also because salbutamol had been developed by Glaxo.' E-mail to Dr Daphne Christie, 10 January 2005. For the protocol used in the UK study, see Appendix 5, pages 101–8. For a later meta-analysis of β -agonists as tocolytics, see Tsatsaris *et al.* (2001). For the background to the discovery of salbutamol as an asthma treatment, see Reynolds and Tansey (eds) (2001): 37–42.

³⁸ Professor Jane Harding wrote: 'Some of the findings of the 30-year follow-up suggest that there may be subtle changes in insulin responses in those exposed to antenatal glucocorticoids. These are of no clinical significance in 30-year-olds, but we think that it would be of great interest to see whether those changes persist, and whether they develop into changes of any clinical significance, as these people age.' E-mail to Mrs Lois Reynolds, 21 October 2005.

³⁹ Professor Jane Harding wrote: 'Many babies died in both groups, most in the neonatal period but also a few after this period. We did not make any attempt to trace these mothers; indeed we tried to avoid contacting any whose babies had died, to avoid any distress that might be caused by reminding the parents of their loss.' E-mail to Mrs Lois Reynolds, 21 October 2005.



Figure 3: Investigators in the original Auckland trial [Liggins and Howie (1972)] and its 30-year follow-up [Dalziel *et al.* (2005a and b)]. L to R: Stuart Dalziel (Research Fellow), Mont Liggins, Ross Howie and Jane Harding, July 2005.

gestation was about 28 or 29 weeks, and the average gestation at delivery was around 35 weeks.⁴⁰

Walters: Time moves on, and obviously steroids are now used for much shorter gestation babies.

Hey: But most of the trial evidence was still based on the old data from the pre-ventilator days, and now we might say that all the data that showed that steroids saved lives antedates the arrival of surfactant. There hasn't been a trial done, as far as I know, looking at the additional benefit of steroids as well as surfactant.

Harding: There have been at least four trials in the 1990s and I am sure Dr Crowley will talk about this. But the new Cochrane Review, which is in the process of being produced, will show clearly that the benefit is still there in the surfactant era, in the ventilator era and in the four randomized placebo control trials done in the 1990s.⁴¹

Sir Iain Chalmers: Jane, I don't know whether you have tried to do this already, but it would be wonderful if these mothers and children that you are in touch with came to know just how important a contribution they have made to the

⁴⁰ Professor Jane Harding wrote: 'The youngest was 20 weeks and the mean gestation at delivery was 34 weeks.' Note on draft transcript, 4 September 2005.

⁴¹ See, for example: Carlan *et al.* (1991); Garite *et al.* (1992); Kari *et al.* (1994); Botet *et al.* (1994); Lewis *et al.* (1996); Amorim *et al.* (1999); Patinson *et al.* (1999); Qublan *et al.* (2001) Fekih *et al.* (2002). The new Cochrane Review will not be available until 2006.

history of perinatal care. If you haven't planned to do so already, could you think about letting them know that?

Harding: We tried very hard to emphasize how important they are; this is part of our recruitment process, as you can imagine. Getting 30-year-olds, who are busy with family and life and career and everything else, to come along and have fairly extensive testing is not easy. We did spend a great deal of time and energy trying to explain to the participants and their mothers how important this trial was and how important it was to know what effect it might have in the long term. But as I think I have already said, people were very, very positive about the whole experience of being involved in the trial, which really reassured me immensely about the consent process and the whole management of the trial.

Chalmers: You can tell them now they are formally part of history.

Harding: When we write to them, telling them the results of the follow-up, we will do that.

Professor John Gabbay: We have been left with a slight impression that there was a wonderful element of serendipity with Mary Ellen [Avery]'s coffee room discussion, happening to bump into these people. I would like to test that by asking Mary Ellen if you could say why you chose to go to New Zealand, and why that conversation happened and how it came about that you were discussing that, because I suspect that it's not pure chance. I would like to explore what led to that particular common interest being discussed there.

Avery: At the meeting in Christchurch, with Liggins in attendance, I had given the most boring paper ever, describing the time of onset of a whole bunch of things that we could measure to map out the terrain of the maturation of different organs in the lamb, knowing that we were particularly interested in lambs. Why did we tumble to that? It was partly that Mont wanted information from sheep, some of which were different from what he expected. And the difference turned out to have been that some of the animals got steroids and some didn't, and the ones that were advanced had received the steroids. There was a concern that there would be a permanent effect if they were treated *in utero*, but injured in some way by the steroid; that they would grow up with small lungs or the lung would fail to perform in some way, and so Liggins needed all the information he could get about safety. I think we published our first paper on six sets of twins.⁴² That wasn't a very big series, but six out of six showed the same result. It meant that the data

⁴² Rokos *et al.* (1968).

were pretty secure, but the next question was: what happens when they are ten years old?

Some of the follow-up has been done and it turns out that the lungs play ‘catch up’, just as children do on steroid therapy for a month for whatever disease, and when you withdraw it, you see their growth curves are flat while they are on steroids, and then they catch up and hit the very level that was predicted before. Catch-up growth takes place in these babies. And that is quite remarkable: maturation at the expense of cell division. Take away the stimulus from the cells, they do more than they would have done otherwise and catch up. I think others in this room might be better students of this phenomenon than I am.

Gabbay: If I could just pursue that for one second. You have taken us into the science of it. I was interested, if you like, in the community of scientists who were interacting, and how it was you came to be discussing these topics. It seems to me that what you have said – and I just wondered if this was an accurate impression – is that he [Liggins] actively sought out your data. He came to hear your talk, came to talk to you because it was of particular interest to him, and that we have not so much the coincidence that Richard [Lilford] intimated earlier with his question, but a deliberate conversation between people with a common interest.

Avery: We didn’t know we had a common interest until we were drinking tea that afternoon.

Professor Sir Christopher Booth: How did it happen that you were in Christchurch at that crucial moment?

Avery: They had invited me over as a visiting speaker. They had heard that I was fooling around with surfactants.

Mr Ian Jones: You mentioned that Mont had Wellcome Trust funding. Could you tell us anything about the type of funding he had, and how significant that was to his work?

Harding: The short answer is no, I cannot, but I could go back and ask him. He commented about who gave him the money and I think probably he simply asked for research funding to look at preterm labour.⁴³ I cannot tell you more details about how much it was, not his personal salary, it must have been working

⁴³ See Appendix 3, pages 97–9, for details of the eight years of funding for research assistance from the Wellcome Trust, 1968–76.

expenses. It was for some considerable period of time, because he worked on this for several years.

Dr Stephen Hanney: We have been looking at the ‘payback’ or benefits from this whole stream of work, and I will be talking about that later.⁴⁴ On this specific question, at one stage we did have a figure of £20 000 from the Wellcome Trust for one of these pieces of work, I think it was for the original animal trial. I am not quite sure how that fitted in, how long a period that was, but that is a figure that was quoted. It was obviously a very small grant even in those days.

Harding: I think at that time it would have been a very large grant in New Zealand, and it was probably the only one, because I am pretty sure Mont only had the one block of funding to work on the initiation of parturition in sheep. I have already commented that the clinical trial itself was never funded, because they just did it.

Hey: That included his going to America and learning how to hypophysectomize fetal sheep.⁴⁵

Harding: He did all that before he left New Zealand for California, and when he came back he had the Wellcome Trust funding to start his own lab.⁴⁶

Hey: Hypophysectomizing a fetal sheep, popping it back in and discovering that the ewe never goes into labour, because as we now understand the pituitary drives labour in the lamb, but not in the human.

Harding: That’s correct. He [Liggins] had presumed that that would be the case. When he was on sabbatical at the University of California at Davies he devised a way of doing the hypophysectomy and did the initial experiments there, and then came back to set up a sheep lab in New Zealand with Wellcome Trust funding. So I think that was probably the one and only grant and a very large one at that time for working expenses.

Hey: One of the things that we learn is that sometimes, as Maureen Young will tell us, you cannot jump from species to species. Sometimes you try, but hypophysectomy [in sheep] doesn’t work and steroids do.

⁴⁴ See page 69.

⁴⁵ Surgical removal or ablation of the hypophysis, or pituitary gland, of the fetal sheep. See Liggins *et al.* (1967).

⁴⁶ See Appendix 1, page 86.

Harding: I think they were different questions. Mont knew before he started with the sheep that hypophysectomy made no difference to gestational length in humans.

Hey: We will move on and listen to what happened when people started to do the many other trials. Ross sounded as though he actually encouraged other people to go ahead and do more trials, most of which seemed to have been done in the US.

Harding: That's true. Ross was very much, and still is, of the view that even if a treatment did work – and he was convinced that this treatment did work in his hands – that it was unlikely to work all of the time in all groups of patients, under all circumstances, and he was very concerned about the potential long-term risks as were most other people at that time. He remained unapologetic for that, in the sense that you know medicine is not simple, biology is not simple, and there's no point in pretending that it is. He was convinced that even if this treatment worked, it might not work in some groups, and it might have adverse effects in some groups. He felt it was important that other people test this in other places, under other circumstances, in other groups, and he also thought it was critical that the long-term follow-up should happen, and he himself therefore never recommended – right through, I think, into the early 1980s – that anybody else should act on the basis of their trial alone, and was very encouraging of other trials.

I was asked about the follow-up and the NIH trial, which we will no doubt come to, and the follow-up was still going on at the time that the Auckland trial follow-up was completed.⁴⁷ I asked Ross if he knew about this and he said he couldn't remember if he had known about it, but if he had he certainly would have encouraged them to proceed, because again he thought it important that other groups replicate the trial under other circumstances, and check what specifically was and wasn't helpful about this treatment.

Hey: It is time that we move on to ask Patricia Crowley to tell us something of how the various trials that did get done in the 1970s and early 1980s got put together for the first time. But I suspect after that we need to go back over some of these individual trials and explore, with Mel's help, some of the thinking that

⁴⁷ Professor Jane Harding wrote: "The "follow-up was still going on" refers to the follow-up of the NIH trial, which was published as Collaborative Group on Antenatal Steroid Therapy [(1984)]. The next line "at the time that the Auckland trial follow-up was completed" refers to the two papers by MacArthur *et al.* [(1981, 1982)]." Note on draft transcript, 4 September 2005.

went into the US NIH Collaborative Group trial and how it got interpreted and how it got analysed. Let's have the overview first.

Dr Patricia Crowley: I first heard about antenatal corticosteroids in an undergraduate lecture in 1974. The possibility of preventing RDS made an immense impact on me because the first baby I delivered as an undergraduate died in the neonatal period from RDS, despite weighing seven pounds and being born at 36 weeks. So the scene was set for a life-long interest in this topic. Later, in 1977, as a senior house officer in neonatal paediatrics, I attended a lecture on fetal lung maturation given by Professor Mel Avery, who was an invited lecturer at the Irish Perinatal Society. At a time when young female medical graduates had few role models, an innovative paper delivered by an attractive woman [see Figure 5] made an enormous impression, especially as I was continuing to see premature babies die on a regular basis from RDS.

At that time I was working in the National Maternity Hospital, Dublin, which fostered a culture of nihilism towards most medical interventions, with the exception of those ordained by institutional policy. I encountered a woman whose previous baby had died from RDS, and together with a paediatric colleague, approached the Master (Clinical Director) of the hospital to obtain permission to prescribe antenatal corticosteroids for this patient. That was the first and only time in a two-year spell in obstetrics and paediatrics between 1976 and 1978 that I was allowed to prescribe antenatal steroids.

I then went to work in the Hammersmith Hospital in London and in 1978 attended a meeting at the Royal College of Obstetricians and Gynaecologists (RCOG) marking the publication of the proceedings of the 1977 RCOG Preterm Labour Study Group. Ross Howie had attended this meeting in 1977, and presented a paper jointly authored with Mont Liggins on the outcome of 1068 women and their babies who had been enrolled in randomized trials of antenatal corticosteroid therapy. This showed a massive reduction in neonatal mortality in those babies who were exposed *in utero* to antenatal steroids.⁴⁸ The *Proceedings* of that Preterm Labour Study Group contained 14 papers on tocolysis and only two papers about fetal lung maturation – a clear indication of where the emphasis of British obstetrics lay at that time when it came to preterm labour. Obstetricians were obsessed with trying to stop preterm labour rather than with trying to improve the outcome for the premature baby by accelerating lung maturation. Despite a dearth of objective

⁴⁸ Howie and Liggins (1978).

evidence of efficacy, a variety of betasympathomimetic drugs were being actively promoted by the pharmaceutical industry at this time, whereas no pharmaceutical company was promoting the use of antenatal steroids.

In 1980 at the Hammersmith Hospital, London, Professor Denis Hawkins founded the *Journal of Obstetrics and Gynaecology*. He received a paper from Ben Sachs, a British obstetrician working in the US, which reviewed the adverse effects of antenatal steroids and the lack of evidence to support their efficacy.⁴⁹ He challenged me to write an opposing view to this manuscript. This led to a paper written in 1980 and published in 1981, entitled 'Corticosteroids in pregnancy: the benefits outweigh the costs'.⁵⁰ I was either lucky or lazy, because I decided to ignore observational evidence. Although I had never been taught that the randomized controlled trial was the best form of evidence, instinct led me in that direction. My literature search yielded four randomized controlled trials of antenatal steroids. I based the paper on two tables derived from amalgamating the results of the four trials, showing substantial reductions in neonatal mortality and morbidity in babies whose mothers were randomized to receive antenatal steroids. [See Tables 1 and 2.]

	Maturity (weeks)	Betamethasone-treated group (%)	Control group (%)	Difference
Liggins and Howie (1972)	24–37	4	24	P < 0.002
Block <i>et al.</i> (1977)	<37	10	27	P < 0.05
Papageorgiou <i>et al.</i> (1979)	25–34	18	58	P < 0.005
Tauesch <i>et al.</i> (1979)	<36	13	30	P = 0.085

Table 1: Incidence of respiratory distress syndrome as percentages of live preterm births. Crowley (1981): 148.

	Betamethasone-treated group (%)	Control group (%)	Difference
Liggins and Howie (1972)	4	24	P < 0.002
Block <i>et al.</i> (1977)	10	27	P < 0.05
Papageorgiou <i>et al.</i> (1979)	18	58	P < 0.005

Table 2: Perinatal mortality rates as percentages of preterm births. Crowley (1981): 148.

⁴⁹ Sachs (1981).

⁵⁰ Crowley (1981).

By the time this paper was published in 1981 I had started a nine-month attachment at the National Perinatal Epidemiology Unit (NPEU), which was one of the most rewarding periods of my professional life. Anne Anderson and Iain Chalmers read the paper and invited me to contribute a chapter on antenatal steroids to a book that they were planning on 'Effective Care in Labour and Delivery'. This was intended to follow *Effectiveness and Satisfaction in Antenatal Care*.⁵¹ I started work on a chapter on fetal lung maturation, examining the evidence in relation to antenatal corticosteroids and any other agents that aimed to accelerate pulmonary maturation.

Progress on this proposed book was delayed by the illness and eventual death of Anne Anderson. It was eventually subsumed into a much more ambitious venture, *Effective Care in Pregnancy and Childbirth*.⁵² Meanwhile, led by Iain Chalmers, a group of individuals based at or associated with the NPEU, became involved with the development of the Oxford Database of Perinatal Trials, which aimed to identify, assemble and analyse all published and unpublished randomized controlled trials available in the world literature in perinatal medicine.

I left Oxford in 1981 and returned to Dublin to continue to train as an obstetrician but maintained my contact with the NPEU. My associates working with the Oxford Database regularly alerted me to new trials that had been uncovered by enthusiasts who had searched the literature to find randomized trials. The next three years saw the publication of follow-up data from the Auckland trials and of the results of the US NIH Collaborative Group on Antenatal Steroid Therapy study.⁵³ With hindsight, we could ask whether the Collaborative Group trial should ever have taken place, because at the time when recruitment was taking place for that trial there was already substantial evidence in the literature that antenatal steroids were effective and safe. If we look at the 1000 or so babies who received antenatal steroids in the randomized trials prior to 1980, and the 1000 babies who received placebo in these trials, 130 of the babies who received placebo died, compared with 70 of the babies who received antenatal steroids. Were those who were recruiting participants for the NIH Collaborative Group trials unaware of these results? Had clinicians or parents been aware of these results, it would have been difficult to persuade anyone to be randomized to placebo in the late 1970s or early 1980s.

⁵¹ Enkin and Chalmers (eds) (1982).

⁵² Chalmers *et al.* (eds) (1989).

⁵³ Collaborative Group on Antenatal Steroid Therapy (1984).

As the 1980s progressed, I regularly updated my collection of randomized trials. Because of a series of subgroup analyses emerging from the US NIH Collaborative Group trials, I became interested in subgroup analysis of the outcomes of the accumulated trials. Commentators on the NIH trial reported that antenatal steroids were effective mainly in babies of between 32 and 34 weeks, and ‘worked’ in black females but not in white males.⁵⁴ I went back to the collection of trials that I had accumulated and looked at what happened to white males in Auckland and found they benefited from antenatal steroids. This was how many of the subgroup analyses produced in the original systematic review of randomized trials came into being. It was driven by a need to refute a number of reviews questioning the efficacy of antenatal steroids based on these subgroup analyses, principally from the NIH Collaborative Group study.

Some form of systematic review of antenatal steroids was part of my life in various ways throughout the early 1980s. The proceedings from a conference I attended in Italy in 1984 show that by then I was looking at the outcome of seven trials, loosely synthesizing the outcomes.⁵⁵ In 1987/8 the technology became available at the NPEU to produce a meta-analysis with electronically entered data, and to generate results in the form of odds ratios with confidence intervals. The review of antenatal steroids became the first to be entered on to the Oxford Database of Perinatal Trials. This was a very exciting time, when, after years of collecting data, I saw graphic evidence of the efficacy of antenatal steroids in preterm babies in general and in all relevant subgroups.

By 1989, when the results of the antenatal corticosteroid review were available in an attractive, accessible electronic format on the Oxford Database of Perinatal Trials and on paper in the book *Effective Care in Pregnancy and Childbirth*, I thought that this information was accessible to obstetricians around the world, and believed that no further publications were necessary to promote the use of antenatal corticosteroids. However, I was eventually persuaded by Iain Chalmers to publish a paper version of this systematic review in the *British Journal of Obstetrics and Gynaecology*.⁵⁶

Looking at practice throughout the world with respect to antenatal steroid use, it is only after 1990 that we can see any more than 20 per cent of preterm

⁵⁴ Robertson (1982).

⁵⁵ Crowley (1986).

⁵⁶ Crowley *et al.* (1990).

babies being exposed to antenatal steroids in any country, with the exception of Australia and New Zealand. Work from Melbourne in the 1970s, showed 45 per cent of Melbourne babies in the 1970s were delivered to mothers who had been treated with antenatal steroids prior to delivery.⁵⁷ Elsewhere around the world, it fell often under 10 per cent and never higher than 20 per cent, up to 1990. So the publication of this paper in the *British Journal of Obstetrics and Gynaecology* was a landmark in terms of improving the use of antenatal steroids.

In 1994 the NIH Consensus Conference on antenatal steroids took place.⁵⁸ At that meeting I contributed an updated version of the systematic view of antenatal steroids,⁵⁹ derived mainly from the electronic review published on what was by then the *Cochrane Pregnancy and Childbirth Database of Perinatal Trials*.⁶⁰ The rest of that three-day meeting was taken up with many observational studies, and laboratory-based papers on antenatal steroids and following the three-day meeting a strong recommendation was released, urging obstetricians in the US to use antenatal steroids.

In 1996 I was invited by the Royal College of Obstetricians and Gynaecologists to update a guideline on the use of antenatal steroids issued in 1992.⁶¹ The revised guideline, based on the systematic review published in the Cochrane Library, strengthened the recommendation from the RCOG on antenatal steroids use. By the late 1990s, 70 per cent of preterm babies delivered in the UK were being treated with antenatal steroids prior to delivery.

⁵⁷ Doyle *et al.* (1986). For a discussion on the evolution of paediatrics at the University of Melbourne Department of Paediatrics at the Royal Children's Hospital 1959–2003, see www.cshs.unimelb.edu.au/programs/jnmhu/witness/001.html (visited 2 August 2005).

⁵⁸ National Institutes of Health (NIH) (1994). Their recommendation was to give a single course of corticosteroids – two doses of 12mg of betamethasone given intramuscularly 24 hours apart or four doses of 6mg of dexamethasone given intramuscularly 12 hours apart – to all pregnant women between 24 and 34 weeks' gestation considered to be at risk, clinically, of preterm delivery within seven days. Freely available at <http://consensus.nih.gov/1994/1994AntenatalSteroidPerinatal095html.htm> (visited 28 September 2005). See also NIH Consensus Development Panel (1995).

⁵⁹ Crowley (1995). Fifteen trials were listed in descending order of quality presented at the NIH Consensus Development Conference in Bethesda, MD, on 28 February 1994.

⁶⁰ The first systematic review by Crowley appeared on the Oxford Database of Perinatal Trials in 1987. The 1996 version appears as an example of a Cochrane Review at www.cochrane.org/reviews/exreview/htm (visited 2 August 2005). See also Figure 6.

⁶¹ RCOG, Scientific Advisory Committee (1992).

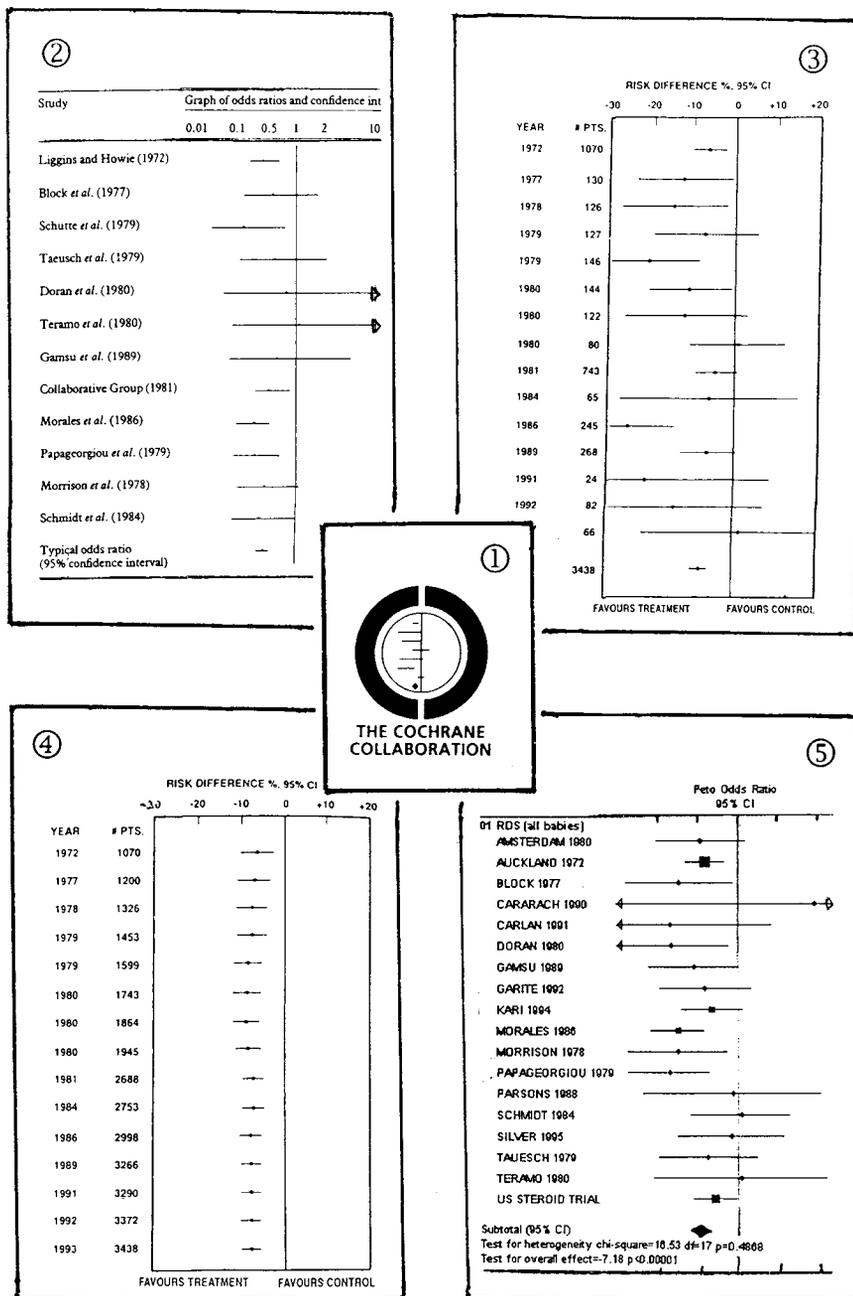


Figure 4: Meta-analyses of corticosteroids in pregnancy, 1992–2004.

1. 7 trials from Crowley (1981) as used for the Cochrane logo, see Figure 6;
2. 12 trials, Crowley (1989);
3. 15 trials, Sinclair (1995);
4. cumulative meta-analysis of first 15 trials, Sinclair (1995);
5. 18 trials, Cochrane Library (2004).

Within a year or two of finally adopting the evidence-based practice of prescribing a single course of antenatal steroids to women at risk of delivering a preterm infant, obstetricians started to prescribe repeated courses of antenatal steroids. The practice of repeated courses of antenatal steroids in women who remain undelivered a week or more following the original treatment crept in rapidly, without any evidence to support its safety or efficacy. All the evidence from randomized trials related to a single course of antenatal corticosteroid therapy.

This widespread practice, unsupported by any evidence, generated the need for a new round of randomized trials to evaluate the immediate and long-term benefits and hazards of single versus repeated courses of antenatal steroids. These trials are currently recruiting. Had the publication of the Auckland trial in 1972 been followed rapidly by a large multicentre trial and by the subsequent use of a single course of antenatal steroids as the standard of care, trials of single versus repeat courses of antenatal steroids would have taken place in the 1980s. So, largely due to a collective professional failure to disseminate and implement evidence concerning an effective intervention, progress in the area remains about 20 years behind where it should be.

Hey: I think it might be sensible to explore something of the debate that went on between 1976, when Liggins presented an update of his findings at the 70th Ross Conference on Pediatric Research – a meeting devoted to the topic of lung maturation and the prevention of hyaline membrane disease, and 1994 – when we end up with the NIH-sponsored Consensus Conference.⁶² It is a long period of time. Mel, you were a witness to much of this.

Avery: It was frustrating.

Hey: Well, you banged the drums quite hard.

Avery: I cannot begin to organize my thoughts for this period. I was not centrally engaged: I am not an obstetrician; I didn't want to tell obstetricians what to do and what not to do. In fact, I didn't have that kind of self-confidence. I wanted a long-term follow-up. I spent hours with Ross Howie, urging him to 'please keep track' because the Swiss were talking about this treatment seriously inhibiting lungs, and even brains weren't growing well if little animals got big steroid doses

⁶² Liggins (1976), where he was able to report on the outcome of 884 spontaneous preterm births rather than the 226 births described in Liggins and Howie (1972); National Institutes of Health (NIH) (1994).

during pregnancy.⁶³ You probably know that. It's kind of scary. It was done by the group in Berne, I think it is Burri at the Université de Paris, the fellow who is still publishing on 'beware, beware,' and I cannot counter that.⁶⁴ I'm glad he's looking at it, and I just think we have to be vigilant and that those of us who spend more time with this have to keep track of the babies.

Lilford: Since this is a history meeting, and while you have been talking about the early 1970s, I have been thinking back into the recesses of my own mind. I was a young doctor in Cape Town and news about this crossed the Indian Ocean and people were interested there. As I can recall it, there seemed to be a notion that many babies would, in retrospect, be found not to have needed antenatal steroids because their lungs were very mature. And so the idea that was being put around then was that one should test first to see if the lungs were already mature. And the person who did that testing was me. So if somebody needed early delivery, then I would do an amniocentesis. We had a thing called a bubble test and I would take the fluid off to a side room and I would mix it with alcohol.⁶⁵ I would shake it and then there was this chart on the wall where the bubble density could be related to maturity. If there were more than a certain number of bubbles, then we could safely proceed with the delivery the next day. If there weren't, then we gave steroids. We would re-test two days later and if there were now bubbles we knew we could go ahead with delivery. So there must have been another scientific climate running at that time which said that [we should] discriminate more before we shove these steroids in. But as far

⁶³ Dr Ross Howie wrote: 'About the possible hazards of steroids to the fetus: I am surprised that in all the discussions I have heard and read, little mention has been made of the work of the Ballards [Ballard *et al.* (1975)]. They measured glucocorticoid levels in maternal and cord serum after prenatal betamethasone therapy, and concluded that glucocorticoid concentrations in cord serum were in the physiologic stress range and not at potentially harmful pharmacologic levels. Many people (I know not Mel Avery) in talking about hazards confuse therapy before birth with therapy after: in the course of ordinary treatment, steroid levels are many times higher in the latter case. The dose Mont Liggins gave to the mother resulted in levels in the newborn comparable to those the baby would have in the course of an illness like RDS. Has anyone ever thought of doing a 30-year follow-up of babies with RDS with this in mind? Of course, as Mont has suggested, there may be hazards of synthetic steroids as opposed to naturally occurring compounds, but I know of no evidence for this.' E-mail to Mrs Lois Reynolds, 26 August 2005.

⁶⁴ Tschanz *et al.* (2003).

⁶⁵ The Clements' shake test or bubble test measures the physical properties of surfactant, the ability of pulmonary surfactant to form a foam or bubble on shaking that remains stable for at least 15 minutes. Pattle (1958); Clements *et al.* (1972); Strang (1977a and b). For Richard Pattle's contribution to lung surface tension and surfactant, see Clements (1996): 218–24. See also Hughes (2001); and Figure 5.



Figure 5: Mary Ellen Avery and Richard Pattle at a CIBA Symposium in 1965. Clements (1996): 222.

as I know, that line of thought ran into the sands, it didn't progress in any way. I just mention that for your edification.

Mrs Brenda Mullinger: At the time of the UK multicentre trial, I was working for Glaxo and I coordinated the trial in the UK.⁶⁶ What I wanted to say relates to what Dr Crowley said about uptake. Although we originally coordinated the study after different clinicians had approached Glaxo, we found that we needed more centres to join the study, and so we did actually approach other centres in the UK. Looking at the paper, I see we got underway in mid-1975, but I was told by Dr Clive Dash, the medic at Glaxo, who unfortunately cannot be here, that many of the UK centres who were approached wouldn't join the study because they were already using betamethasone and they felt that it wasn't ethical to have control groups. So that although your uptake maybe was only 10 per

⁶⁶ Mrs Brenda Mullinger wrote: 'The UK multicentre trial was conducted from mid-1975 to February 1978; 251 women were randomized to double-blind treatment with either betamethasone phosphate (4mg every eight hours for a maximum of six doses) or matching placebo, each given by intramuscular injection. Betamethasone treatment reduced the incidence of RDS relative to placebo – the greatest benefit was seen in those infants born before 34 weeks' gestation. See Gamsu *et al.* (1989).' Note on draft transcript, 6 January 2005.

cent, certainly the research centres, the sort of centres that might have joined the study, were starting to think about using it by the mid-1970s in the UK.⁶⁷

Avery: We have to think in terms of the 1970s versus the 1990s and up to 2000, because up until the 1970s the controlled trials were very supportive of the efficacy of prenatal glucocorticoids, but that was an era when we didn't have lots of babies under 800g. Now the story is different. We have babies weighing 600g, 700g and 800g, who are getting glucocorticoids, and we assumed that they wouldn't have any serious toxicity. But along came Petra Huppi from Geneva, who worked with us at Harvard and had developed a great experience with imaging studies of the brains of these babies. There is no question that there can be white matter problems which she has documented and published.⁶⁸ I'm not prepared to take a stand, I'm only saying this is one group where there could be toxicity, and where we really don't know the cost–benefit of accelerating the lung versus some white matter problems in the baby. This is a new frontier, and I just wanted to put this on the table. I don't know any more about it than I have just said.

Crowley: Through all the systematic reviews of the trials we have kept an eye on intraventricular haemorrhage (IVH) and periventricular leukomalacia (PVL). There is good evidence that these adverse outcomes are reduced by antenatal steroids across the gestational ages. The use of early postnatal steroids is associated with an increased risk of adverse outcome. Antenatal steroids are protective in

⁶⁷ Dr Clive Dash wrote: 'The UK multicentre study [Gamsu *et al.* (1989)] was designed in 1974, largely stimulated by the publication of Liggins and Howie (1972) and their prior animal studies. The idea for a UK study was an amalgam of interest from some obstetricians and neonatal paediatricians and from within the Medical Department of Glaxo in the UK because of the organizational link with the Antipodes. A taxing question in the design and analysis of the UK study was the imprecision in estimating gestational age at the time of recruitment. Maternal dates and obstetrical palpation were the only antenatal assessments available then – so different from the current techniques! The clinicians documented both estimates for the analysis. These were augmented (or confounded) by neonatal assessment [Farr *et al.* (1966); Dubowitz *et al.* (1970)], which were also recorded. Clinicians' views can change during the planning and conduct of long-term studies (about four years to plan and complete recruitment and follow-up for the UK study). All the clinicians involved in the early planning recognized that more clinical work was needed to confirm the results from New Zealand. Everyone involved in the study's planning recognized that it was important to have commitment from an obstetrician and paediatrician at each participating hospital. By the time the study recruitment started (about one year later), some of the clinicians did not wish to recruit patients to the study for various reasons, even after Ethics Committee approval.' E-mail to Dr Daphne Christie, 10 January 2005. See Appendix 5, pages 103–8, for the protocol used in the study.

⁶⁸ Murphy *et al.* (2001).

terms of neonatal neurology, whether you look at the brain at autopsy or with imaging techniques for PVL. Would you agree with that, Jane?

Harding: If I could come back briefly to address Richard Lilford's point and then go back to some of the reasons, perhaps, why steroids weren't used. I have just dragged out the report of the 70th Ross Conference on Pediatric Research, which was I think about 1979, but I don't have a date on the paper. [From the floor: 1976]. It was one of the places where Mont Liggins reported the outcomes of the Auckland trial. He also reports the outcomes of ratios in amniotic fluid before and after steroid treatment, and points out that they don't change consistently, so that amniotic testing for fetal lung maturation did not reflect clinical lung maturation. I was reminded of his concluding paragraph, which is why I dragged it out:

We have not attempted to select patients on the basis of assessment of pulmonary maturation from amniotic fluid analyses. In pregnancies beyond 34 weeks in which the risk of RDS is low, a strong case can be made for giving glucocorticoids only when the results of amniocentesis indicates pulmonary immaturity. Before 32 weeks, the likelihood of RDS is so high, and finding a mature pattern in amniotic fluid is so low, that treatment without prior amniocentesis is probably justified.⁶⁹

So back then, they had considered the phenomenon, had picked the subjects to include, and concluded that it wasn't worth doing, except perhaps in pregnancies more than 34 weeks.

If I could go back to the question of why, perhaps, uptake wasn't as widespread as it might have been in the 1980s. I have asked both Ross and Mont quite carefully about why they thought that it took so long for this treatment to come into widespread use, and they have both given me the same two general answers. The first is that, particularly in the UK, they felt, 'Nothing good could come from the colonies,' and the fact of where the trial was done was very relevant. The other thing that they both said to me was they felt that in many places the paediatricians were the people who were discouraging use, since they felt that they could manage lung disease, that there was not really a problem, and that the obstetricians were treading on their territories, or at least on their toes. It was actually paediatric versus obstetric issues in many centres that discouraged its use.

⁶⁹ Liggins (1976): 103.

Mr John Williams: I am a humble obstetrician, who is a recipient of the literature rather than a contributor, but I was developing during the era of these publications, and here are some of the things that struck me. The first was an oration by Sir Stanley Clayton [President of the Royal College of Obstetricians and Gynaecologists, 1972–75] in 1975 at the American Congress of Obstetricians and Gynecologists, where he said that in his experience as the editor of the grey journal, the *Commonwealth Journal* as it was then, how much rubbish was submitted for publication.⁷⁰ He wished that registrars didn't have to do research to get jobs, and it was time it was all stopped. That was the first thing that hit me. And I was then at a meeting in Cardiff where Cliff Robertson spoke, and he seemed to be of the opinion that obstetricians shouldn't be treading on the toes of paediatricians, and that they were very good at looking after babies and we didn't need to interfere. He went on to pour scorn on quite a lot of the uncontrolled and poor publications, and again this struck me. I said, 'Why were these published if they were such bad studies?' He replied, 'You know, people having a glass of whisky and refereeing a paper, if it's somebody they know they will put it in, if it's not they won't'. He was fairly scornful of the poor quality publications, and it gave the impression, certainly in Cardiff, that we shouldn't be using steroids. And that set me back a little way.

The poor publications continued to come out and were very confusing. In fact I wrote to Iain [Chalmers] asking what was going on: 'I want to carry out best practice'. Paediatricians where I was then working in Chester were very keen that we *should* be using steroids based on the original work, and I said that everyone else says it's rubbish. And it wasn't until the systematic reviews and the guidelines came out that we actually introduced it as an overall practice; we had been giving it to certain selected patients, but not overall. I think that was a common view among obstetricians in this country in the non-academic world.

Dr Roger Verrier Jones: There are two maternity hospitals in Cardiff: I worked in St David's and John [Williams] was at the University Hospital of Wales maternity unit. The reason I am here is that Iain Chalmers kindly asked me when he reminded me of a letter I had written to him in 1980, about a retrospective study using steroids that we had done at St David's, and that the results seemed to be quite startling. [See Tables 3 and 4.]

⁷⁰ The grey journal is the *British Journal of Obstetrics and Gynaecology*, known as such from its cover. Originally the *Journal of Obstetrics and Gynaecology of the British Empire* from 1902 to 1961 when the name was changed to *British Commonwealth* and in 1975 to its present title.

	Steroid	Non-steroid
Sex (M:F)	8:3	22:14
Mean gestational age (weeks)	32.1	32.3
Mean birth weight (kg)	1.63	1.59
Mean Apgar score at 1 minute	5.8	5.5
at 5 minutes	8.2	7.9
Twin pregnancies	1	2
Mortality	0 (0 %)	10 (28%) (p<0.001)
Incidence of RDS		
RDS	2 (18%)	21 (59%)
No RDS	9 (82%)	15 (41%) (p<0.001)

Table 3: Retrospective analysis of steroid and non-steroid use in preterm births, St David's Hospital, Cardiff, 1979–80.⁷¹ Unpublished letter to Sir Iain Chalmers from Dr Roger Verrier Jones, 24 November 1980.

	PROM	No PROM
1. Steroid group (n=11)	(n=4)	(n=7)
RDS	1 (25%)	1 (14%)
No RDS	3	6
2. Control group (n=36)	(n=10)	(n=26)
RDS	6 (60%)	16 (62%)
No RDS	4	10
TOTAL	(n=14)	(n=33)
RDS	7 (50%)	17 (51%)
No RDS	7	16

Table 4: Effect of prolonged rupture of membranes (PROM) on steroid- and non-steroid-treated preterm births, St David's Hospital, Cardiff, 1979–80. Unpublished letter to Sir Iain Chalmers from Dr Roger Verrier Jones, 24 November 1980.

⁷¹ Exclusions: severe pre-eclamptic toxemia (PET); congenital anomalies; uncertain gestational age; and delivery within 24 hours of steroid administration. In his letter sent in response to Dr Verrier Jones' request for advice on whether the observational data from St David's Hospital should be submitted for publication, Iain Chalmers stated that he found the data difficult to interpret because of uncertainty about whether the way in which the comparison groups had been assembled had been sufficiently unbiased. He listed references to ten reports of RCTs, noting that these seemed to suggest that steroids were useful in preventing RDS, and advised Dr Verrier Jones against submitting for possible publication. Letters circulated at the Witness Seminar by Dr Verrier Jones. The correspondence and complete observations will be deposited with all the records of the meeting in GC/253, Archives and Manuscripts, Wellcome Library, London.

We had started using steroids in the late 1970s, I think, based on the work that Liggins and Avery and others had done. Our obstetricians were fairly conservative, so not all premature pregnancies were given them. However, we were able to look retrospectively at 47 babies, of which 11 had steroids and 36 did not. The mortality rate was zero in the steroid group and 28 per cent in the non-steroid group. The incidence of RDS in the steroid group was 18 per cent and 59 per cent in the non-steroid group. On the basis of that, certainly in St David's Hospital, we continued to use steroids in premature births, but my memory is that as time went on and ventilation techniques got better, that the controversy about steroids seemed to be reduced, and then surfactants came along, so that there wasn't a controversy about whether one should use steroids or not.

Hanney: The point was raised by Jane about Ross Howie's perception of the attitude in the UK. I don't know whether people here were at the earlier Witness Seminar on 'neonatal intensive care' that was undertaken a few years ago, but exactly that point was made by somebody at the time who felt that in the UK there was this attitude and that was one of the reasons why there had been a slower prenatal/antenatal steroid uptake.⁷² I am very interested, Patricia, when you raise the issue of the role of the NIH Collaborative Group trial, because we were trying to trace through uptake levels and it did seem to us that in the 1970s there had been some increase in uptake: there was a supportive review, in the *Lancet*, for example, in 1979,⁷³ and there had been the survey of use by Members and Fellows of the Royal College [RCOG] which showed that quite a lot of them were using it in 1980.⁷⁴ It then seemed that things happened in the 1980s, as I think you were saying, that did seem if anything to increase the opposition. There was, for example, the editorial in the *British Medical Journal (BMJ)* written by Cliff Robertson, based on the NIH Collaborative Group subgroup analysis that's been criticized.⁷⁵ So I would just like to ask you how far you think that subgroup analysis perhaps did reduce usage?

Crowley: I think first the results of the US Collaborative Group trial set things back, because this was the first of the randomized trials published that didn't show any difference in neonatal mortality, even though it showed a difference in respiratory distress and in particular the duration and the cost of neonatal

⁷² Christie and Tansey (eds) (2001): 55–60.

⁷³ Ritchie and McClure (1979).

⁷⁴ Lewis *et al.* (1980).

⁷⁵ Robertson (1982).

care. This was the first trial that looked at economic outcomes. But nonetheless, the lack of difference in neonatal mortality seemed to get a lot of press and then the excessive performance of subgroup analyses was given undue emphasis, even though these subgroups had not been specified at the start of the trial. They were produced following data-dredging after the trial had concluded, and these were emphasized, for instance, in that editorial by Cliff Robertson.⁷⁶ You referred to the survey of Members and Fellows of the Royal College of Obstetricians and Gynaecologists, which asked obstetricians about their practice and what they said they did, which is not the same as what we actually do.⁷⁷ While 44 per cent of obstetricians surveyed in 1979 said that they used antenatal corticosteroids ‘often’, only 12 per cent of preterm babies recruited to the UK Ten Centre Study of artificial surfactant had been exposed to steroids antenatally.⁷⁸

Hey: That was a huge trial in 40 or 50 hospitals, wasn’t it?⁷⁹ It was the first time any paediatrician in the UK had been able to get their hands on surfactant. And it was free, so everybody joined the trial. The analysis of that study when it came out showed that nationally in 1990/1 – which was when that trial ran – fewer than 12 per cent of British babies who were potentially eligible for treatment were being treated.

Dr Sam Richmond: That’s absolutely true. We did a subanalysis of the regional data. The whole of the northern region entered this study and we published results looking back at steroid usage and found very similar results.⁸⁰ Some hospitals approached 25 to 30 per cent usage, and others, by far the majority, scarcely reaching 10 per cent.

I wanted to ask two other things. From my perspective at that stage as a paediatric registrar interested in neonates and the business of steroids, I think that there

⁷⁶ Robertson (1982).

⁷⁷ Lewis *et al.* (1980).

⁷⁸ Lewis *et al.* (1980); Ten Centre Study Group (1987).

⁷⁹ Open Study of Infants at High Risk of or with Respiratory Insufficiency – the Role of Surfactant (OSIRIS) Collaborative Group (1992). In 1990/1, 6774 babies were recruited to an international multicentre trial to assess when administration of Exosurf, a synthetic surfactant, should be started and how often it should be given.

⁸⁰ Dr Sam Richmond wrote: ‘I would point out that the price difference between steroids and surfactant mentioned in the last paragraph of the letter [Khanna and Richmond (1993)] contains a basic arithmetical error – the price of surfactant being nearly 100 times that of steroids rather than ten times.’ Letter to Mrs Lois Reynolds, 26 June 2005.

were a number of the subanalyses in the US Collaborative Group study which were useful, such as the long-term outcome worries which were one of the major concerns.⁸¹ What I found interesting were two aspects of that study. One was the vast number of mothers who were eligible but excluded, 88 per cent of those thought eligible to be considered but not actually entered, they were excused for various reasons, the vast majority being excluded because they weren't thought to be delivering within the time frame. I wondered what actually happened, whether they did or they didn't deliver within the time frame, I can find no evidence to show what happened. But the other issue is whether there ever was any biological plausibility to the reasons for the subgroup analyses? Why would we expect betamethasone to work differently according to sex of the fetus?⁸² I wondered if anyone had any clues as to that. I am not a laboratory person, but I cannot see any particular reason why one should divide on the basis of the sex of the fetus in relation to likely outcome. I could be completely wrong. But that seemed to be one of the major issues that it was a waste of time, unless you were expecting a black female baby, and that's clearly incorrect.⁸³ But why did anyone think to look in the first place?

⁸¹ Dr Sam Richmond wrote: 'I was particularly interested in the subanalyses of the collaborative study because of concern over long-term adverse effects in babies exposed to antenatal steroids, and thus the wish to be more discriminating in its administration. What I thought significantly undermined the conclusions drawn were: firstly, the number of eligible mothers excluded from the study (7197/7893 = 91 per cent), which must raise some questions, and secondly the illogical interpretation of some of them. One might expect a medication to have a greater effect among a subgroup at greater risk – such as among Caucasians rather than African Americans of equivalent gestation, or among males rather than females of equivalent gestation – that does mean that steroids don't work in the lower risk group, one merely requires a larger sample to show an effect.' Note on draft transcript, 26 June 2005. See Collaborative Group on Antenatal Steroid Therapy (1981).

⁸² Dr Ross Howie wrote: 'Outcome according to sex of baby: this is something I had not analysed in the Auckland study, and when I heard of the NIH findings I went back to check. This showed that in our hands, in contrast to the NIH study, betamethasone appeared to be more effective in boys than in girls. I concluded that the difference may have been due to the fact that we are in the southern hemisphere.' E-mail to Mrs Lois Reynolds, 26 August 2005.

⁸³ Dr Sam Richmond wrote: 'I know of no biologically plausible reason to expect any such difference (other than the well-known fact that girls of an equivalent gestation are at less risk of death than boys) and thus I could not understand why the subanalyses by sex were made in the first place – nor why this aspect was so vigorously pursued. If one undertakes a large number of subanalyses of any dataset one will find some statistically significant differences purely by chance.' Note on draft transcript, 25 June 2005. See Robertson (1982); Collaborative Group on Antenatal Steroid Therapy (1981); see also Lucas and Robertson (1982).

Avery: First, there is definitely a difference between male and female, and white and non-white. The Asian population is more advanced, yet when you look at these differences they are real, even into 20 weeks. I don't think they are big enough to swamp all the other things that are going on. It's a very interesting issue, I think, taking into consideration the chance that you might have all girls and look at the output in terms of scoring.

Richmond: I fully accept that there is a difference in survival based on race and sex, but I didn't think there would necessarily be a difference in response to steroids based on that. It just means that you get more informative clients if you choose the ones with the higher risk, but is there a differential response to steroids based on sex or race?

Avery: I cannot give you chapter and verse, but I think there is a difference.⁸⁴ Maybe somebody else has a reference.

Chalmers: I want to comment on extrapolation from data in animals, pathophysiological data in humans, and observational data in humans. One of the most remarkable things about the Auckland story is that Mont and Ross went directly from hypotheses they had tested in animals to assess the relevance of the hypotheses to women and their babies. People working with animals who generate hypotheses – whether it's about brain damage in the long term or some other matter – too often fail to exercise the scientific self-discipline shown by Mont Liggins and Ross Howie. I'll give you an example. Geoffrey Dawes was one of the hubs of perinatal physiological research in this country.⁸⁵ He and I often had arguments about the behaviour that I have just been complaining about. I had the impression that he was very annoyed that he hadn't made the discovery that Mont and Ross had made. I remember how in the 1990s he telephoned me in some glee to say that he had discovered – in an observational study – that prenatal steroid administration was associated with a pattern of fetal breathing movements that he regarded as worrying. I said to him, 'So what? You have now a mass of data from women and babies. If you have a hypothesis that is worth testing in terms of the relevance of your observations to human health, then test

⁸⁴ Professor Mel Avery wrote: 'A male infant has 1.5 to 2.0 times the risk of fatal hyaline membrane disease [also known as respiratory distress syndrome (RDS)]. See Wood and Farrell (1974).' Fax to Dr Daphne Christie, 21 June 2005. See also Farrell and Wood (1976); Avery (2000).

⁸⁵ See biographical note on page 130–1. Sir Iain Chalmers wrote: 'Liggins notes that Joseph Barcroft's work on fetal physiology was largely ignored by obstetricians until the mid-1960s, when Geoffrey Dawes' Nuffield Institute became the "hub of the universe" in terms of fetal physiology.' E-mail to Dr Edmund Hey, copy to Dr Tilli Tansey and Dr Daphne Christie, 17 April 2004.

it, using the mass of data that's now available from human experiments'. There is this bizarre lack of scientific self-discipline among people who know how to design experiments in animals, but actually don't know how to design, or even exploit, experiments in human beings.

Walters: Having done a lot of work in the lab and also done some clinical trials, I would do lab work every time. It is very hard to do clinical trials because of the obstacles that are currently in our way, particularly in this country. I mean ethics committees, 60-page ethics forms, trying to get support from the institutions and even more European hurdles to get through even now, with having to record our clinical trials centrally. Also on a scientific basis, the variables in clinical trials are much more difficult to control than they are in the lab. So as a humble physiologist trying to get into clinical work, give me the lab every time.

Avery: Just a note, Mont Liggins spent a sabbatical in Geoffrey Dawes' lab and specifically was told by Dawes that he [Dawes] would not allow anyone to do any work on, even discuss, surfactants for the whole time that Mont was there.⁸⁶

Hey: Well, that's straight from the horse's mouth.

Avery: One petty observation, but I couldn't resist.

Hey: I will just interject that in the Ross conference report that you mentioned in 1976, there are five papers from the US saying that they tried to do a trial and it was too difficult.⁸⁷ We moan now about trials being difficult. You go back and find

⁸⁶ There was some discussion between Avery, Liggins and the editors on this point. This correspondence, along with tapes and other records of the meeting, will be deposited in CG/253, Archives and Manuscripts, Wellcome Library, London.

⁸⁷ Dr Edmund Hey wrote: 'In introducing the contribution by Professor Liggins, the Chairman, Professor T D Moore, said: "The information which is most likely to reduce the uncertainty associated with decisions dealing with the safety and effectiveness of drugs is obtained from tightly controlled, double-blind clinical studies. As you will learn from subsequent discussion sessions, such studies are extremely difficult to execute. Not only must the clinical investigator have the blessing of the Human Research Committee, he must also have complete cooperation from his medical colleagues and their patients. You say impossible? Most of the time, yes. However, on rare occasions someone is able to pull it off. When that happens, we have a classic piece of research on which many others can build. Such is the case with Dr Liggins' studies of the effect of prenatal treatment with betamethasone on the prevalence of RDS." Clinicians from centres in Quebec, Canada, San Francisco, Texas and from two medical schools in Boston, all indicated during the subsequent discussion that they had found it impossible to undertake such a study. Liggins (1976): 97, 119.' Note on draft transcript, 27 August 2005.

that they have always been saying that they are difficult. I think they are getting more difficult, but it's always been difficult. Yet sometimes it goes very well.

Gyte: I am moving away and back to a theme that was mentioned before. As a consumer representative, I have always been very interested in the implementation of research findings, and my experience in this area came when I was a consumer representative on the ORACLE trial, which was a trial looking at antibiotics in preterm labour.⁸⁸ In the development of that protocol, the researchers wanted to do a second randomization of steroids within the main trial, and as it was actually not our organization, the National Childbirth Trust (NCT), but another consumer organization, the Association for the Improvement in Maternity Services (AIMS), who put their foot down and said it was unethical to randomize women to steroids, and that actually all women should be given them within this multicentre trial, so that second randomization was removed.

Hey: Just remind us of the date of the ORACLE trial.

Gyte: We are doing a seven-year follow-up now, so it was 1995.

Hey: It was 1995, the results came out three years ago in the *Lancet*.⁸⁹ The relevance is that one of the uncertainties that remains about steroid use is whether it is a wise thing to do for the mother's sake, when there is premature rupture of membranes, because you may, in doing something good for the baby, increase the risk of the mother developing a generalized septicaemia. So presumably the consumers couldn't see the unanswered question there.

Gyte: I went to *Effective Care in Pregnancy and Childbirth*⁹⁰ to read Patricia [Crowley]'s chapter to find an NCT perspective, and I remember thinking that there were some areas of uncertainty, but certainly that randomization was removed from the study.

Dr Peter Brocklehurst: I suppose I was just thinking about how we now approach the use of antenatal steroids, how we have heard today that it was very difficult to get antenatal steroids used in clinical practice, particularly in the UK, and then, within a very short space of time, we were throwing them around like Smarties. I suppose what nobody has mentioned yet is that in order to get 90 per cent coverage of babies admitted to the neonatal unit exposed to

⁸⁸ Kenyon *et al.* (ORACLE Collaborative Group) (2001a and b).

⁸⁹ See Kenyon *et al.* (2001a and b).

⁹⁰ See note 52.

antenatal steroids, you have to give them to an awful lot of pregnant women. I have heard it said that in some hospitals a pregnant woman under 34 weeks only has to burp to be given antenatal steroids. And then there was the use of multiple courses of steroids that is becoming very frequent. Now, of course, what are being considered more and more in the literature are the potential adverse effects, not just of multiple courses of steroids, but the potential long-term hazardous effect of a single course of antenatal steroids on brain development, which John Newnham's group at Perth is coming up with evidence about.⁹¹

I think a lot of what is difficult about this issue is that we are not very good at predicting preterm birth, and if we were better at predicting who was going to deliver preterm we would probably feel much more comfortable about using steroids in a more targeted way. The concern is that currently at least 50 per cent of women who get antenatal steroids do not deliver preterm and therefore if there is long-term harm, it will be in these babies that it will manifest itself. If we could target our use of steroids better, we would all probably feel a bit more comfortable. So I think we are beginning to go the other way, where people are actually being more cautious now with steroids than they were maybe even five years ago.

Crowley: Could I remind you that in the Auckland trial a lot more babies died in the placebo group, and therefore one might have expected an increased incidence of adverse neurological outcome in the survivors from the steroid-treated group compared with the control group. These survivors have now been assessed at 30 years of age, and if there's no difference between the two groups at age 30, it's unlikely that there is any hazard associated with a single dose of antenatal steroids.

Harding: There are a number of comments I could make. I think you are quite right about the issue that you had to treat a lot of women. In fact, if you look at the studies that we were able to put together in a systematic review overall, 40 per cent of women who were entered into the trial did not deliver after one week.⁹² So when you get into the issue of, well, how long did the effect last, and what do you do with the women who've been treated and haven't delivered after a week – you have a lot of women to consider.

To come back to the issue of ruptured membranes, and I think it is fair to say in the mid-1990s there was still confusion about the issue, but the solution

⁹¹ Their earlier work includes Newnham and Moss (2001); Newnham *et al.* (2002).

⁹² McLaughlin *et al.* (2003).

was not to do a new trial. The solution was to go back to the old trials. At that time there had been over 4000 women randomized, and the data were present from the original trials, they had just never been analysed. In about 1994/5 – I cannot remember the exact date – we had a debate around a clinical case at a clinical conference at my hospital, after which David Knight, who was the Director of the nursery at the time, said to me, ‘Isn’t that question answered? Surely the data must be there?’ Now just parenthetically, David Knight was at the Barcroft Symposium in 1973 at which Mont presented the data.⁹³ That was one of the reasons that David came to New Zealand and ended up as Director of the nursery. He got all excited about antenatal steroids and thought that he would come to Auckland. That’s a slight aside. But it was David’s question to me that prompted me for the first time to go back to Mont and Ross to ask, ‘You know all those files in the locked cupboard in the corridor where my office was, how would you feel about our getting them out and doing a new analysis, because I think the data might be there and we need to know the answer to a question that you hadn’t asked at the time’.

With enormous generosity they agreed that I could do that. I would hate somebody to come along 30 years later and ask for my data from any of my studies and re-analyse it, it’s a very scary thought, and I think they were very brave. But they said, ‘Yes, that would be fine’, and the original trial data sheets, beautifully handwritten by Ross, were still in the locked cupboard in the corridor.⁹⁴ They have lived in my office, under lock and key, ever since. We were able to retrieve the data from those data sheets, there was a code on the coding sheet that said ‘ruptured membranes at trial entry, yes/no’, so we were able to retrieve about 400 women who had ruptured membranes at trial, and even more remarkably we were able to go back to the hospital clinical records section and get out 80 per cent of the clinical records, which I think is phenomenal 30 years later, but they were still there. They have also lived in my office under

⁹³ Liggins and Howie (1973).

⁹⁴ Dr Ross Howie wrote: ‘On retention of records: the records were kept for just this purpose, for possible future use. There was hardly enormous generosity on my part, and I was delighted that Jane and others were able to make use of them. One possible reservation: I was once told early in my career *never* to let anyone else look at my raw data. The reason given was that there are many ways of analysing them, and some people would be only too willing to do so in such a way as to make you look a fool, or a fraud, or both. The person who told me this was one of the finest scientists I have known and no more paranoid than the rest of us. I had no hesitation about Jane’s use of the material. I imagine there would be no problem of this kind in these days of grand multiplicity of authorship, but we did not have that luxury in the early 1970s.’ E-mail to Mrs Lois Reynolds, 26 August 2005.

lock and key ever since, and we were able to go back, retrieve the original data, redo the systematic review, and show, I think, very clearly that there was still considerable benefit in the presence of ruptured membranes, and that there was no evidence of adverse effects.⁹⁵

Hey: The answer for Gill Gyte was that the data were there but, 20 years later, it had still not even been analysed. Who can put their hands up and say that, of a trial completed and published more than five years ago, that they can still find the original raw paperwork? One of the most amazing things that I found in reading around before today's meeting, was to come across this paper by Jane Harding in the *American Journal of Obstetrics and Gynecology* on just this subject, published in 2001, and this is control trial data, and it has sat there all that time.⁹⁶

Harding: I think there are a number of messages. One is that the data were still there and still in a form that we could use, which I think is very impressive. The second is that new questions have come up that the trials weren't necessarily designed to answer at the time, but it's terribly important that the data are still there.⁹⁷ Thirdly, someone might like to comment on the length of time it took us to get that paper published. The study was done in 1996/7, we wrote it up in 1998, it was rejected by two journals, submitted to the *American Journal of Obstetrics and Gynecology* in 1999, and it was eventually published in 2001. I do think the people who publish have something to contribute to this very prolonged process.

If I could just go on to the other issue that was raised: what about the women who get steroids and don't deliver within the next week? We have been concerned about this with respect to the repeat steroid issue. There has been a multicentre randomized trial run by Caroline Crowther out of Adelaide for the past seven years.⁹⁸ We hope to finish recruiting this month. It includes 980 women, and we have been doing huge detailed studies of the babies in Auckland, the second largest centre recruiting to this trial. It occurred to us early on in that trial that we still didn't have good data about risks and benefits for the group who receive

⁹⁵ Harding *et al.* (2001).

⁹⁶ Harding *et al.* (2001).

⁹⁷ See Peter Elwood's description of planning the Caerphilly study in Reynolds and Tansey (eds) (2005): 81.

⁹⁸ See also Crowther and Harding (2003).

steroids but then don't deliver within the next week; the group who don't stand to achieve the greatest benefit for the infant and are potentially at the greatest risk. Once again, we thought the data weren't out there, but I bet it was in the original trial. We were able to go back to the original data, look specifically at that group, write a new meta-analysis which has also been published after many rejections, after a very long time, which showed, in fact, that there may be adverse effects in that group.⁹⁹ Therefore people need to randomize them to the new trials. We were in fact trying to help recruitment of the randomized trials. It took so long to publish that I think it's had very little effect on recruitment to the trial, but the data are nevertheless there. Yet another outcome that was not relevant at the time, the question has come up subsequently.

Hey: Would Glaxo still be able to find the data?

Professor Harold Gamsu: Oh yes, I have all the data in my office.¹⁰⁰ It's still there, all the data sheets, because I was hoping to do a long-term follow-up on the adults, and in fact things haven't turned out that way, but that's still available for people to do if they would like to.

Hey: Because people are still asking the questions: 'Does it work in twins?' or 'Should you give it in mothers with hypertension?'

Gamsu: Our numbers, of course, are very small.

⁹⁹ McLaughlin *et al.* (2003).

¹⁰⁰ Gamsu *et al.* (1989). See Appendix 5 for the Protocol, provided by Dr Clive Dash. The sample case record used in the 1975 UK study will be deposited along with other records from this meeting in GC/253, Archives and Manuscripts, Wellcome Library, London. Dr Clive Dash wrote: 'The retention of clinical trial data in the 1970s–80s was poor. This has changed in recent years. When Harold Gamsu persuaded us to do a detailed analysis of the UK study, the computer software had changed and so had most personnel acquainted with the prior system. Luckily, Alex Paton at Glaxo was able to interrogate the database and through her efforts we were able to meet Harold's expectations and answer his critical questions. Also, Harold volunteered to keep safe the original case record forms and other study documentation when Brenda Mullinger and I left Glaxo to pursue other career opportunities. I believe Harold always hoped to trace the babies in adult life to address the question of the long-term safety. It is due to his diligence and enthusiasm that he persuaded us (again, pleasantly) in 2001 to begin the process towards a 30+ years follow-up. His untimely death occurred in August 2004, soon after this witness meeting. We hope to continue this project with the support of NPEU in Oxford provided external support can be mobilized and plan to dedicate any outcomes to his memory.' E-mail to Dr Daphne Christie, 10 January 2005. Mrs Brenda Mullinger wrote: 'The idea of undertaking a follow-up of babies born in the UK study was mentioned at the seminar – this is a real possibility because Professor Gamsu was diligent in retaining all the trial record forms (and randomization codes) long after others' interest in the study had ceased.' Letter to Dr Daphne Christie, 6 January 2005.

Hey: So are everybody's, but if people have kept their data, there are more that can be analysed. Could anybody find the NIH data? Would the NIH people share their data?

Avery: I have no idea.

Gamsu: May I ask a question about this study by Newnham *et al.*? My feeling is that it is in animals, but could you tell us a little bit more, because it sounds very significant if it's not in animals.

Brocklehurst: I cannot tell you very much more, because I heard it presented in Glasgow about six weeks ago, but I have seen nothing in press yet.¹⁰¹ My recollection is that it was in animals, but we'll be able to explore this further when the study is published.¹⁰² Having tried to do one of the large trials of multiple courses of steroids, I think one of the issues for clinicians about the use of multiple courses of steroids is that their [clinicians] threshold for starting antenatal steroids is lower, because if they are wrong, and the woman doesn't deliver soon, they have felt that they can always give a second course. If people are restricted to giving a single course of steroids they may delay starting until there is stronger evidence, if you like, of impending preterm birth. So the groups of women selected into these trials are likely to be quite different from the multiple steroids group and that will make the interpretation of the results interesting.

Lilford: I recently had a debate with my 14-year-old daughter Philippa about whether history is just an interesting thing to read, or whether it helps us to design our own futures. Listening to Jane speak makes me think that there really are occasions when history has a lesson for the future. Hearing you speak about finding these records has been very interesting, but I suspect that many people

¹⁰¹ Professor John Newnham from the King Edward Memorial Hospital, University of Western Australia, Perth, Australia, delivered the British Maternal and Fetal Medicine Society (BMFMS)'s Lecture, 'Antenatal Steroids and Outcome', at their Ninth Annual Conference, 1–2 April 2004, Glasgow. He presented results from human and animal studies where infants had been exposed to steroids before birth. See the full report by Dr Margaret M Ramsay, Honorary Secretary, BMFMS at www.bmfms.org.uk/presssummaryofglasgow04.doc (visited 18 July 2005). Professor Jane Harding wrote: 'A large amount of Professor Newnham's animal work has been published, but obviously the speakers here are not familiar with this. Some of the relevant articles include: Quinlivan *et al.* (1998); Sloboda *et al.* (2000, 2002a and b); Huang *et al.* (2001); Moss *et al.* (2002, 2003).' Note on draft transcript, 4 September 2005.

¹⁰² The lecture will be published as Newnham (2006).

in this room were amazed that you really could find those source materials after 30 years, that you could find the trial documents and so on. When Harold Gamsu moves the documents from his office, goodness knows where they might go. So the lesson that we might want to learn from this is the importance of some sort of systematic paid-for archive for trial information, and I don't know if you might want to comment. I know that the Economic and Social Research Council (ESRC) archive their most precious data and build the cost of so doing into the grant.¹⁰³ The more I hear, the more I think this might be something we ought to try to take forward as a matter of some urgency.

Chalmers: The MRC has a working party under the chairmanship of Peter Dukes, which is creating circumstances through which it would be possible for anyone receiving an MRC grant to archive their data.¹⁰⁴ So biomedicine is catching up with the social scientists.

Dr Dino Giussani: I wanted to draw together some of the many comments, in particular one made by Iain Chalmers, as to how we translate evidence that we find in animal studies to the human situation. We haven't talked about many of the more subtle effects of antenatal glucocorticoid therapy that may prove detrimental in the long term to the adult. In the animal, there is overwhelming evidence now accumulated that antenatal steroid therapy, in doses and dose intervals used in human clinical practice today, has detrimental effects on the development of the adrenal gland. For example, fetuses that have been treated by steroids have an overreactive adrenal function, which may lead to detrimental long-term consequences in adult life. We have not talked about maturational effects on other systems, such as the cardiovascular system. We

¹⁰³ The Economic and Social Data Service (ESDS) Qualidata is a specialist service of the ESDS led by the UK Data Archive (UKDA) at the University of Essex. The service provides access and support for a range of social science qualitative datasets. Established in 1967 the UKDA holds the largest collection of digital data in the social sciences and humanities in the UK, funded by the ESRC, the Joint Information Systems Committee (JISC) of the Higher Education Funding Councils, and the University of Essex.

¹⁰⁴ Dr Peter Dukes wrote: 'The MRC's policy is that population and trials datasets should be managed such that they sustainably accessible (through preservation) and shareable [see www.mrc.ac.uk/index/strategy-data_sharing_policy.htm (visited 30 September 2005)]. From 1 January 2006, investigators are required to submit brief data sharing and preservation plans with their grant applications. To create awareness and support preservation, the MRC has commissioned guidelines for both investigators and peer-review committees. Following a jointly commissioned study by MRC, BBSRC, DTI, JISC, NERC and the Wellcome Trust, these funders expect to assess during 2006 the requirement(s) for coordinated support for data preservation, curation and sharing.' E-mail to Mrs Lois Reynolds, 30 September 2005.

know that glucocorticoids in fetal life increase blood pressure in a sustained manner at a time that mechanisms that are going to control the blood pressure of the individual in adult life are being programmed, such as the baroreceptors. We have evidence that antenatal glucocorticoid therapy resets the arterial baroreceptors to run or to maintain blood pressure at a higher level. And of course we don't know whether that would lead eventually to detrimental effects. We all agree that glucocorticoids are life-savers, but we have to begin to think as to whether some of these more subtle side-effects may become detrimental in later life.

I was also wondering whether we will talk later about refining some of the dosing regimens of glucocorticoid therapy today, in an effort to maintain the beneficial effects, but to 'weed out' the unwanted, adverse side-effects.

Harding: If I can make a very brief comment about that? This is another example of a new question for which the old data already had the answers. The blood pressure of the six-year-old children was recorded, but never analysed and published, and it will be published very shortly in *Pediatrics*.¹⁰⁵ We found the archives in the roof of the hospital, dragged them down, and said, 'Would you mind if we analysed these and published them?' There is no difference in blood pressure at six years or, incidentally, at 30 years, but I think the issue for this conference again is one of new questions to which old data actually has the answer.

Dr John Hayward: I wonder whether this is an opportunity to look at getting research into practice, one of the future topics after the tea break, just to hold in our mind some of the questions that have been raised.

What strikes me is that during my own career as a GP – becoming interested in systematic reviews, training in public health, and then returning to public health – the same issues keep cropping up. There is always a concern whether we have looked at the subjects correctly? What will the long-term detrimental effects be? Everybody is actually influenced by some horror that they have come across. That's perhaps not so much the case for steroids, but it's certainly true if you look at external cephalic version (ECV) of breech presentation, for example. My statement later will be about how we looked at getting research evidence into practice. I think the danger is that everyone worries about some rare outcomes 30 years hence as justification for sitting on your hands and not doing anything.

¹⁰⁵ Dalziel *et al.* (2004, 2005a and b).

The outcome of interest here was death, compared with survival, and I think that's the critical thing to hold in our minds and presumably there are children, now adults, who would not be here at all if their mothers hadn't consented to take part in the original trials and been fortunate enough to have the coin fall on their side, who got the intervention rather than the control. I would have thought that those adults who are alive now would accept a certain amount of hypertension or some other problem as an alternative to not being here at all.

Hey: I think we had better draw this to a close for tea. We haven't got as far as we should have. Death isn't the only outcome, there are cost-benefits apart from that and we must move on.

Mugford: My background is a degree in economics. I graduated from the University of Stirling in 1972: health economics as a discipline didn't exist then. I think the first Penguin book of readings for students of health economics was published in 1973.¹⁰⁶ I looked at it and wished that I had studied health economics. There wasn't at that stage even postgraduate training in it. I finished my economics degree quite disillusioned with the subject, because it was very much centred on the formal economy – that is how people trade goods and services using the money mechanism and adjustments of it through the public services as a method. So I finished a Master's in monetary economics and then dabbled in bits of health of economics research. I joined the NPEU in Oxford, as a researcher in statistics with Alison Macfarlane, but also to work in the unit on other topics, including incorporating economics alongside randomized trials with Adrian Grant. This was a very new notion of building economic evaluations using evidence from syntheses of evidence of effectiveness, building on the work that Iain Chalmers and others were pioneering in the Oxford Database of Perinatal Trials (as it later became but wasn't when I first joined the unit in 1981).

In the early 1980s when I was still working on the book of statistics of pregnancy and childbirth with Alison Macfarlane, Iain Chalmers asked me to keep a file in my filing cabinet on neonatal intensive care, because it was an issue that was of increasing interest in the health services and it was going to be of economic importance.¹⁰⁷ And so I did.

¹⁰⁶ Cooper and Culyer (1973).

¹⁰⁷ Macfarlane and Mugford (eds) (1984).

At that time, health economics was emerging and that's another whole historical story which has been documented elsewhere.¹⁰⁸ My connection with it was really through Professor Alan Williams at York, who was probably the founding father of health economics in the UK, and his visit to the unit. I think he was examining a dissertation in Oxford with Iain and I asked him how I could qualify as a health economist. He replied, 'What you have to be able to do if you are a graduate economist is to stand up and say that you are a health economist in front of a bunch of doctors.' So I girded my loins and worked on subjects, including the systematic review of steroids, that seemed to be relevant to our brief in the NPEU and to the enthusiasm of people within the unit. I remember the day when the results were being worked through by Patricia and Iain before it was published. The coffee room was buzzing and this was very exciting. At the same time I was host and supervisor to a series of students from York, where they had a new health economics Master's degree and they looked for placements for their students during the summer to do dissertations. One of them, James Piercy, came to me to work on the economics of antenatal corticosteroids. He did some observational work in the neonatal unit in Oxford to try to assess the costs of treating babies at risk of preterm delivery and eligible for steroids. In fact, the surfactant question was also – I was going to say 'bubbling' – around at that time. He and I with Iain wrote a paper which was a modelling exercise, a very, very simple decision-modelling exercise, based on different assumptions about initial birth weight and mortality risk, based on the cost data, which James had gathered for his dissertation, and the evidence of effectiveness from the systematic review. That was published by *Archives of Disease in Childhood*, having been rejected by the *British Medical Journal*, in 1991, after the systematic review.¹⁰⁹ So as far as I am concerned, that wasn't quite the end of the story because the Oxford Regional Health Authority had introduced the Getting Research Into Practice and Purchasing (GRIPP) programme.¹¹⁰ We are going to hear more about that later, I think.

One of the things I was asked to do by the public health doctors was to model the impact in the Oxford region of this particular policy, GRIPP, on increased uptake beyond current uptake, which I think we assumed conservatively to be about 10 per cent, I can't remember.¹¹¹ We worked out that implementing the

¹⁰⁸ Croxson (1998).

¹⁰⁹ Mugford *et al.* (1991).

¹¹⁰ Dopson and Gabbay (1995).

¹¹¹ Mugford (1993).

policy in the Oxford region might reduce not only mortality but also the costs of neonatal intensive care after paying for the drugs, which were not a great cost to the health service, and that reduction would probably be in the region of 10 per cent of the cost of neonatal intensive care for those babies. Although when I talked to the finance director in the health authority, as it then was, he was a bit dismissive and said, 'If you cannot tell us how many cots we can close, it's not really very interesting to us, because those paediatricians will just fill the cots anyway, they will put someone else into them'. I replied that this was not the point of the economics. The point of the economics is that it is better if you can do more with what you have got.

Hey: Your study came in just at the time when if you didn't give steroids you might have had to end up giving surfactant at £250 per ampoule, wasn't it?

Mugford: I think it was more than that. Up to £600.

Hey: And it has still not gone down. So you did it at exactly the right time, I think.

Mugford: There's just one other thing which I think Mary Ellen Avery referred to, and Patricia [Crowley] too, and that was that the analysis we did was quite unsophisticated, but we did make some effort to model the impact in the smaller babies and the more preterm babies, and in those cases there wasn't a predicted cost saving. One of the problems we had with people was the assumption that that is not then cost-effective, which isn't true, because society has shown that it is willing to pay for neonatal care, to pay for the benefits of having survivors. So it's not just that they need to save money, it's that there's a willingness to pay for the benefits beyond the straight, evident cost savings. Among economists, it is not very fashionable to look at areas where in fact there is a win-win situation. The exciting academic work goes on at the fringes, where benefits perhaps might not be worth the costs.

Hey: I have been doing a little bit of economic work myself recently, and you realize, of course, that the cost of neonatal intensive care is nearly all the cost of the doctors' salaries, and what isn't the doctors' salaries is the cost of the nurses' salaries, and that's what your treasurer means when he wants to close a bed. He wants to be able actually to use fewer nurses, and those are the driving costs which put most of the other costs into second place. Last time I looked at a hospital budget for a neonatal intensive care unit, and that is a unit with a lot of expensive drugs in it, they still only account for 10 per cent of the annual budget of the unit.

Gamsu: I agree with you. The cost of anything is almost always invested in the cost of salaries, particularly nurses, of course, because they have to be there all the time.

Hey: And at night as well. They are now expected to have only one baby in their care.

Mugford: We can say that over the past 20 years the resources devoted to neonatal intensive care have expanded incredibly – you [the History of Twentieth Century Medicine Group] held a different Witness Seminar on this subject, but I haven't looked at that transcript.¹¹² There are very many more nurses, doctors, ventilators and techniques for the care of preterm babies than there were 20 years ago.¹¹³

Hey: I think we shall move straight on, because we examine next how to get research into practice. I am going to ask Iain to explain how it came about that he chose to use a very early version of Patricia's meta-analysis as late as 1992, at a time when there were twice as many trials involved in her analysis for his Cochrane Centre Logo.

Chalmers: It's good that Patricia Crowley has already described some of the history. Given that I am going to be talking about the Cochrane Logo, I might as well start with Archie Cochrane, whose famous book – *Effectiveness and Efficiency: Random reflections on health services* – was published in 1972.¹¹⁴ I read it in 1973 and it changed my life!¹¹⁵ In spite of the fact that I had been 'licensed to kill' six years earlier after studying at the Middlesex Hospital Medical School, London, to qualify as a doctor, I had not previously been aware of the term 'randomized controlled trial (RCT)'. Cochrane showed me how I might adjudicate among incompatible clinical opinions about treatments – a common situation faced by me and other junior doctors – and it was after reading Cochrane's book that I started to collect reports of RCTs. A librarian at the University of Cardiff, Steve Pritchard, designed a Medline® [online version of *Index Medicus*] search to identify these studies for me, and I started noting those in my special area of interest (perinatal care) during my reading of journals and books.

¹¹² The Witness Seminar, 'Origins of Neonatal Intensive Care in the UK', was held on 27 April 1999. See Christie and Tansey (eds) (2001), also freely available online at www.ucl.ac.uk/histmed following the link to Publications/Wellcome Witnesses.

¹¹³ Macfarlane *et al.* (1999).

¹¹⁴ Cochrane (1972).

¹¹⁵ Chalmers (1999).

In 1976, because it was clear that this was an insufficiently systematic method of finding reports of RCTs, I outlined a plan for using a more systematic approach both for finding published reports, and for identifying unpublished studies, because biased under-reporting of RCTs means that unpublished studies tend to have less dramatic results than those that get into print. This plan, which was set out in a letter to Martin Richards, a psychologist in Cambridge, also stated an intention to use statistical synthesis of the results of similar but separate studies (meta-analysis) to reduce type 2 errors (false negatives) in estimating treatment effects. My letter to Martin Richards happened to be sent to him during the same year as the term 'meta-analysis' was introduced by the American social scientist Gene Glass.¹¹⁶

The first opportunity that I took to do a systematic review using meta-analysis related to different ways of monitoring babies during labour.¹¹⁷ Electronic fetal heart-rate monitoring had been introduced in obstetrics not long previously, sometimes accompanied by fetal scalp blood sampling to assess fetal acid–base status, particularly if the heart rate had raised concerns. It was being suggested by some people that these more intensive methods of intrapartum fetal monitoring should replace intermittent auscultation using fetal stethoscopes. I set about analysing three published reports of RCTs comparing different methods of intrapartum fetal monitoring, and the findings from one unpublished RCT, which were kindly made available to me by the investigators. About 2000 babies had been born to the women who had been entered into these four trials: 13 of their babies had had neonatal convulsions. With the help of a medical statistician – Klim McPherson – I analysed the distribution of these babies among the comparison groups in the RCTs.¹¹⁸ This revealed that the pattern was very unlikely to have occurred by chance (less than 1 in 100): the analysis suggested that continuous electronic fetal heart rate monitoring with scalp sampling might reduce the risk of neonatal convulsions.

I was very impressed by this observation which had not been picked up in any of the individual RCTs, and it influenced the design of a very large RCT (in which over 13 000 women and their babies participated), done at the National Maternity Hospital, Dublin, while Patricia Crowley was working there.¹¹⁹

¹¹⁶ Glass (1976).

¹¹⁷ Chalmers (1979).

¹¹⁸ See, for example, McPherson (1990).

¹¹⁹ MacDonald *et al.* (1985).

The results of the Dublin trial of fetal monitoring confirmed the hypothesis generated by my systematic review and meta-analysis. That seemed to me to provide encouraging evidence that systematic reviews and meta-analyses could be useful for generating and testing hypotheses about the effects of healthcare interventions. Furthermore, it was becoming clear that this approach was regarded as promising in other fields, particularly in cancer and cardiovascular disease.¹²⁰

As has already been noted by Patricia Crowley, hundreds of people volunteered during the following decade to collaborate in helping to prepare systematic reviews of RCTs assessing the effects of interventions during pregnancy, childbirth and early infancy. For example, to identify relevant studies for a register of RCTs,¹²¹ some of these people searched over 70 obstetric and paediatric journals back to their 1950 issues,¹²² while others developed an agreed methodology for analysing the data from these studies.¹²³ Some of the resulting systematic reviews were published in journals (we were encouraged particularly by Frank Hytten, David Paintin and Sheila Duncan at the *British Journal of Obstetrics and Gynaecology*), and all of them were published in books¹²⁴ as well as electronically, so that the analyses could be kept up to date.¹²⁵ It was very important that an institutional base for this work existed – the National Perinatal Epidemiology Unit (NPEU). The Unit was funded by the Department of Health, which recognized that systematic reviews of existing evidence were a relevant way of identifying priorities for new research.

So what about the logo of the Cochrane Collaboration? The publications that had come from this ‘pilot study’ in the perinatal field were quite widely well received. Importantly, an oncologist, Michael Peckham, who had been appointed in 1991 to establish a new NHS research and development programme, commented favourably on our work in a *Lancet* article about his

¹²⁰ Stjernsward *et al.* (1976); Chalmers *et al.* (1977); Anonymous (1980).

¹²¹ National Perinatal Epidemiology Unit (1985).

¹²² Chalmers *et al.* (1986).

¹²³ Chalmers *et al.* (1989).

¹²⁴ Chalmers *et al.* (eds) (1989); Enkin *et al.* (1989); Sinclair and Bracken (1992).

¹²⁵ Chalmers (1989–92). The contents were subsequently transferred to and maintained in The Cochrane Database of Systematic Reviews, accessible through the Cochrane Library at www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME (visited 2 June 2005).

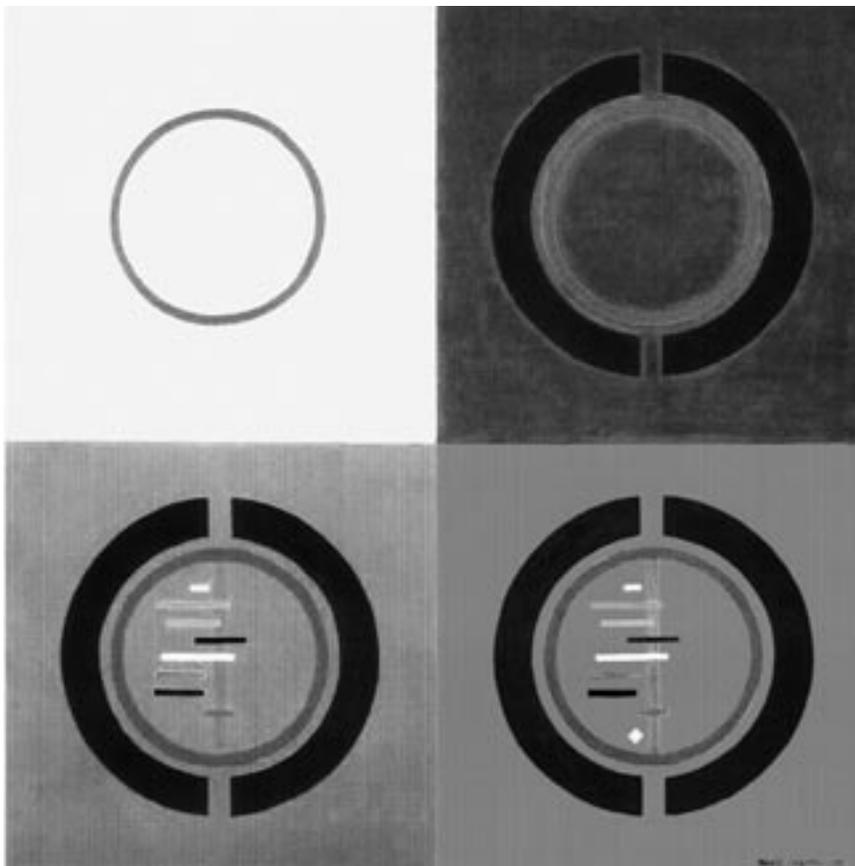


Figure 6: The story of the Cochrane Logo, 1992.

In 1992 Iain Chalmers asked David Mostyn to design a logo to illustrate the objectives of the Cochrane Centre, which was being established in Oxford later that year. On leaving the Cochrane Collaboration ten years later, Iain commissioned David to produce a painting to illustrate how the Cochrane Logo had been conceptualized and created.

The circle in the upper left panel reflects global objectives and international collaboration. The addition of the mirror image Cs in the upper right panel initially stood for Cochrane Centre and subsequently for Cochrane Collaboration. The horizontal and vertical lines added in the lower left panel show the results of several RCTs of prenatal corticosteroids, a simple and inexpensive treatment to reduce problems experienced by premature babies. The reason there are eight horizontal lines in the painting compared with only seven in the official Cochrane Logo is because Iain had inadvertently overlooked one of the 1991 studies. The diamond added in the remaining panel is a statistical summary of the information derived from the individual studies above it. This summary statistic shows that prenatal corticosteroids, which were not then in widespread use, reduced mortality in premature babies.

The Cochrane Logo thus illustrates the human costs that can result from failure to perform systematic, up-to-date reviews of controlled trials of healthcare. The Cochrane Collaboration was established to do something about this unsatisfactory state of affairs.

See www.cochrane.org (visited 22 November 2005).

plans for the new programme.¹²⁶ He also responded encouragingly in that year when I suggested that a centre might be established to facilitate extension of the methods we had used to other areas of healthcare. His advisers subsequently agreed that it was worth giving the proposal three years to see whether we could make anything of it. As I have never had a contract for longer than a few years, I accepted this challenge, and the (UK) Cochrane Centre was opened in 1992.¹²⁷

Part of the Centre's logo shows the results of the first seven trials of prenatal corticosteroids. I overlooked, inadvertently, an eighth trial that had been published during this time period. It happened to have exactly the same confidence interval as one of the others, and I had thought that we might have been double counting. The reason that we used the steroid trials was that we wanted to show that within ten years of the Liggins and Howie trial,¹²⁸ there had been crystal-clear evidence that this was a very important way of reducing neonatal deaths. In launching the Cochrane Centre, we wanted to make the point that this very important information had been available more than a decade earlier, yet it was still not being acted upon sufficiently in practice. In the brochures we produced and the talks we gave to introduce the objectives of the Centre to others, we made the point that tens of thousands of babies had suffered and died unnecessarily (and cost health services more than they need have done) because information had not been assembled in a systematic review and meta-analysis to show the strength of the evidence. In 1993, a year after the Cochrane Centre had opened for business, we convened the meeting at which the international Cochrane Collaboration was founded, and the Centre's logo was adopted by the new organization.¹²⁹ [See Figure 6.]

I want to end with a statement that may sound rather carping, but I am keen that it should be on the record, given that this seminar is supported by the Wellcome Trust. Although the Trust supports clinical trials in some other parts of the world, it has always discouraged applications for support of clinical trials in the UK. In addition, I have it on good authority that some of the governors of the Trust have not only been unsupportive, but actually dismissive of the

¹²⁶ Peckham (1991).

¹²⁷ Chalmers (2003). See www.cochrane.org/docs/orderformarchiecochrane_backtothefront.doc (visited 1 June 2005).

¹²⁸ Liggins and Howie (1972).

¹²⁹ Chalmers (1993a); Chalmers *et al.* (1997).

kind of research I have described here – RCT registration, systematic reviews and meta-analysis. Indeed, the Trust’s website declares unambiguously that it will not support systematic reviews of clinical trials.¹³⁰ Given that those assessing payback from research and others recognize the crucial importance of systematic reviews of clinical trials for patient benefit, I and others continue to resent the Trust’s unwillingness to engage in discussion with outsiders about the scientific rationale for its attitudes to clinical trials and systematic reviews.¹³¹ It is time that the Trust and other funders of biomedical research assessed more rigorously and transparently the cost-effectiveness of their research funding decisions.¹³²

Hey: The problem with your logo, of course, as my maths teachers would have said, is that it doesn’t have a scale on it.

Chalmers: Is there no artist in you?

Hey: And the little blobs on the bottom. This is all very well, but it doesn’t actually tell you that you halve the chance of the baby getting respiratory distress. Getting research into practice: we have already started down the path, haven’t we?

Lilford: It’s a great honour to be here today to say a few words about moving knowledge into clinical practice. I was plucked from obscurity in 1991, I think it was, by the then President of the Royal College of Obstetricians and Gynaecologists, Stan Simmons. He called me into his office and said that he wanted me to take over the audit committee. I had not been on the committee before, so I went down to the first meeting as their Chair. It was a very boring meeting; it didn’t seem to go anywhere. The idea of guidelines was coming into people’s consciousness at around this time, and on the train back home the idea came into my head that what I should do with the committee was promulgate guidelines. So I told the council how I was going to do this, and they must have had something else on their minds that day, because they nodded it through, and moved on to the next item. I then had a mandate to produce guidelines for dissemination. The next thing to decide on was the context of the guidelines. Iain Chalmers along with his colleagues had recently published his book, *Effective Care in Pregnancy and Childbirth*, and so I thought, ‘That’s what we will do: we

¹³⁰ See the Wellcome Trust Funding for Clinical Trials at www.wellcome.ac.uk/doc%5Fwtx022708.html (visited 5 August 2005). Chalmers (2005).

¹³¹ Hanney *et al.* (2005).

¹³² Chalmers (2000).

will go through all these trials, and come out with lots of guidelines.’ So I called a small group together – Marc Keirse, who was an obstetrician and an associate of Iain’s, now working in Australia, and a chap called Jim Thornton, my clinical partner – and we went through this whole dataset in a day. [From the floor: In a day?] Yes, in a day, a long day, I can tell you, but it was a day. I remember that it went on into the evening and Marc came round to our house for supper after. I thought we would have, say, 100 guidelines, as the book was very thick, but when we went through it, we could make only 21 ‘yes’ or ‘no’ statements. That really surprised me, as I had no idea it would be as few as that.

How many trials were there in those days? There would have been about 20 000 trials? [Chalmers: Three-and-a-half thousand.] From these 3500 trials, what do you get? Twenty-one guidelines that say categorically ‘do this’ or ‘do not do that’. Even some of these were not completely uncontentious. The one that worried me most was the ventouse.¹³³ In any account, most of the guidelines were based on very convincing evidence and these included the injunction to prescribe steroids in the case of premature labour. Anyway this was our yield, 21, and we showed them to a bemused council who approved dissemination. So it was that the guidelines were distributed to all the people practising obstetrics and gynaecology in the country, under the President’s signature.¹³⁴ Of course, as so often happens in life in our modern complex society, a number of other dissemination activities occurred at around this time. Liam Donaldson, who was then a regional director of public health, published a commentary in the *British Medical Journal* on the use of steroids, although, as we shall see, his was an eulogical study.¹³⁵ Then there was a publication from the British Association of Perinatal Medicine (BAPM), and in 1993 there were letters in the *Lancet*.¹³⁶ An NHS Management Executive letter, EL(93)115, was [also] dispatched in 1993.¹³⁷ There was an NIH consensus development conference

¹³³ An alternative to forceps delivery, where a traction cup is attached to the head of the fetus when delivery has not progressed sufficiently or the fetus is distressed. Negative pressure is applied through the suction tube fixed to the cup. When the baby’s head emerges, the cup is removed and the rest of the baby is delivered.

¹³⁴ Simmons (1992).

¹³⁵ Donaldson (1992).

¹³⁶ Joint Working Group of the BAPM and the Royal College of Physicians of London. (1992). See letters in the *Lancet* (1993) **341**: 172–4; Chalmers (1993b).

¹³⁷ NHS Executive Letter (1993). Appendix B, Development of audit measures and guidelines for good practice in the management of neonatal respiratory distress syndrome, cites BAPM and RCP (1992); BAPM and Neonatal Nurses Association (1992).

in 1994.¹³⁸ So there was quite a lot of buzz going on, and I didn't realize that my idea was so unoriginal until Edmund Hey made me aware of these other activities, but there again, that's life. We did disseminate our guidelines, and I rested myself content.¹³⁹ In fact we went on to produce further guidelines about communication in maternity services and organizational standards, but those were studiously ignored. With Lesley Page, Professor of Midwifery Practice at Queen Charlotte's Hospital, I then applied for a prize from BUPA, who give an annual prize to he or she who communicated best during the year.¹⁴⁰ We didn't get it, and the reason we didn't, again quite properly, was that all we had done was propagate these guidelines; we hadn't investigated what effect they had. So then I applied for a grant to do a study on the uptake of guidance with Jenny Hewison, Jim Thornton, Ian Watt, David Brauholtz and Michael Robinson. Edmund Hey also sent me a paper by a very nice man called Jack Sinclair, and in it he says,

Despite the evidence of efficacy and effectiveness of steroids in reducing RDS and death rates, the use by obstetricians of antenatal corticosteroids has remained low by many accounts.¹⁴¹

For example, in the Canadian multicentre trial of neonatal surfactant, it was found that many of the mothers had not had steroids. This was in the early 1990s.¹⁴² So the question was what happened after that – did the practice move on following dissemination of the guidelines and the other activities in the early 1990s? After all, if it wasn't necessary to have systematic reviews, if it wasn't necessary to put them into databases, and if it wasn't necessary to show that they

¹³⁸ National Institutes of Health (NIH) Consensus Statement (1994); NIH Consensus Development Panel (1995).

¹³⁹ The Royal College of Obstetricians and Gynaecologists (RCOG) *President's Newsletter* of December 1992 noted a single page of advice from the RCOG Scientific Advisory Committee that 'antenatal corticosteroid administration reduces the incidence of neonatal respiratory distress syndrome'. See Simmons (1992): 4–5. See also note 158. A series of national evidence-based guidelines funded by the Department of Health followed in 1996. For the current antenatal corticosteroid advice, see www.rcog.org.uk/index.asp?PageID=73&BookCategoryID=2&BookTypeID=5 (visited 30 June 2005). See also Mann (1999); Scottish Intercollegiate Guidelines Network (1999).

¹⁴⁰ For further discussion of maternal care, see Christie and Tansey (eds) (2001).

¹⁴¹ Sinclair (1995).

¹⁴² Long *et al.* (1991); Canadian Paediatric Society, Fetus and Newborn Committee (1992); Smyth *et al.* (1995); McMillan *et al.* (1995).

had societal endorsement, then why embark on all these activities? That was what our study was designed to find out. We took four guidelines: the ventouse, stitching up of the perineum using the correct materials, antenatal steroids, and antibiotics in preterm labour. Then we added one on the hoof, because during the course of the study, Lelia Duley and her colleagues published a spectacular trial – it must be *the* trial of the 1990s – which showed that magnesium was the optimum treatment for eclampsia.¹⁴³ So we quickly took the opportunity of observing the effect of this seminal publication. The results of the study have been published.¹⁴⁴ There is one thing to say about these results with particular reference to corticosteroids and that is this. Right from the start, we realized that simply looking at all mothers who had given preterm birth to see whether or not they had had corticosteroids, was not going to give the right information. This would produce a logical fallacy, because not all women who give birth prematurely would have had indicators for steroids. What we really needed to know was the proportion of women receiving or not receiving steroids (a) who were recognized to be in preterm labour; (b) in whom birth was not so imminent as to negate any possible benefit; and (c) in whom there were no contraindications.

The same situation arises in the audit of treatment of people with a heart attack. We know that one of the tenets of good care if you are having a heart attack is that you should be given aspirin and a clot-busting drug like streptokinase. Some studies have shown that only 50 per cent of people who had a heart attack received the clot-busting drug. But this gives a considerable underestimate of proper care, because the clot-busting drug can only be given for a short period of time after the onset of pain (a day or so). Furthermore, some people do not have clear evidence of heart attack on admission, such as raised ST segments on the ECG. The clot-busting drug can have some nasty side-effects (brain haemorrhage) and it is properly withheld in these cases. So you need to look at people who have presented with clear features of heart attack, not those coded as having had a heart attack.¹⁴⁵

We took a lot of trouble and your money to really make sure that the people who were judged not to have received antenatal steroids should have had them. What we showed in respect of all four guidelines was a massive change in the

¹⁴³ Collaborative Low-dose Aspirin Study in Pregnancy (CLASP) Collaborative Group (1994); Duley (1998).

¹⁴⁴ Wilson *et al.* (2002).

¹⁴⁵ For details of the streptokinase trials see Reynolds and Tansey (eds) (2005): 93–112.

uptake and if you have got a copy of the paper you can see it in the graphs:¹⁴⁶ a massive change in practice in line with the evidence over the period of study [1988–96]. So the notion that the doctors do not use the evidence is no longer true, there is massive change.

Now, is it perfect? No. With reference to steroids, for example, only 80 per cent of eligible women received the correct treatment, so there was a 20 per cent shortfall. On some of the other standards, it's more like 70 per cent compliance, so there is still work to be done. I am not saying everything is perfect. And indeed, when this result was published it was called in a newspaper, the *Observer* I think, 'a shameful result'. The result can be 'spun' either way. But one thing that it did show was the amount of change in line with the evidence.

Since I have titivated you, I will mention magnesium as well. Within a year of the publication of Lelia Duley's study, magnesium use improved from zero to 80 per cent of women in this country. That was without any guidelines. But it was a particularly powerful study.¹⁴⁷

I have one last thought to leave with you. The whole notion of diffusion of information into a community of experts is one that has been studied for a long time. I understand that it started with two sociologists, Ryan and Gross, who were looking at the uptake of effective agriculture practice among farmers back in the 1930s.¹⁴⁸ Later a man called Everett Rogers analysed the original 'diffusion curve' in terms of communications theory, showing that some people are very avant-garde and adopt a new method right away, some are in the middle ground, and then a few laggards, who are very slow to take it up.¹⁴⁹ Now, you can think of that in two ways: one is in terms of a particular technology. Are the farmers using the latest and best fertilizer? Are the obstetricians using the latest treatment for a particular condition? That's one way to track the diffusion of a specific technology. But, of course, underneath all that lies an epistemological issue: what is perceived by the society of experts, the society of farmers, or the society of obstetricians, as constituting authoritative knowledge? What I believe, and we can discuss this later if you wish, is that not only have

¹⁴⁶ Wilson *et al.* (2002). See Figures 1–4 on page 178, which were distributed at the meeting.

¹⁴⁷ Collaborative Low-dose Aspirin Study in Pregnancy (CLASP) Collaborative Group (1994); Duley (1998).

¹⁴⁸ Ryan and Gross (1943).

¹⁴⁹ Rogers (1962).

obstetricians adopted these particular technologies, but they have also adopted the very idea of evidence-based practice. Not only have specialists taken on the idea of particular treatments – clot-busting drugs in cardiology or antenatal steroids in obstetrics – but they also have taken on the idea that practice should change in line with the evidence. So the notion of evidence-based practice has also been ‘sold’. Throughout my professional career there has been a sea change in that respect, so I don’t think we need to be quite so pessimistic in the future as we have been in the past about the uptake of new practice. That is the first part of my last point.

The second part is that not only has there been a change in the hearts and minds of practitioners, but there has also been a change, in a societal sense, in how we organize ourselves to receive new evidence. Back in the 1970s and 1980s many trials were done, and the whole idea of doing trials had to be sold. Those ideas were coming, but what we didn’t have was a method, a societal method, to assimilate the results of the trials. Trials would be done and that would be that. No one knew what to do with the results. How do you react to these trials? When is trial evidence sufficient for a guideline to be developed? So what I did back in those early days of 1992 was to start to provide some kind of societal mechanism to pick up the results of research. It’s not surprising that it took us a while to learn how to do this, and, of course, that’s now been formalized much more, some would say too much, with organizations such as the National Institute for Clinical Excellence (NICE) and its equivalents in other parts of the world.¹⁵⁰

Williams: For practising clinicians a new accelerating factor is the Clinical Negligence Scheme for Trusts (CNST), which gives a discount in your insurance for a hospital if you are following evidence-based guidelines and can show that you have these in place. To actually achieve CNST grade-1 status, you have to jump through a lot of hoops and it’s all about practising evidence-based guidelines.¹⁵¹ I think that’s a new accelerating factor in the application of research into practice.¹⁵²

¹⁵⁰ NICE was established in 1999 to give guidance on the use of new and existing medicines and treatments; the appropriate treatment and care of people with specific diseases and conditions; whether interventional procedures used for diagnosis or treatment are safe enough and work well enough for routine use. From April 2005 it joined with the Health Development Agency to become the National Institute for Health and Clinical Excellence, still known as NICE. See www.nice.org.uk/ (visited 29 June 2005).

¹⁵¹ For further details of the scheme, see www.nhs.uk/Claims/Schemes/CNST/ (visited 5 August 2005).

¹⁵² For a review of this field, see Hicks and Mant (1997). See also Mant *et al.* (1999).

Gabbay: I like Richard's analysis at the end, but when you talked about the epistemological change I thought you were going to say something slightly different, which I would think is the case and that is that what people count as evidence and what we as researchers and members of the Cochrane Collaboration might wish to count as evidence may not be the same thing. I was very struck by the wonderful vignette earlier on from our colleagues in Wales, John [Williams] and Roger [Verrier Jones], when they were faced with the dilemma of whether to move to using steroids or not. What seemed to sway things in the first case that Roger described was a very unscientific retrospective analysis of a case series, which was done locally and which was quite persuasive, and John was saying that it was probably as persuasive as the trials and systematic reviews that we as researchers would wish people to use.¹⁵³ So I just wanted to add to Richard's analysis that it's also a shift in what people count as legitimate evidence and the kind of mechanism that John has just described, where it has to be scientifically based evidence in order to get your points and get more money or whatever it is you are after.

Maybe part of the mechanism we need is to shift people's views of what evidence is, because in the work I have been doing, watching clinicians using evidence, stories, anecdotes, personal experience, and of course what the great and the good around you are saying – local opinion leaders – counts at least as much as what we, as rational scientists, would like them to use as evidence.¹⁵⁴ I would like to hear more about that interaction between different forms of evidence in people's minds as they develop their policies.

Mugford: I have an anecdote to add to John's point, to strengthen it. When James Piercy and I went to the Department of Obstetrics in Oxford, at the end of his dissertation period, to present our economic modelling, Professor Alec Turnbull was in the audience. He was very gracious and kind and very gentle with us as young researchers, but at the end of all the questions from midwives and neonatal nurses and house officers, he stood up and said but of course this is all – I cannot remember his exact words, and I won't even try – but he very gently poured a lot of cold water on it, because we hadn't taken account of the effect on women, and the increase in risk of infection in women. And so I bowed to his authority, I couldn't deny it, but I said as far as I knew the systematic review had not shown any effect in that respect, but I wasn't confident enough. So my

¹⁵³ See page 64 for a comment on the use of steroids at St David's Hospital.

¹⁵⁴ Gabbay and le May (2004).

feeling was that the general mood of the audience at the end was that what we had done had been a bit of a waste of time.

Chalmers: Alec Turnbull was Professor of Obstetrics and Gynaecology in Oxford at the time. He was also one of the people looking at the maternal mortality experiences for the reports on *Confidential Enquiries into Maternal Deaths*.¹⁵⁵ I know that he was very influenced by a particular case, a woman who had died of septicaemia, who had received corticosteroids, and I think that was the basis for his opposition. If you have seen someone have a haemorrhagic stroke after you have given streptokinase,¹⁵⁶ it makes it far more difficult to say that this is a policy that we should adopt, because you actually don't know which of your patients would have died if you hadn't given it to them.

Just to clarify the experience in St David's Hospital in Cardiff, because John Gabbay misunderstood what had happened: they had adopted steroids on the basis of the trials. The unpublished analysis that Roger Verrier Jones did was a retrospective assessment.¹⁵⁷ The staff at St David's had taken up steroids to a greater extent than the University Hospital of Wales, based on the Liggins and Howie trial.

Hayward: I wonder whether it might be useful to describe briefly an intervention that I led over a two-year period, which was partly triggered by Richard's list of suggested effective interventions that should be used for prospective audit by obstetricians under the banner of the RCOG.¹⁵⁸ I am Director of Public Health in Newham, but I am here because in 1994 I was a public health specialist in training at Camden and Islington Health Authority. I have also known Iain [Chalmers] for years, because I married his sister.

It took me ten years to get a grip on what Iain had been going on about evidence-based treatment. But there's nothing like a convert late in life to become a passionate advocate, and this made me very interested to know why other people were having equivalent problems. A number of things happened to coincide, as is usually the way when you start an initiative, and someone who had seen the draft of those clinical audit suggestions was on the Maternity

¹⁵⁵ See, for example, Department of Health and Social Security (DHSS) (1986).

¹⁵⁶ For a discussion of the streptokinase trials, see Reynolds and Tansey (eds) (2005): Appendix 3, 93–112.

¹⁵⁷ See Tables 3–4 on page 35.

¹⁵⁸ Royal College of Obstetricians and Gynaecologists, Scientific Advisory Committee (1992).

Services Liaison Committee (MSLC) for Camden and Islington that covered three maternity units – the Whittington, the Royal Free and University College Hospital (UCH), just round the corner here. We hatched an idea over a beer in one of the local pubs that it would be interesting to look at four of those interventions,¹⁵⁹ and to take them around three units, using the Camden and Islington MSLC. What made it uniquely different was that there would be women, the users of services, involved and at the centre of the work. Out of that a two-year project emerged called the Effective Care Project, subsequently published in *Quality of Health Care* in 1997.¹⁶⁰ My guess is that nobody will have read it, and it certainly isn't on Richard's reference list. Like most of these things, it didn't get into the *British Medical Journal* either. It was advocated as an example of good practice for MSLCs nationally, but my guess is that very few of them have been able to do what we did, because we had an unusually committed bunch of users who were really passionate to get into it, and we also had three units to deal with. Most MSLCs only deal with one. It's much easier to deal with three, because you can compare your information automatically.

What we did was to visit each of the units, asking them to share with us their policies on these four interventions, giving them an advance section of what was later going to be the *Cochrane Library*, but in those days was the *Cochrane Pregnancy and Childbirth Database*, and we still referred to ECPC – *Effective Care in Pregnancy and Childbirth*.¹⁶¹ All our users had already received the users' copies, I may say.

We took the evidence that was in the actual trials, and made certain that every unit had them so they knew what information we were using. We used the blobograms, and it's nice to see four different varieties of those blobograms from Patricia Crowley's original work.¹⁶² I remember ringing Patricia in Dublin at the beginning of this project and she was extremely helpful. We reserved the right that we might ask a statistician to help us resolve complex issues about odds ratios or whatever, but we never needed one. The women understood it instinctively, because blobograms graphically are so striking. You immediately

¹⁵⁹ The four interventions were: use of steroids prior to likely preterm delivery; prophylactic antibiotics for caesarean section; management of perineal repair; and external cephalic version (ECV) for breech presentation at term. See description on page 60.

¹⁶⁰ Berrow *et al.* (1997).

¹⁶¹ See note 52.

¹⁶² See Figure 4 on page 28.

see the effect size, and the size of the wings on the aircraft, as it were, give you an idea of the confidence level, about the precision of the results. They understood that instantly. [See Figure 4.]

So we went round with the four interventions – steroids, suture materials, antibiotics for caesarean section and the fourth one – one you didn't mention, Richard [Lilford], the difficult one – ECV for breech presentation near term.¹⁶³ We did steroids first, because we knew that they were all supposed to be using them, and ECV last, because we knew they certainly weren't and the other two interventions were in between. The main thing that emerged from the study in relation to steroids is that everybody was 'signed up' to using them – the guidelines in the three units were not quite the same but they had never shared them before, so we shared them. What was not transparent was the eligibility and exclusion criteria, the crunch to determining how many actually got steroids and when. What they had not done was a prospective audit, and they had not shared it with the MSLC, and they undertook to do that. Eventually a prospective audit was reported to the MSLC from three different maternity units on their use of steroids. It was, again, between 80 and 90 per cent, broadly. That had never been done before. I suspect it's not been done since, but my goodness it didn't half concentrate the minds of the clinicians in the room. The women asked laser-like questions, such as, 'Why aren't your figures as good as "St Elsewhere's?"' – not very easy to answer, but really important questions.

We ran into less trouble with steroids than we did with the others and I want to say that we did persuade one hospital to introduce vicryl for the midwives to repair the perineum, whereas otherwise only the doctors had been given these expensive sutures.¹⁶⁴ That was a dramatic change. One hospital that used antibiotics for caesarean section had realized, of course, that it's the anaesthetist who tended to give it, but when the anaesthetists had audited it, actually only 60 or 70 per cent of women who should have been getting antibiotics actually were. That was changed. And, the most difficult thing was ECV, where the baby is breech presented, and there's an opportunity to turn the baby round *in utero* before labour, provided it is done close to term, with an operating theatre

¹⁶³ See discussion on page 48.

¹⁶⁴ A polyglactic-acid suture. Christine Kettle, a midwife at North Staffordshire NHS Trust, Stoke-on-Trent, conducted a randomized trial comparing suture materials by following up the treatment of 1500 women over 12 months. Vicryl Rapide, a quickly absorbed synthetic thread, was the most effective. Kettle *et al.* (2002). See also Kettle and Johanson (2000).

available and consent for an emergency section obtained. You can, if necessary, bail out by doing an emergency section if anything goes wrong.

What we discovered were the main barriers for these interventions. Steroids had few major barriers, just bits of detail. Suture was a misunderstanding about cost and appropriateness. Antibiotics were restricted by lack of an audit done by the right people. But ECV was different. The main barrier here was fear of death of baby or mother. I remember as a medical student having seen an ECV done in the antenatal clinic and every so often there would be cord entanglements, or placenta abruptions, haemorrhages and disasters. When we got into the meetings, one Camden and Islington unit was using ECV regularly and felt that everybody should do so. One used it intermittently and the third, somewhere near Hampstead, was not using it at all, except a few junior doctors who had tried to introduce it and had been told that they were not to use it because it was dangerous. We had the following sorts of discussions: the clinicians would say, 'It's a dangerous procedure, there's no evidence to support its effectiveness, except the trials that have been published in South Africa'. We would answer that there were trials from Zimbabwe and California, Denmark, and Holland, and plonk the evidence on the table. 'Oh, it doesn't apply to us', they said, 'and anyway our women's pelvises are different. ECV is easier in South Africa and doesn't apply to our case mix.' Excuse me, we are in London. But what emerged after this hostility was actually that they had all experienced a death or near miss, and that was the barrier to implementation.

Apart from power, I think that vested interests, empire-building and struggles and political competition between trusts were barriers – this was the time of the purchaser–provider split and market competition was a really important issue around 1995/6. The main barrier was fear of something going horrendously wrong. People would then distort their perception of the evidence and vigorously resist being told to do something that they didn't think was safe to do, regardless of the evidence. After about six months the staff went through a series of educational events at this particular hospital and eventually decided to start to introduce ECV and as far as I know it is now common policy. But we couldn't make them do it, they had to decide to do it themselves, and they had to take their clinicians with them. I think it was a painful and difficult process for them.

May I just mention the main conclusions from this particular piece of work? Don't expect to get this sort of study into the *British Medical Journal*. It won't be

accepted.¹⁶⁵ Secondly, advocates are really important when it comes to getting guidelines adopted and I think opinion leaders are really important within institutions, but the important thing is that the guidelines have got to be written in such a way as to be usable, understandable and accessible to those who are going to implement them. That means clear inclusion and exclusion criteria. Another important agent for change is the users, and if you have women asking these sorts of questions, after a while people do get a bit embarrassed coming up with the same answers that clearly won't be supported by evidence or by colleagues. I would like to see women users being far more involved in ways in which we can encourage the implementation of best practice. I am not surprised that there was no sign of managers actually implementing any change in Richard [Lilford]'s study. It's a scary business. There was blood all over the carpet when we were dealing with the ECV meetings, and it required somebody – like the users who were tough, or somebody like me who's a public health specialist and who has been a GP and is not afraid of consultants – to hold the line if necessary. Managers cannot do that, and I don't think we should expect them to. I think it's exceedingly difficult. The most important barrier, the most important influence to achieve change, is the personal experience of the person making the clinical decision. When new interventions are being rolled out we must encourage people to be at the centre of it, so they get feedback of the positive results. Then it is much easier to get change implemented.

Hey: That rings true for a lot of us, I think, you said something very important. Harold [Gamsu], while you were out of the room we did hear that quite a lot of units said that they couldn't join your trial, because they were already using it so widely, at a time when we know that in most maternity units in the UK less than 10 per cent of the mothers meriting steroid treatment were getting it.¹⁶⁶ Did being involved in the trials themselves influence the centres? Did the centres that had been involved in the research take up the outcome of that research more than those who only read about it?

Gamsu: I don't know the answer to that, I am afraid. We didn't follow that point up, but Brenda Mullinger might know something about it. All I can say is that there were local reasons that indicated against the use of steroids. There was quite a lot of gossip about this and we have heard some examples of this today:

¹⁶⁵ Dr John Hayward wrote: 'It was rejected by *BMJ* (submitted as a short report) and not submitted to the *Lancet*. A longer version was published by *Quality in Health Care* [Berrow *et al.* (1997)].' E-mail to Mrs Lois Reynolds, 21 October 2005.

¹⁶⁶ Khanna and Richmond (1993).

the risk of infection, especially in ruptured membranes, and the unexplained deaths in hypertensive women from Liggins' original report, which turned out to be spurious.

The other thing that I found that was influencing obstetricians was the increased risk of pulmonary oedema, which people widely accepted as a complication of steroid therapy. In fact, it was a complication of tocolytic agents that were used, especially when those agents were given in large volumes of fluid. As far as I know, steroids given alone were not tocolytic agents and did not result in pulmonary oedema. So I think we had quite a lot of persuading to do, even in those places that accepted that they would be in the trial. I know that Brenda Mullinger and Clive Dash from Glaxo had a lot of difficulty keeping the momentum up, trying to persuade centres to recruit women, even though investigators had agreed to participate in the trial and had obtained ethics committee approval. As you possibly remember from the paper, 60 per cent of the cases came from patients who were recruited from three hospitals, the rest of the centres just put it [the request] away.¹⁶⁷

Hanney: We at Brunel have been looking at the benefits from health research for about ten years now, and this particular stream of work seems to us to have been one of the most interesting that I have worked on with Miranda, Martin Buxton and Jonathan Grant. I apologize for checking my notes from time to time, because I am trying to pick up what various people have said today in what I think is an interesting session.

For instance, John [Hayward], we at least read your work. There is a paper that sets out most of this in detail in press and will be published in *Social Science and Medicine*.¹⁶⁸ I will just highlight all the key points for now. Perhaps it's just worth spending a minute going over our payback framework so you can see how we tried to drop this stream of work into a framework that we had already developed. Apologies to those who have already heard this many times before. Basically, there are two aspects to our payback framework: a multidimensional categorization of benefits, and a model to examine how they arrive. The categories that we suggest are five: knowledge production; the targeting of future research and building research capacity; better informing policies, with the term 'policies' being widely interpreted; health gain and benefits to the health sector;

¹⁶⁷ Gamsu *et al.* (1989).

¹⁶⁸ Hanney *et al.* (2005).

and the broad economic benefits. There's a series of stages in the model in which we think these various benefits can be identified. A key feature of our model is to attempt to identify actual levels of uptake so that we can then say what the benefit has been, and this, of course, links with previous discussions.

There's always a problem when doing this type of analysis as to where you start. Various initial presentations today showed clearly that research builds on previous research etc., and so whenever one chooses a starting point, it is always artificial. On the other hand, I do think the nature of the discussions today, and what Mary Ellen [Avery] says, has provided a realistic basis for saying we will start by looking at the work of Liggins and Howie. In terms of knowledge production, clearly the 1969 paper from Liggins, and the 1972 paper from Liggins and Howie, were very important.¹⁶⁹ There are lots of weaknesses in citation analysis, but it does indicate whether people have taken notice, and these are two very highly cited papers, especially the 1972 paper which has been cited over 1200 times.¹⁷⁰

There has been some bibliometric analysis in this field undertaken by the Policy Unit here at the Wellcome Trust.¹⁷¹ Various generations of papers were traced backwards and showed again that this was the most important work in this field in several generations. Clearly knowledge production is very high. In terms of affecting future research, again citations indicate that it has influenced much subsequent work. It's also interesting that many of the other pieces of work, trials etc., actually start with a reference to the work of Liggins and Howie, which again I think emphasizes their importance for further work. And it's also been mentioned that Ross Howie felt that further trials should be undertaken rather than necessarily saying that people should act on the findings. Nevertheless, there was quite an uptake in some places, on the basis of this very important trial and the ensuing publications from it. In the UK the figures in the 1980s are somewhat unclear, but it was definitely higher in Australia and New Zealand.

¹⁶⁹ Liggins (1969); Liggins and Howie (1972).

¹⁷⁰ Dr Stephen Hanney wrote: 'The article pre-dated the start of the electronic record of citations, therefore I calculated this figure from the post-1981 electronic data plus hard copies of ISI data from earlier years [Hanney *et al.* (2005)]. Mont Liggins had an article in the *Citation Classics* series in March 1982 and by then the number of citations for the 1972 paper was already 565.' Note on draft transcript, 12 July 2005. See Mont Liggins' article of 29 March 1982 freely available at www.garfield.library.upenn.edu/classics1982/A1982NF37800001.pdf (visited 14 June 2005).

¹⁷¹ Grant *et al.* (2003).

By the early 1990s there seemed to be this consensus that the take-up rate in the UK was between perhaps 10 and 20 per cent, and Miranda's analysis shows that at a 20 per cent take-up level it could be said to lead to at least 150 deaths annually being averted in England and Wales. So it is clear that even in the 1970s and 1980s there were substantial health gains, primarily from the Liggins and Howie work with the other trials providing a bit more evidence. Not only were deaths avoided and less morbidity due to the reduced incidence of RDS, but also there were the cost savings, even if these were in terms of more resources being available to treat other babies.

Richard [Lilford] raised the interesting analysis from Rogers' work on the diffusion of innovations.¹⁷² From the analysis that I have, I agree with you that, on the whole, the profession is much more receptive now. One of the things that Everett Rogers did say was that often when an innovation gets to between 10 and 20 per cent uptake, in fact diffusion becomes almost impossible to stop, it tends to escalate.¹⁷³ What I find interesting in this case is that it is clear that the bottom level of where take-off should be impossible to stop, was achieved and then it just didn't take off for quite a long time. There was stalling at exactly the point when Rogers suggested that usually there would be this take-off. So what was it that gave it the nudge to start going again? This is where the systematic review comes in as being very important. It was published in 1989/90, we have heard, and perhaps particular attention was focused on this systematic review for several reasons.¹⁷⁴ The link, as explained earlier with the logo of the Cochrane Collaboration and Miranda's subsequent cost-effectiveness studies, showed that this was one of the few areas where there had been economic cost savings as well as health gains.

A few years later there were several policy statements advocating the use, in the form of clinical guidelines from professional bodies and, as is said in the paper,¹⁷⁵ these did cite the systematic review, again emphasizing the importance of this particular review.¹⁷⁶ I hadn't realized until he spoke quite how explicitly Richard

¹⁷² Rogers (1962, 1995).

¹⁷³ Hanney *et al.* (2005): 938. For details of the S-shaped curve of diffusion of innovation, see Rogers (1995): 259.

¹⁷⁴ Crowley *et al.* (1990).

¹⁷⁵ Hanney *et al.* (2005).

¹⁷⁶ Joint Working Group of the British Association of Perinatal Medicine and the Research Unit of the Royal College of Physicians (1992); Royal College of Obstetricians and Gynaecologists, Scientific Advisory Committee (1992).

[Lilford] looked through systematic reviews to produce the clinical guideline on that, and clearly the systematic review there influenced the policy guidelines. There were also these important implementation initiatives. There's one that's been mentioned. All these factors seem to have resulted in quite a dramatic increase in uptake during the 1990s. There's the figures from your study, Richard, and figures in 1997, from your survey, Peter [Brocklehurst],¹⁷⁷ which show a very large uptake by the end of the 1990s. Miranda's analysis suggested that with 75 per cent uptake there would be more than 400 deaths averted annually in England and Wales. So clearly, there has been quite a big health gain. The problem though, as has already been mentioned, without putting a precise figure on this, is that with the use of surfactant and the improvement of the neonatal care, it is not clear of course that all these deaths would have actually happened if there hadn't been the use of steroids. But nevertheless, as has been said, there is also evidence that even if some of them would never have happened, surfactant wouldn't have stopped all of them. What I think is unclear, is whether there is an actual measure of how many. So, definitely, this has had substantial health gain as well as impact on policy, knowledge gain, impact on further research.

Mention has been made of the US NIH consensus conference.¹⁷⁸ This was broadly endorsed by the American College of Obstetricians and Gynecologists and it is claimed that this consensus statement had more impact than most of them.¹⁷⁹ An implementation project found that after a year of passive dissemination, implementation of the guidelines went up to 58 per cent, which is quite substantial.¹⁸⁰ But following active dissemination it went up from 33 to 68 per cent. So it does seem that there are many elements of this whole stream of research that have produced benefits. Perhaps the key thing from our work on this stream of research that is different from some other perspectives in the debate about research utilization, is that our work has been concentrated on showing that benefits have been achieved even when the uptake level has been less than optimum.

¹⁷⁷ Brocklehurst *et al.* (1999).

¹⁷⁸ National Institutes of Health (NIH) (1994).

¹⁷⁹ American College of Obstetricians and Gynecologists, Committee on Obstetric Practice (1995, 1999).

¹⁸⁰ Leviton *et al.* (1999).

Hey: It was nice to hear from somebody totally outside the field, an outsider looking in on us. We hear many of the same themes coming up, so perhaps it might be true. Perhaps we ought to say that there are more benefits than just preventing death and respiratory distress. Shall we remind the rest of the audience of the other outcomes that you get from giving steroids that you don't from giving surfactants?

Crowley: Probably a very important one is the reduction in the risk of intraventricular haemorrhage (IVH) and that's a particular benefit for the most premature babies. Also a reduced number of days on mechanical ventilation for babies who do get RDS.

Harding: The new systematic review will also suggest benefits in terms of childhood developmental outcome.

Chalmers: We keep on talking about benefits in terms of the baby, but what about the parents? The reduced exposure to the terrible courses that babies would go through before death, and indeed before surviving – and the accompanying anxiety – those things haven't been made explicit. We had hoped that there would be a woman here who had received prenatal corticosteroids. I was impressed by Barbara Stocking, now Director of Oxfam GB, saying that in her first pregnancy she had delivered prematurely and her son went through a really rough time.¹⁸¹ After she read Patricia's systematic review before her second pregnancy, she insisted that she should have steroids if she went into preterm labour again. She became a big advocate of prenatal steroids when she was a senior manager in the NHS. I have come across more than one mother – maybe Gill Gyte can enlighten us here – who has lobbied to have this. Obviously, as parents, they think this is important, because they are worried about their children. But possibly also so that they have less to worry about themselves.

Gyte: I don't have any personal experience of antenatal classes, but I do know that the National Childbirth Trust (NCT) does lobby to implement evidence-based care.

¹⁸¹ Ms Barbara Stocking wrote: 'Iain nicely cites my story in the seminar but it isn't quite right. I still consider it a real blessing (a) that I knew the evidence at the time of my first pregnancy and (b) I had an obstetrician who knew it too and was committed to being at the forefront of best practice. The neonatal intensive care/special care period was hard, but infinitely better than Andrew, my son, never had to be artificially ventilated, plus, I guess, had fewer IVHs [intraventricular haemorrhages], hence [his] ending up healthy and bright (now at Cambridge doing economics). It's true I'd have asked for it second time around too. Fortunately, I didn't have to due to three months enforced lying down. Very good for me (in retrospect!).' E-mail to Mrs Lois Reynolds, 7 September 2005.

Oakley: This is slightly beside the point, or perhaps not, because I think this issue of the role of the users of health services and the extent to which they are demanding evidence is a very important one and it's something that we need to know more about. But, of course, one of the problems with that, or one of the issues in that area, is that first of all the user needs to be dissuaded from the belief that experts know what they are doing.

I remember one of the early projects that I worked on in 1974 involved an observational study of an antenatal clinic at a hospital in London that, of course, has got to be nameless, and I hung around this clinic for about a year observing what the doctors were doing. I was absolutely astonished. In my second week, there was a changeover in junior doctors, and two of them came to me and they asked me what Consultant X would recommend in a particular case, because they didn't know what they were supposed to be doing because they hadn't met their consultant yet. I didn't realize that the eight different consultants who ran this clinic all had different policies. I was learning what those policies were and then I was passing on this information to the junior members of their team, so that they could also practise non-evidence-based medicine. That was a long time ago, but I think it is still the case that many people believe that doctors and other experts know what they are doing.

Another issue in all of this is about the epistemological shift in society's understanding that experts, including those in other fields, often don't engage in evidence-based practice. I spend a lot of my time at the moment with professors of education who don't believe in systematic reviews of the evidence. This is about the role of the expert, and the relationship between research, evidence and policy across a lot of different sectors.

Crowley: As an obstetric senior registrar in 1985, I took over the care of a woman who was having an antepartum haemorrhage at 37 weeks' gestation. We thought she was 37 weeks because of an error in estimating the dates made earlier in the pregnancy. Because of continuing antepartum haemorrhage I induced labour following consultation with a supervising consultant. She had not had antenatal steroids. She was, in fact, only 33 weeks' gestation and the baby went on to develop severe RDS and after prolonged ventilation survived with severe cerebral palsy. His mother sued the hospital, my consultant colleague and myself. The patient was awarded €4 million compensation in an out-of-court settlement in 2003 because I had failed to give her antenatal steroids. The decision by the protection society and the legal team was that whereas other obstetricians might be able to defend themselves against not giving antenatal

steroids in 1985, the papers I had published demonstrating the evidence in favour of antenatal steroids prior to 1985 rendered my failure to prescribe antenatal steroids indefensible. So a very disabled 20-year-old man and his parents have suffered a lot as a result. This medico–legal event contributed a further chapter to my 30-year personal involvement with the antenatal steroid story.

Hey: One of the good things that came out of the book, *Effective Care in Pregnancy and Childbirth*, was a version which has been widely read by parents, wasn't it?¹⁸² Not many other branches of medicine have pursued it through to that point yet, have they?

Mugford: Following on from Patricia's story and also what I said earlier, that the impacts on the economic side that we measured were purely the health services facts. Many economic studies are just cost-effectiveness analyses from the point of view of the health service for the efficient running of the health services. But the impact on family is terrific and there's a long-term impact of children with disabling chronic lung disease.¹⁸³ We did a study in the NPEU with another York MSc student, Birgitta Rudbecke, who looked at the cost of babies going home on oxygen. And it was terrific. Parents gave up their whole careers to look after their children. If we redid the steroid analysis taking account of family and household impact it would just emphasize the same answer, it's even more of a 'win-win'. We don't really need to do the study, but sometimes you have to do the study to have the impact.

Hey: I think I am going to move on, because we are almost finished. We have started preening ourselves, we have done something good, and we have now rolled it out, and it's happening, so perhaps Peter Brocklehurst might remind us that some of the questions posed 30 years ago are still not answered.

Brocklehurst: I am conscious that I have been asked to speak about current research and where the research gaps are in a session about twentieth-century medicine. So we are already a bit beyond the twentieth century in terms of what I intend to discuss, although hopefully in a few years time this will be history and you can tell me that I was completely wrong in guessing where we were

¹⁸² Dr Edmund Hey wrote: 'The first edition of *A Guide to Effective Care in Pregnancy and Childbirth* was published in 1989 [Enkin *et al.* (1989)]. There have been two further editions, each with varying editorial panels, the most recent having appeared in 2000. The book provides a synoptic summary in non-technical language of the many systematic reviews that first appeared in the two-volume book also published in 1989 [Chalmers *et al.* (1989)].' Note on draft transcript, 27 August 2005.

¹⁸³ Hallam *et al.* (1996).

going to go. I want to talk about some of the issues that have come up today in terms of how we are now looking at the evidence that we have and what is beginning to come out. I am going to discuss the issue of the use of multiple courses of steroids, but there are a couple of other issues that I wanted to touch on which have been brought up this afternoon, one of which is the choice of agent that we use for antenatal corticosteroids.

A very interesting paper has been published in the *American Journal of Obstetrics and Gynecology* by Alan Jobe and Roger Soll,¹⁸⁴ which looked at the available trials and separated them into those that have used dexamethasone and those that have used betamethasone. The interesting thing is there have been no head-to-head comparisons of dexamethasone versus betamethasone, which have looked at substantive neonatal outcomes.¹⁸⁵ There have been trials that looked at antenatal fetal heart rate, which seem to be irrelevant if they are not related to the outcome for the baby.¹⁸⁶ Jobe and Soll suggest that betamethasone is preferable to dexamethasone, because the betamethasone trials, compared with placebo, have a marked reduction in the incidence of death, and RDS, while dexamethasone has no statistically significant effects on neonatal death. Although one of the things they report is that the number of trials using betamethasone is substantially larger than the number of trials using dexamethasone, and the numbers of participants in each trial of betamethasone are larger. However, they have suggested some biological plausibility for this, and I am sure we are going to see a lot more about what agent we should be using. One of the issues that they

¹⁸⁴ Jobe and Soll (2004). Dr Ross Howie wrote: 'I wonder how much of the apparent difference between the two drugs in effect on mortality may have been due to differing standards of newborn intensive care at the times and places the trials were carried out.' E-mail to Mrs Lois Reynolds, 25 September 2005. See also Appendix 2, page 89, paragraphs 3–4.

¹⁸⁵ Dr Clive Dash wrote: 'Various preparations of betamethasone are available in different countries. The preparations are all designed to release the active sterol, betamethasone, but at different rates. The soluble phosphate preparation is suitable for intravenous administration, like hydrocortisone, as well as intramuscular injection. The acetate preparation is not suitable for intravenous (IV) use. Some products are a mixture of the acetate and phosphate derivatives (e.g. *Celestone*®, Schering). In some countries dexamethasone is more readily available than betamethasone and this is why it has featured in some studies. These two steroids are isomers in which the methyl group differs in its orientation (dexamethasone is 9- α -fluoro 16- α methyl prednisolone; betamethasone is 9- α -fluoro 16- β methyl prednisolone)[Sweetman (2002): 1063 and 1067]. In the usual pharmacological tests of corticosteroid potency, they are equivalent. In general, the mode of action (pharmacodynamics) seems similar, so they should be therapeutically equivalent.' E-mail to Dr Daphne Christie, 10 January 2005

¹⁸⁶ See for example, Senat *et al.* (1998); Subtil *et al.* (2003).

raised is the availability of the drug, because no drug companies hold a licence for steroids for antenatal indications. The ability to get hold of dexamethasone and betamethasone in the US is becoming more and more difficult, because no company is producing it, because it doesn't have a licence. So people are using all sorts of other steroids, some of which clearly do not cross the placental barrier and may not be effective at all. They also raise issues about whether oral steroids may be as good as intramuscular steroids and also discuss different ways of giving steroids to the baby, whether you can give it into the intra-amniotic fluid, or give it directly intramuscularly into the fetal thigh, which seems a little bit more invasive than a quick intramuscular injection into the mother's thigh. I suspect we are going to see a lot more about the choice of the agent in the future.

We have heard a lot about long-term follow-up after a single dose of antenatal steroids and the 30-year follow-up of the original Liggins and Howie trial will be extremely useful. I think we probably need to do more follow-up, much longer-term follow-up of the other trials that have been done to try to strengthen the evidence base on the long-term effects, if only to be reassured that there are no adverse effects, even though the death rate has decreased and therefore one might expect a worse outcome in the steroid arm.

Another issue is the one of twins and there is an ongoing debate about what you should do with twins and higher-order births. I was very interested when I saw the title of a paper in the *American Journal of Obstetrics and Gynecology* in 2002, looking at twins.¹⁸⁷ Unfortunately it was comparing prophylactic multiple doses of steroids with a single course of 'rescue' steroids when the women presented in preterm labour and which showed no difference. But it certainly didn't elucidate whether the dose that they were using was appropriate or whether it was benefiting twins. Studies of individual patient data meta-analysis of the existing trials may well take us forward on that issue, if we can ever get the data or the money to do it.

Finally, I want to touch briefly on the issue of repeated doses of antenatal steroids that has been brought up time and time again today. I think here there are lessons to be learnt. As Patricia [Crowley] said, within a very short space of time of our beginning to use steroids, we were liberally splashing them around and giving them to everybody we possibly could, often on a weekly basis, to

¹⁸⁷ Murphy *et al.* (2002).

the point where we were giving prophylactic steroids weekly to twins from 20 weeks. Certainly, lots of clinicians were giving it to their triplets weekly from 20 weeks, until they got to 34 weeks or when the risk of preterm delivery was no longer thought to be present. Because of this a great deal of effort went into designing a number of trials around the world to compare a single course of steroids and multiple courses of steroids to look at the outcome for the baby. When we originally thought about this, following our survey of practice in 1997, there were five trials designed that would have added up to a total of 10 000 women randomized.¹⁸⁸ Five trials around the world, one of which we have already heard about in Australia, two in the US, one in Canada and one in the UK, and in Europe, which I was going to be leading from the NPEU.¹⁸⁹

I want to update you briefly on where those trials are, because I think it is crucial in telling us whether we will ever get an answer to the single course or multiple course of steroids debate. Ours was the largest of those trials, the Trial of the Effects of Antenatal Multiple courses of Steroids (TEAMS) trial, which was going to include 4000 women and would have measured the primary outcome at age two.¹⁹⁰ We did undertake a pilot trial, but unfortunately we went to the MRC at the time when the MRC had no money – you may remember that event – so despite achieving the highest grade that we could possibly get for the quality of our trial, there was no money to fund it. That trial would almost have been finished now if we had got the funding. The Canadian trial, which aimed to recruit over 1900, is still recruiting. It was due to finish several years ago, but has currently enrolled 900 women. I don't know whether it will ever get to 1900 because it might take as long again to reach the target. The Australian trial is getting close to the 980 it wanted to recruit, although 980 is

¹⁸⁸ Brocklehurst *et al.* (1999).

¹⁸⁹ Dr Peter Brocklehurst wrote: 'Unfortunately I can find no reference to these trials in any of the literature. They are not included in our website and the transcript of this meeting may be the only place where they are explicitly referred to in such detail.' Letter to Mrs Lois Reynolds, 23 August 2005.

¹⁹⁰ The Trial of the Effects of Antenatal Multiple courses of Steroids versus a single course (TEAMS) study was designed to test whether the administration of more than one course of steroids to those at risk of preterm labour (PTL) does or does not reduce perinatal death, respiratory distress syndrome (RDS) or intraventricular haemorrhage (IVH) and have a long-term adverse effect on later health and development, when compared with a single course. Originally planned to recruit 4000 women at risk of premature delivery, randomized, after one course of antenatal corticosteroids if gestational age was less than 32 weeks, the study was stopped in March 2003 due to lack of funds, having recruited 154 women. See www.npeu.ox.ac.uk/teams/ (visited 26 July 2005).

too small to look at long-term outcomes. The US trial aimed to recruit 1000, but was stopped early by the Data Monitoring Committee (DMC) at 500, because they decided it was futile to continue as they wouldn't be able to detect the short-term benefit.¹⁹¹ The other large trial of 2500, run by the Maternal Fetal Medicine Unit Network, was also stopped by the DMC at 500, because they found a slightly lower birthweight in the group receiving multiple courses of steroids. So it looks likely that we may end up with about 3000 women recruited around the world in trials on multiple courses of steroids versus a single course, instead of the 10 000 women. I am very sceptical whether in five years time we will actually have enough information to answer the question of the long-term outcomes. The short-term respiratory outcomes look as if they may be favourable for multiple courses of steroids, but clearly that is only part of the question. So the fact that we didn't get the original trials into practice very quickly has not necessarily taught us to improve on past performance when it comes to evaluating antenatal corticosteroids.

The other thing to mention, I suppose, is that in the absence of trial evidence about long-term outcome, people will rely on observational studies of long-term outcome. The one observational study with repeated courses of steroids which has been published is from the Western Australian group. It suggested a statistically significantly decreased incidence of cerebral palsy with multiple courses of steroids versus a single course, but a statistically significant increase in significant behavioural problems among the children who survived to the age of six years.¹⁹² I was discussing this with Jane [Harding] during the break this afternoon and the fact that in Australia and New Zealand the amount of steroids used is going down. I think it is going down in the UK when I talk to clinicians, because of these uncertainties and concerns about the harm associated with multiple courses of steroids. How we ever get people to interpret what we say correctly, I am not sure. Clearly the messages that are coming out at the moment are not that steroids are bad, but that we need to be more sophisticated in how we use them and how that information is interpreted appears to be to stop using them.

The issues for the future in terms of our current gaps are: the biggest one is that we cannot currently identify women who are going to deliver preterm very effectively. We can agree we are going to deliver them preterm electively, but for

¹⁹¹ Guinn *et al.* (2001).

¹⁹² French *et al.* (2004).

the vast majority of women who deliver spontaneously, we are not very good at recognizing them. And things like fetal fibronectin and cervical length on ultrasound screening may help us to identify a group of women who are at a much higher risk of preterm delivery, and we can target our intervention more effectively. I am sure that we will see much more of this in the future.

As to the gestational age at which to use steroids, what formulation, what dose, and what route of administration, I think these are questions that we will have to tackle in the future. What gestational age to give steroids? Nobody has mentioned yet the trial that has only been published in abstract that Peter Stutchfield did in Wales, where they recruited women who were going for elective caesarean section at greater than 37 weeks.¹⁹³ They randomized nearly 1000 women to receive steroids or not and showed a significant decrease in admissions to the neonatal unit with respiratory symptoms in the group receiving steroids. So even beyond 37 weeks, if you deliver electively by caesarean section, steroids seem to offer some advantages. The issue about whether there is a cut-off when you don't give them is going to be re-opened. The multiple course of steroids debate is, as I said, still wide open, although we will see more evidence about this over the coming years, and it may hopefully answer some of our questions.

A big lesson that has come out of the steroids trials – not only antenatal steroids, but postnatal steroids – is that with perinatal interventions we really, really have to look at the children, if not the mothers as well, in the longer term, because these babies don't stop developing the minute they are born, they go on and on and on.¹⁹⁴ I was reading in *Time* magazine recently about a study where they had done serial MRI scans in teenagers and they are suggesting that the

¹⁹³ Dr Edmund Hey wrote: 'The abstract to which Dr Peter Brocklehurst was referring appeared in *Archives of Disease in Childhood* 2004 **89** (Suppl. 1): A5. However the full paper reporting the trial was published online ahead of publication (22 August 2005) in the *British Medical Journal* on 24 September [(Stutchfield *et al.* 2005) along with an editorial by Philip Steer (2005)]. I think it is worth recording that the whole ASTECS (Antenatal Steroids for Term Elective Caesarean Section) trial involving the randomization of 998 women from ten different maternity units over a seven-year period, 1995 to 2002, was undertaken with the support of a single £10 000 grant from the Welsh R&D Office. The original trial by Liggins and Howie was also managed on a shoestring of external funding, but the regulatory requirements that have come into operation in the past few years mean that any trial of this nature could now almost certainly cost at least ten times as much as this.' Note on draft transcript, 27 August 2005.

¹⁹⁴ Dr Clive Dash wrote: 'The response by the delegates at the RCOG meeting in 1977 may also have been tempered by the anxiety, certainly among many clinicians with whom I spoke at that time, that the long-term effects might prove to be significant.' E-mail to Dr Daphne Christie, 10 January 2005. See also note 22.

brain does not stop developing until age 25, which seems a perfectly reasonable justification for raising the age at which you can vote.¹⁹⁵ But babies develop, they develop for a long, long time and something like steroids has an enormously potent effect on all the systems of the body, and yet we think we can just look at RDS and ignore the potential long-term effects. I think we are beginning to realize that we cannot do that, that interventions which show short-term benefits, like neonatal dexamethasone, may be countered by long-term harm. Not just that there is no benefit in the long term, but that the long-term effects may be in the opposite direction. This means that long-term follow-up studies of these trial cohorts become essential and yet the current situation of data protection and confidentiality issues in the UK, I would suggest, is making it more and more difficult, and more and more expensive in terms of being able to follow up people.

Hey: I would just add one thing that you didn't raise. One of the issues about which steroids may have adverse effects is that some of the steroids have sulphides added to them as a preservative, but nobody reads the label, they think betamethasone *is* betamethasone. You can get betamethasone with a sulphide preservative in it and that was what was used in the recent French observational study.¹⁹⁶ Liggins managed to choose the very best steroid in the very best dose that required just two injections. The preparation he used was also preservative free.

Brocklehurst: I think there is an issue here about preparations, because I remember the investigators from the Canadian study got in touch with us about

¹⁹⁵ Wallis (2004).

¹⁹⁶ Dr Edmund Hey wrote: 'The two key papers pointing to the possibility that a sulphite excipient in some formulations of perenteral dexamethasone may be neurotoxic are: Baud *et al.* (1999, 2001). Interestingly no drug company has, even now, sought a licence from the regulatory authorities to recommend betamethasone, or any other steroid, for use in cases of threatened early labour. As a result such use remains an unlicensed use of a licensed product – a situation that the general public find quite baffling. It is easy to see why the drug companies have not spent the money necessary to get their licences modified when the basic product is no longer patent protected, but less easy to see why the regulators [the Food and Drug Administration (FDA) in the US and the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK] have not pressed to get this anomaly rectified. The use of steroids in pregnancy receives hardly a mention in the otherwise excellent *British National Formulary (BNF)*. The most that it is prepared to offer is the negative comment that "there is no evidence of intra-uterine growth restriction following short-term treatment (such as prophylactic treatment for neonatal RDS)". [*BNF* 49 (2005): 359.] Lack of action by the regulatory authorities must have contributed, over the years, to the under-use, and the over-use, of this drug.' Note on draft transcript, 27 August 2005.

our TEAMS trial, and asked, ‘How did you get a placebo for your betamethasone, because ours is cloudy?’ We replied that ours was completely clear. The original trial doesn’t specify what the betamethasone preparation was and we were using the betamethasone that was available in this country, and in the UK you can only buy betamethasone in a solution, not a suspension.

Gamsu: This is why, of course, with the advice of Glaxo we chose the three-dose regimen of betamethasone phosphate to try to achieve the same sort of levels as the 12-hourly regime that was used in New Zealand and also the placebo that was used was the vehicle and has the same appearance as the steroid that was used. And, of course, there’s a slight caveat about the use of cortisone acetate as the placebo in the Liggins trial, in which way it influenced things, if it did at all, one cannot say.

Hey: Perhaps we had better clarify that. Rather than having a negative placebo in the original trial, they [Liggins and Howie] used a corticosteroid that was only one-seventieth as powerful, because it didn’t cross the placenta.

Gamsu: It did cross but in much smaller quantities.

Hey: But by choosing that, they had something that looked visually identical. So one of the good things about the original trial was that they were genuinely blinded and I keep on hearing stories about how the second biggest trial, the US NIH Collaborative Group trial, is seriously flawed because there were unblinding issues.

Harding: If I could just comment on that? Mont did actually check the effects of the cortisone acetate, the placebo, on the babies, and in, I don’t know how many, women, but he measured cord blood steroid levels and showed that twice the dose used as placebo had no effect on cord blood steroid levels and that reassured him that that was an appropriate placebo.

To come back to Peter Brocklehurst’s point about how come they chose the best dose and the best drug, I don’t think we know that they did. Nobody’s looked and almost all of the issues that Peter has raised – the repeat steroids, which dose, which drug, how often, at what gestation, to which pregnancy – all of those things were raised by Liggins and Howie in their original publications and said these were the things that needed work, including long-term follow-up. When Stuart Dalziel, the key person in the 30-year follow-up, presents this data, he starts off by saying, ‘Why do we do this?’ He then puts up a quotation from the original papers, and says, ‘Because they told us we had to 30 years

ago'.¹⁹⁷ To complete that story, recently at a meeting at the National Women's Hospital, Stuart said, 'I expect that it will be my PhD student in 20 years' time who will have to do the 50-year follow-up'.

Hey: I think this is a good point on which to finish. Thank you all very much for your attendance. There will be an opportunity for you to see a transcript of what you have said. Much more importantly, I hope some of you have had your memories triggered or your curiosity disturbed and it may be that, for some of the things you have said, you can now go away and find the paper, or the quote, or get the year right. This has just been a first outing, to stir your grey cells. You have all got to go away now and see what more you can add to this story, having heard what others have jogged your memory about.

¹⁹⁷ Dalziel *et al.* (2005a and b).

Appendix 1

Letter from Professor Sir Graham (Mont) Liggins to Sir Iain Chalmers [6 April 2004]

Dear Iain,

As you say, it would be nice to be fit enough to do this face-to-face. I will do my best to answer your queries. There is no video-recording of an appropriate interview. Nor can I provide pages from a lab book. Lacking your sense of history, all my records were consigned to the scrap heap when I retired. The best I can do is a slide of a photo [see Figure 7] taken of those very first lungs showing partial inflation after fetal infusion with cortisol at 118 days of gestation. The lamb had delivered during the night. To my great surprise, I found it still alive in the morning, gasping but surviving. I was fully occupied with studies of parturitional physiology and was not inclined to pursue it further at that time. However, I did tell Mel Avery who was visiting NZ soon afterwards. She got on the phone and called one of her Fellows in her lab and told him to give cortisol to some fetal sheep. Our observation was published in 1969 and was soon followed by deLemos and Avery in 1970 which confirmed the finding as well as providing direct evidence of accelerated appearance of surfactant as we had postulated.¹⁹⁸

When I returned to a position as Senior Lecturer in Obstetrics and Gynaecology at the National Women's Hospital in 1959 after six years of clinical work and no research in the UK, I realized that my academic appointment required me to do some research. I asked my friend, Bill Liley, of fetal transfusion fame how to choose a topic. He said to look for a major problem which was potentially soluble. The major problem was easy. Prematurity stood out above everything else. I naively thought that all I had to do was solve the ancient question of what controlled the onset of labour at term and the reason for premature onset would become apparent. I thought it might be a fetal activity although at the time it was generally believed maternal activity via release of oxytocin from her pituitary. But I had some circumstantial evidence to support my idea. Sheep browse on *Veratrum californicum* or skunk cabbage in the mountains.¹⁹⁹ They don't like it, but will eat it in times of drought. Binns *et al.* in 1960 described

¹⁹⁸ Liggins (1969); deLemos *et al.* (1970).

¹⁹⁹ Keeler (1990).

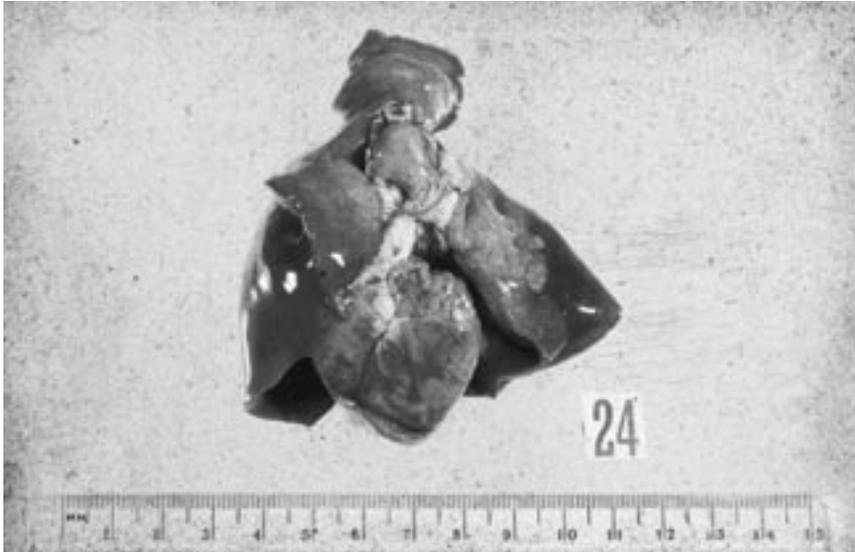


Figure 7: Lamb lungs showing partial inflation after fetal infusion with cortisol at 118 days of gestation, birth at 120 days, photographed at autopsy. The pale areas are tissue inflated with air. The dark areas are uninflated lung.

how the lambs were cyclopic and had prolonged pregnancies.²⁰⁰ At autopsy they found defective pituitaries. With this tidbit I set out to hypophysectomize fetal sheep. Having no money and no animal lab I called on friends at Ruakura Agricultural Research Station, 80 miles south of Auckland. They generously provided everything I needed. So over the next sheep season I worked out how to do fetal hypophysectomies and adrenalectomies. The following year I had a sabbatical and went off to the Vet School at the University of California at Davis, and put the techniques to the test. The results were dramatically successful. Pregnancies continued on and on after hypophysectomy.

Back in Auckland I needed a lab and money. The Hospital gave me an abandoned shed and the Wellcome Trust, courtesy of that wonderful man, Peter Williams, gave me money.²⁰¹ My first experiments were to test the idea that the effects of the pituitary were mediated by the fetal adrenal. Infusion of cortisol or ACTH caused premature delivery at any gestational age. With that lengthy background we have arrived at the subject of the seminar, although there is plenty more to the parturition story.

²⁰⁰ Binns *et al.* (1960). For the background of Dr Wayne Binns' work, see James (1999).

²⁰¹ See Appendix 3, pages 97–9.

When I saw the inflated lungs [Figure 7] and correctly guessed that cortisol had induced one or more enzymes responsible for surfactant synthesis and/or release, it seemed very likely that this was not a species-specific response since cortisol was well known to induce a variety of enzymes in a variety of species. So no time was lost in enlisting the collaboration of my neonatal colleague, Ross Howie, who I knew to be meticulous almost to a fault. We worked out what we thought was a rigorous protocol, but as simple in design as possible. An immediate problem was what to give the mothers and how much of it. It happened that I had been studying the effects of corticosteroids on human fetal adrenal function by measuring urinary oestriol excretion, which is a product of the fetal zone of the fetal adrenal. So I knew the dose of corticosteroid required to cause marked inhibition of adrenal function. To simplify administration to the mothers in the trial a once daily dose was desirable so we chose a mixture of a long-acting and a short-acting corticosteroid. This created a problem since all long-acting preparations are insoluble and in suspension. The placebo had to be identical in appearance. We finally chose cortisone acetate which is a suspension but one-seventieth of the potency of our active agent. The choice of active agent came down to what drug company was willing to supply the active and placebo ampoules. Glaxo, originally a NZ company, came up trumps and the trial soon began. Glaxo could see that no profit was to be made but were happy to do it for goodwill. It was by chance then that our choice of agent has turned out to be the best. Ethics committees hadn't arrived in 1969, but all clinical studies had to be submitted to the Senior Hospital Medical Committee for approval. The main purpose was to let the staff know what was going on and to enlist their co-operation. There were no conditions. We had told them that verbal consent would be obtained. The staff gave their full support so that 287 mothers were recruited in 22 months. The trial ran within the clinical care of each mother and no funding was required.

We offered our manuscript first to *Nature*, which promptly rejected it without sending it out for review on the grounds that it lacked general interest.²⁰²

Judging by the number of trials that soon followed there was a lot of interest amongst obstetricians particularly in the US. I got the impression on visits to the UK that paediatricians there were lukewarm, perhaps because there was a

²⁰² Professor Sir Graham Liggins wrote: 'Yes, *Lancet*, not *Nature*.' E-mail to Mrs Lois Reynolds, 2 September 2005. See also Professor Liggins' description of the event when the article appeared as a Citation Classic in 1982, having been cited over 565 times in the ten years after publication, at <http://garfield.library.upenn.edu/classics1982/A1982NF37800001.pdf> (visited 26 September 2005).

perception that their territory was being encroached on. Judging by the 20 years that it took the RCOG to come out in favour, despite your constant nagging, there was a problem with British obstetricians too, though I don't understand it.

Best wishes, Mont

Appendix 2

Prenatal glucocorticoids in preterm birth: a paediatric view of the history of the original studies by Ross Howie, 2 June 2004

For the Wellcome Trust Centre seminar, London, 15 June 2004

Firstly, my warmest greetings to Mel Avery, who was in at the very beginning of the whole surfactant story. My only regret for her is that she is not yet in at the end of it, at least as a major public health problem. If anyone had asked me at the time Mont Liggins and I first published in 1972 how I thought the New Zealand work would be viewed in the year 2004, I would have replied that by then advances in our understanding and management of preterm delivery and its associations would surely have made it irrelevant.²⁰³ Which only goes to show, yet again, how naive it can be to try to divine the future.

I write with reservations, which had better be stated before they become too obvious. This account is largely from memory, and after more than 30 years faculties tend to blur. I have been long out of touch, and have been unable to consult most of my papers (in storage after a recent house move) or to visit libraries. But as there appear to be some misconceptions abroad about the early history of the work it may be useful to have something on record, however scrappy.

At the outset, it may be worth reminding others that the project was only a sideline of the main work of both Mont Liggins on the one hand and myself on the other. Mont has his much more widely ranging research into reproductive endocrinology for which he is so justly renowned. My own main interest was in health rather than science, especially in helping develop newborn services in New Zealand, and I just happened to be around at the time. But I helped design the trial, supervised the collection of data and did all the work of analysing them. If I hadn't been around, I imagine trials would not have been done in Auckland and would not have been as large, at least from one centre.

A word on the setting. Possibly few single centres in the world could have carried out such a trial at that time. It needed one with a large number of births that was also academically well enough developed. Overseas, academic units tended to have relatively few births, and the large obstetric services tended not to have close academic ties. In Auckland, the National Women's Hospital (NWH) then

²⁰³ Liggins and Howie (1972).

had about 5000 deliveries a year, among which were concentrated mothers and babies of the highest risk from about 15 000 in the region. The hospital had within it the Postgraduate School of Obstetrics and Gynaecology, which had a background of research starting with Bill Liley and his rhesus work, which Mont Liggins rejoined shortly after.²⁰⁴

Nor, in other places, did it seem common for obstetricians and paediatricians to talk much with each other. The two disciplines had differences of outlook and values that were not always easy to bridge, but a good collaboration had been established at NWH. This was thanks very largely to successive heads of the Postgraduate School, Harvey Carey and Dennis Bonham, to the then senior paediatrician, Jack Matthews, and to Bill Liley. Drs Liley and Matthews had set up a Rhesus Committee about 1960, which brought together the obstetric, paediatric and other staff likely to be involved with the rhesus deliveries. From his coming in 1964, Dennis Bonham (fresh from his monumental work with Neville Butler in the British Perinatal Mortality Survey) reinforced this approach.²⁰⁵ In my medical school years (1952–56) I never heard the word ‘perinatal’ and the outlook the word implies was in many places some time in the future.²⁰⁶

At the time Mont was doing his relevant basic research in the late 1960s, the death rate of babies in the newborn period was at least five times the present. By far the leading cause of death then was respiratory failure in babies born early. I was the only person in Auckland (and for that matter in the whole of the country) who could ventilate babies. I did not do it very well: techniques were crude, equipment limited, and nursing staff and other support short. This

²⁰⁴ For Liley’s rhesus work, see Christie and Tansey (eds) (2005): 11–12, 17, 53–4, 57.

²⁰⁵ Bonham (1961).

²⁰⁶ ‘On the history of the word ‘perinatal’, I [Ross Howie, writing in June 2004] wonder whether anyone in the Wellcome Trust Centre can enlighten us. The coining of the word was a landmark that surely deserves recognition. A quick check of the US NLM website PubMed for occurrences of the words ‘perinatal’ and ‘perinatale’ in titles of journal articles showed none earlier than 1952, when there were three. I tentatively concluded that the first use of the word may have been in Europe in a language not English, French or German, but possibly Dutch, Scandinavian or Eastern European. At this point I found myself out of my depth and in need of more expert help.’ Dr Ross Howie later wrote: ‘Sir Iain Chalmers passed my query on to the noted US pioneer, Dr William Silverman, who replied: “The origin of the word ‘perinatal’ can be traced to Peller (1948), who coined the term to mean ante-, intra-, and postpartum, the period around and including the time of birth”. [Silverman (1961): 4.]’ E-mail to Mrs Lois Reynolds, 22 August 2005.

was to my oft- and forcibly expressed regret, strongly supported by my two paediatric colleagues, Jack Matthews and Leo Phillips. The facilities of modern newborn care are now taken for granted, but it was a long and hard fight to get them. In those days I felt I spent altogether too much time up at nights looking after babies, and was very ready to welcome any development that might reduce that need – never to mention, of course, benefit to the babies in sparing them the tender mercies of intensive care.

The development came in a way that, if not familiar to members of your seminar, will presumably be explained by Mont himself. I still remember the excitement I felt at my first evidence of it, when he handed me the lungs of twin lambs for pressure–volume studies. The lambs had been delivered very early: one had been infused with glucocorticoids and the other not. Lungs of the infused lamb were perfectly stable after inflation: pink, fluffy and floated in water [see Figure 7]. In total contrast, the lungs of the other remained solid and liver-like, and sank. After Mont had confirmed the effect in further animal studies, he looked to set up the first human trials and called me in. He looked after the maternal side and I that of the babies.

My side was not, I thought, likely to be simple, as anyone with any knowledge of the field will appreciate. Babies born unfinished, sent ‘before [their] time into this breathing world’ form, collectively, probably the most complex situation in human biology.²⁰⁷ It is complex partly because of the variety of associations of preterm delivery, but more because of the effects on every body system, not just the breathing; effects varying with gestational age and many other factors. It was not to be expected that one size would fit all.

If the therapy worked at all, it seemed *a priori* that it would work under some conditions and not others, and under yet others might be hazardous. In the words of Claude Bernard, what is true in general is likely to be false in particular. I was also conscious of the history of so many ‘advances’ in medicine, which have come in phases: the first of initial and uncritical enthusiasm, followed by one of debunking, and finally – if the development is worth while – one of a more sober balance. We were keen to see the project through all these phases and find out as much as possible of the limitations of the therapy before others did. I set myself up at the outset as a chief sceptic, and have remained so.

We felt that only a very large study could hope to give results of any reliability. As a result the trial may have been kept going for longer than would meet with

²⁰⁷ William Shakespeare’s *Richard III*, Act 4, Scene 1. See also Anonymous (1976).

the approval of an ethics committee today, but the results may be on a firmer footing as a result.

The analysis was carried out using Hollerith punch cards.²⁰⁸ I wonder how many people at the meeting are ancient enough to have had any experience of them. Our equipment could be described (politely) as somewhat temperamental, especially the card sorter, which at times would chew up one in every 500 cards put through the machine. The work could be tedious and time consuming, but I felt I had a handle on the data and could fairly promptly recognize and rectify ‘garbage out’. I have had no experience of analysis of research data by computer, but sometimes wonder whether those who by this means can get almost instantaneous results today have the same feel for their raw material. Incidentally, I was fascinated to note that in that *fons et origo* of high technology, the US, punch cards were used in their last Presidential election.²⁰⁹ I felt like offering my services as a technical consultant for the next one.

The first paper attracted a lot of interest, among others from the World Health Organization, specifically its Human Reproduction Program. They proposed an international multicentre controlled trial, involving places like Bangkok and Leningrad (as it was then), with the aim of determining whether a treatment that appeared to work in Auckland would work as well in the possibly very different conditions of the other countries. Much as I would have liked to visit these exotic places, the prospect did not appeal. The conduct of a controlled trial must of course be meticulous, and I had found this difficult enough in Auckland. Confusion of the most vital data in even a very few subjects, e.g. recording therapy as treatment when it was actually control, or recording the presence of RDS when it was actually absent, would have had the effect of eliminating genuine differences between treatment and control groups, and hence making the results valueless. We did not relish the prospect of WHO going to vast trouble and expense to ‘disprove’ our results.

We asked them instead, and they very kindly agreed, to fund us to carry out long-term follow-up studies. ‘Long-term’ to us then meant to six years. The 30-year follow-up would at the time have seemed an impossible dream. In this we were singularly well placed by having a happy association with Barton MacArthur, an educational psychologist in the University. He was (and still is) New Zealand’s

²⁰⁸ For an example of an early Hollerith machine and punch card, see Ness *et al.* (2002): 35.

²⁰⁹ For the importance of the chad, or imperfectly punched card, in the 2000 election, see www.usconstitution.net/elec2000.html#e (visited 25 October 2005).

leading authority on tests of cognitive function in young children, and brought to his work a meticulousness and rigour unmatched among psychologists in my experience.²¹⁰

Overseas I was often asked what management I would recommend for a mother in preterm labour. My standard answer was that I was there purely to present our work and findings and could not tell them what to do; it was hazardous to base management on the findings of only one trial. That may have disappointed some, who told me that researchers were expected to *sell* their research. If my low-key approach contributed to the delay in acceptance of the therapy, I have no apologies. The matter is not simple and it does no service to over-simplify. If, as has been suggested, the message was not clear, it seemed to me to be clear enough to those who wanted to hear it, and it had its main intended effect of encouraging further trials.

But I welcomed Patricia Crowley's meta-analysis and the stimulus the history gave to the work of Iain Chalmers and others in setting up the Cochrane Collaboration. This was a major advance and long overdue, even if I think rather too much has come to be expected of 'evidence-based medicine'. More recently I have welcomed another development, the 30-year follow-up by Stuart Dalziel, Jane Harding and Anthony Rodgers. If, apart from its main purpose, it gives support to David Barker's ideas of considering fetal origins of disease (or health) I shall be more than happy.²¹¹

Another point of contention may be the effect of antenatal steroids on mortality. I have heard it said that the therapy has saved hundreds of thousands of lives. It would be pleasant to think so, but I wonder how this number was calculated: if the Auckland figures came into the reckoning I would have to doubt it. It may be more accurate to say 'helped to save'. The reason, of course, is the development of newborn intensive care since the time of our trials. It is not to be expected that the therapy would save lives these days, at least in developed countries. On the other hand it should do so in some more advanced developing countries, in places where newborn services are at the level ours were in the early 1970s.

I well remember January 1975 – just after the trials finished – as a watershed in the development of our own services. In 1974 I was away from the unit for two weeks in Geneva discussing our proposed follow-up studies with WHO,

²¹⁰ MacArthur *et al.* (1981, 1982).

²¹¹ Barker *et al.* (1989).

and found on my return to Auckland that during my absence two relatively large babies had died from uncomplicated RDS. Both, I was sure, would have survived if treated very simply with George Gregory's technique of continuous positive airway pressure (CPAP).²¹² I hit the roof and sent in my resignation. For some reason the powers that were felt it necessary to talk me out of it, but we did achieve more staff. Our first full-time clinical specialist, Sue Sayers, took up her post in 1975, and only then did 'neonatal intensive care' become a sustainable reality in our hospital.

In all developed countries to my knowledge, perinatal survival improved strikingly in the second half of the twentieth century.²¹³ In New Zealand it improved possibly more than most due to a remarkable nationwide effort very ably led by the successive heads of the Postgraduate School of O&G, Harvey Carey and Dennis Bonham. In the 40 years after the hospital was established, the national perinatal mortality rate by the WHO definition of the time fell by nearly 80 per cent, from 34.6 per 1000 births in 1950 to 7.4 in 1990.²¹⁴ Steroid therapy was a welcome advance during this time, but it would be hard to attribute to it more than a fraction of the improvement.

But I am sure it has a place. In fact most advances in medicine are only marginal, but for those on the margins, as so many are, specific interventions may be crucial. And mortality is only a crude measure: nowadays the benefit may be more in reducing morbidity (short- and long-term) and the workload of newborn services. Recently my wife and I had a family experience of its use: a daughter-in-law delivered at 31 weeks after antenatal steroid therapy, which I did not hesitate to support. Our grandson had a completely uneventful course and is now a lively two-year-old, developing well. Whether his outcome in relation to the steroid therapy was *post hoc* or *propter hoc* I have no idea, but I was happy with the odds.

If some of what I have written seems provocative, I can at least claim that is in a good early National Women's Hospital tradition. It is one that various pressures have caused to be sadly less in evidence during the past 20 years. If there was any greatness in that hospital in its early days (as I believe there was), much of it was

²¹² See notes 30 and 31.

²¹³ See Christie and Tansey (eds) (2001): 28.

²¹⁴ Perinatal mortality as stated then: fetal deaths after 28 weeks' gestation plus first-week neonatal deaths, expressed per 1000 total births.

due to an environment of questioning conventional wisdom and challenging authority, and doing so constructively and with rigour. It was one especially fostered by the second head of the Postgraduate School, Harvey Carey (1955–62), who encouraged, for example, Bill Liley and fetal transfusion (everyone knew that blood could not be absorbed intact from the peritoneal cavity), and Mont Liggins with the work that was the basis of the advance related in this account (everyone thought that it was the mother that determined the onset of parturition). I felt privileged indeed to be part of the hospital in those times.

Acknowledgements

It needs to be said of both the Hospital and Postgraduate School that the environment was extremely supportive of the effort, and without this the project could not have succeeded. Thanks are most due to the subjects of the trials: the mothers who agreed to take part, many of whom did so at the considerable discomfort of early medical efforts to delay delivery. But their contributions, and those of the authors of the reports, would have been of little effect without the willing help of very many others, who included John Stewart (radiologist), David Becroft (pathologist), Ray Laurie (pharmacist) and successive research nurses who kept the initial records, notably Margaret Hollins.

My part of it had at different times the welcome, and crucial, financial support of the Auckland Medical Research Foundation, the Medical Research Council of New Zealand, the University of Auckland, and the World Health Organization. But much of the expense of the work was carried by the hospital authority, the Auckland Hospital Board, in its ordinary budget. For all its other problems, the Board at the time actively encouraged research in its institutions, thanks to the enlightened attitude of a number of its people, notably Sir Harcourt Caughey and Dr Wilton Henley, Chairman of the Board and Superintendent-in-Chief respectively.

Finally, I thank the Wellcome Trust Centre for providing the stimulus to write this note. Although on record as saying that all history (at least our understanding of it) is to some degree ignorant and biased, I remain very grateful to those who strive to make it less so, and see the work of the Trust as vastly impressive. I hope the seminar will help to reduce any remaining ignorance and bias around this topic, and would welcome comments that may help to reduce mine.

Appendix 3

Premature sheep and dark horses: Wellcome Trust support for Mont Liggins' work, 1968–76 by Tilli Tansey²¹⁵

In February 1968 the Trustees of the Wellcome Trust made a grant of £15 000 'to enable Professor Liggins to investigate the mechanisms responsible for the initiation of human parturition'. Three years later, a summary of the work carried out under the grant made remarkable reading – a number of sensitive hormone assays had been developed; the role of the fetus in initiating parturition in the sheep and rabbit had been extensively examined and several causative factors and pathways identified.

Two discoveries stood out in particular:

7. We made the original observation of the phenomenon of induction of pulmonary surfactant in fetal lungs [of sheep] by glucocorticosteroids. This has subsequently been confirmed in sheep by Kotas and Avery and extended by them to rabbits.²¹⁶

8. We performed the first clinical trial of antepartum corticosteroid treatment in the prevention of respiratory distress syndrome in the human neonate. A controlled, blind trial involving over 300 women in premature labour has shown a reduction in the incidence of respiratory distress in babies born at 26–32 weeks of gestation from 75 per cent in the control group to 8.3 per cent in the treated group ($p < 0.02$).

The impact and furtherance of those discoveries have, of course, been the subject of this meeting.

The Wellcome Trust went on to support Liggins and his team for a further five years; with a grant of £23 050 to cover research expenses and assistance for further work in 'a study of the hormonal control of ovine parturition'. This

²¹⁵ Details taken from 'Liggins G C', File 4078, Records of the Wellcome Trust, consulted and reproduced by permission of the Wellcome Trust and Sir Graham Liggins.

²¹⁶ Kotas and Avery (1971).

was supplemented by £3185 in 1974 to cover the effective loss to the original grant by a revaluation of the New Zealand dollar. That grant too provided outstanding results. Liggins' final report to the Wellcome Trust in 1976 lists 'a new physiological system' – the fetal control of parturition; 'a new disease' – placental sulphatase deficiency; and 'a new treatment' – the prenatal use of corticosteroids. As the report emphasizes:

Our discovery of acceleration by corticosteroids of maturation of lung function in fetal lambs and our subsequent application of this phenomenon to prevention of the Respiratory Distress Syndrome in the human neonate by fetal treatment with corticosteroids is now beginning to have a worldwide impact on the incidence of this disorder.

In 1971 when the second grant was being considered, the Wellcome Trust suggested that financial liability for Liggins and his group might be passed to the New Zealand Medical Research Council. Discussions between officers and a Trustee (Sir John McMichael) of the Trust, staff of the NZ MRC, and Liggins and colleagues in the University of Auckland resulted in a transfer of financial responsibility for the work in 1976. The final correspondence between Liggins and the Director of the Wellcome Trust, Dr Peter Williams, is illuminating.

18 February 1977

Dear Dr Williams,

I want to add my personal thanks to you to the more formal appreciation conveyed in my final Report. It is difficult to convey the extent of my gratitude to you for the support you gave me as a 'dark horse' which has had such a profound effect on my career.

Kindest regards,

Yours sincerely,

Mont Liggins

28 February 1977

Dear Professor Liggins,

I am writing to thank you very much for your kind comments both to myself and the Trustees about the support for your work. It is very satisfactory to know that such a 'dark horse' came in as a front runner.

It is possible that I may be visiting New Zealand later in the year in which case I would hope to be able to come and see you and get a first hand account of your work.

With kind regards,

Yours sincerely,

Peter Williams

Appendix 4

Prenatal corticosteroid therapy: early Auckland publications, 1972–94

Ross Howie, January 2005

This has been compiled for the historical record because of continuing interest, and because most of the trial reports were published in books or conference proceedings, and hence are not included in the online database PubMed. The list includes reports of the initial follow-up studies, but not abstracts, or trials of TRH with betamethasone.

Liggins G C, Howie R N. (1972) A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. *Pediatrics* **50**: 515–25.

Liggins G C, Howie R N. (1973) Prevention of respiratory distress syndrome by antepartum corticosteroid therapy. In Physiological Society, Barcroft Sub-Committee editorial board, Comline K S *et al.*, *Foetal and Neonatal Physiology: Proceedings of the Sir Joseph Barcroft Centenary Symposium*, held at the Physiological Laboratory, Cambridge, 25–27 July 1972. Cambridge: Cambridge University Press, 613–17.

Howie R N, Liggins G C. (1973) Prevention of respiratory distress syndrome in premature infants by antepartum glucocorticoid treatment. In Villee C A, Villee D B, Zuckerman J. (eds) *Respiratory Distress Syndrome*. New York, NY: Academic Press, 369–80.

Howie R N, Liggins G C. (1974) Clinical trial of betamethasone for the prevention of the respiratory distress syndrome. Proceedings of the XIV International Congress of Paediatrics, Buenos Aires, 3–9 October, 1974. In *For A Healthy Child in A Better World: Fourteenth International Congress of Paediatrics, Buenos Aires, 3–9 October 1974 and five other recent paediatric congresses*. Annales Nestlé series no. 35. Zurich: Nestlé Scientific Services.

Liggins G C, Howie R N. (1974) The prevention of RDS by maternal steroid therapy. In Gluck L. (ed.) *Modern Perinatal Medicine*. Chicago, IL: Year Book Medical Publishers: 415–24.

Howie R N, Liggins G C. (1976) Maturation of the lung: present understanding and practical implications. *Bulletin of the Postgraduate Committee in Medicine of the University of Sydney* special issue: 19–30.

- Liggins G C. (1976) Prenatal glucocorticoid treatment: prevention of respiratory distress syndrome. In Moore T D. (ed.) *Lung Maturation and the Prevention of Hyaline Membrane Disease*. Report of the 70th Ross Conference on Pediatric Research. Columbus, OH: Ross Laboratories, 97–103.
- Howie R N, Liggins G C. (1978) Clinical trial of antepartum betamethasone therapy for prevention of respiratory distress in pre-term infants. In Anderson A, Beard R W, Brudenell J M, Dunn P M. (eds) *Preterm Labour: Proceedings of the fifth study group of the Royal College of Obstetricians and Gynaecologists, 1977*. London: The College, 281–9.
- MacArthur B A, Howie R N, Dezoete J A, Elkins J. (1981) Cognitive and psychosocial development of four-year-old children whose mothers were treated antenatally with betamethasone. *Pediatrics* **78**: 638–43.
- Howie R N, Liggins G C. (1982) The New Zealand study of antepartum glucocorticoid treatment. In Farrell P M. (ed.) *Lung Development: Biological and clinical perspectives*. Vol. 2: *Neonatal respiratory diseases*. New York, NY; London: Academic Press, 255–65.
- MacArthur B A, Howie R N, Dezoete J A, Elkins J. (1982) School progress and cognitive development of 6-year-old children whose mothers were treated antenatally with betamethasone. *Pediatrics* **70**: 99–105.
- Howie R N. (1984) Pharmacological acceleration of lung maturation. In Raivio K O, et al. (eds) *Respiratory Distress Syndrome: Proceedings of the Eighth Sigrid Juselius Symposium*, Helsinki, 9–12 August 1982. New York, NY; London: Academic Press, 385–96.
- MacArthur B A, Howie R N, Dezoete J A, Elkins J, Liang A Y. (1989) Long-term follow-up of children exposed to betamethasone *in utero*. In Tejani N. (ed.) *Obstetrical Events and Developmental Sequelae*. Boca Raton, FL: CRC Press, 81–89.
- MacArthur B A, Howie R N, Dezoete J A, Elkins J, Liang A Y. (1994) Long-term follow-up of children exposed to betamethasone *in utero*. In Tejani N (ed.) *Obstetrical Events and Developmental Sequelae*, 2nd edition. Boca Raton, FL: CRC Press, 81–9. [Largely unchanged from 1st edition.]

Appendix 5

Protocol for the use of corticosteroids in the prevention of respiratory distress syndrome in premature infants

From the 1975 UK Study²¹⁷

Purpose of the study

To investigate the effectiveness of betamethasone 21 phosphate ('Betnesol', Glaxo Laboratories Ltd) in preventing respiratory distress syndrome (RDS) in the premature fetus (< 34 weeks' gestation).

Rationale

There is evidence from animal studies that surfactant is secreted into the fetal lungs if stimulated by corticosteroids. Liggins and Howie (*Pediatrics* **50**: 515 [1972]) produced data in humans which indicated that the risk of developing RDS was reduced by maternal injection of 12mg betamethasone daily for two days. There was no indication of obvious adverse effects to mother or fetus. The trial proposed here is to confirm these clinical findings as well as to investigate more formally any likely adverse effects.

Selection of patients

The patient's consent to participate in the trial should be sought according to the policy of the hospital. Patients will be classified into two main groups:

Group I Women at less than 34 weeks' gestation (ie end of 33rd week) who are in clinical spontaneous premature labour either:

a) With ruptured membranes

or b) Without ruptured membranes

Group II Women at less than 34 weeks' gestation (ie end of 33rd week) who are not in premature labour but:

a) For whom early elective induction is indicated, and who show low lecithin concentrations or L/S ratios;

b) For whom early elective induction is indicated but for whom no data is available on lecithin concentrations or L/S ratios.

²¹⁷ Gamsu *et al.* (1989).

Exclusions from study

- 1) Patients in whom steroid treatment is contra-indicated.
- 2) Patients for whom a delay of >24 hours before delivery is not in the interest of mother or fetus.
- 3) Diabetics.
- 4) Amnionitis. (If amnionitis is diagnosed after admission of patient to the trial an indication of how the diagnosis was made should be recorded. Further trial data for such a patient should still be recorded.)

Patient number

During the year results will be subject to periodic review and the total number of patients to be included will depend on the significance of these results.

Design of trial

Double-blind trial comparing intramuscular doses of 'Betnesol' with placebo.

Drugs and dosage

Intramuscular injections of 'Betnesol' or matching placebo will be administered in a dosage of 1ml (= 4mg betamethasone 21 phosphate) every eight hours over a 48-hour period (total of six doses). Only one course of 'Betnesol' or placebo treatment may be given.

Allocation of patients to either placebo or active groups will be done according to a random code. The ampoules will be provided in numbered boxes to facilitate this.

Procedure

- 1) Patients will be examined on admission. Each patient will be allocated a trial number, a data sheet and a box of ampoules bearing her trial number.
- 2) Relevant patient details will be noted on the data sheet.
- 3) Group I
 - a) Inhibition of uterine contractions will be attempted using salbutamol according to a standard scheme, (see Table 5).

If possible labour will be delayed for at least 48 hours. If delivery occurs in less than 48 hours all data should still be recorded.

- b) Each patient will receive an intramuscular injection of 'Betnesol' (4mg) or placebo according to a random code.
 - c) 'Betnesol' injection (4mg) or placebo will then be administered at eight hourly intervals over a period of 48 hours.
 - d) Antibiotics will not be routinely administered in cases of spontaneous ruptured membranes.
 - e) If the patient goes into premature labour again after the sixth (last) injection of 'Betnesol' (or placebo) salbutamol may be re-used at the discretion of the physician, but on no account should further 'Betnesol' or placebo be given.
- 4) Group II(a)
- i) In these patients amniocentesis will be carried out. Those who show a low lecithin concentration or L/S ratio according to the standards of each hospital, will receive an intramuscular injection of 'Betnesol' (4mg) or placebo. This will be repeated at eight hourly intervals over a 48 hour period (six injections). The standards for interpreting the amniocentesis results should be defined at the beginning of the trial.
 - ii) 48 hours after the start of the treatment period (or as soon as possible thereafter) amniocentesis will again be carried out to determine the lecithin concentration or L/S ratio.
- 5) Group II(b)
- i) Amniocentesis is not applicable for these patients, therefore no data on L/S ratios or lecithin concentrations will be available. The patients will receive an intramuscular injection of 'Betnesol' (4mg) or placebo every eight hours for six injections.
- 6) Groups I, II(a) and II(b)
- i) The clinician will decide clinically on the optimum time interval between completion of steroid treatment and

delivery (ideally between 48 hours and seven days after the start of 'Betnesol' or placebo treatment).

- ii) Maturity will be assessed 24–48 hours after birth in a well baby; this assessment may be postponed in a baby who is very ill. Signs of hyaline membrane disease, as listed on the record form, will be noted. In the case of post mortem, tissues should be retained for inclusion body counts which will be performed centrally.
- iii) Adrenal function of baby. Approximately 5ml of cord blood from the umbilical vein should be collected immediately after the end of the third stage of labour, preferably by syringe and needle, and placed in a heparinized bottle. If taken at night, whole blood may be stored in a fridge (4°C). All samples should subsequently be centrifuged and the plasma deep frozen (-20°C). Plasma 17-hydroxycorticosteroids will be estimated centrally or in the individual hospitals, depending on the facilities available.
- iv) In *some* centres adrenal function of mothers will be monitored for several days following delivery (method to be decided).

Withdrawals

Any patient may be withdrawn from the trial at the discretion of the clinician. A reason for withdrawal should be stated on the data sheet.

Side-effects

Any side-effects attributed to the treatments used in this trial should be notified to Glaxo Laboratories immediately. This is a requirement of the Committee on Safety of Medicines.

In the event of any queries please contact: Dr C H Dash/Mrs B M Mullinger, Medical Department, Glaxo Laboratories Ltd, Greenford, Middlesex. Tel: 01-422 3434 Ext 363.

Table 5: Use of salbutamol in Group 1 patients for the management of premature labour for trial of corticosteroids in the treatment of RDS.

Patients:	All patients in Group I presenting in spontaneous premature labour without evidence of amnionitis, thyrotoxicosis or cardiac disease. The physician should be satisfied that premature labour has commenced, ie regular contractions occurring at intervals of ten minutes or less. Salbutamol treatment will then be started immediately.
Assessment before salbutamol treatment:	Cervical dilatation and effacement will be recorded on the record form together with maternal blood pressure, pulse rate and fetal heart rate.
Composition of salbutamol infusion:	5ml = 5mg salbutamol injection should be added to 500ml 5 per cent dextrose solution to give a concentration of 10 μ g salbutamol per ml equivalent to 15 drops from a normal giving set.
Treatment:	<p>Patients will receive an infusion of salbutamol through a forearm vein. The infusion will be started at 10 drops per minute (6.7μg salbutamol/minute) and increased by 10-drop increments at five to ten minute intervals until contractions cease or an infusion rate of 50 drops per minute (33μg/min) is reached. If contractions have not ceased, the infusion will be increased by 10-drop increments at 20-minute intervals. Treatment should be stopped if any of the following occur:</p> <ol style="list-style-type: none"> 1. An infusion rate of 80 drops per minute (53μg per minute salbutamol) does not reduce contractions in strength, duration or frequency; 2. The cervix has dilated significantly after six hours of treatment; 3. A steady maternal pulse rate exceeding 140/min is reached.

Once contractions have ceased, the infusion will be maintained at this steady rate for one hour. The infusion rate will then be reduced by half and maintained at this lower rate for six hours. The infusion rate will then be reduced by half again and maintained for a further six hours, before starting oral treatment with 14mg salbutamol (Ventolin) tablets qds for one week.

In the event of unacceptable side-effects occurring such as tremor or palpitations, salbutamol dosage by infusion or oral routes may be reduced.

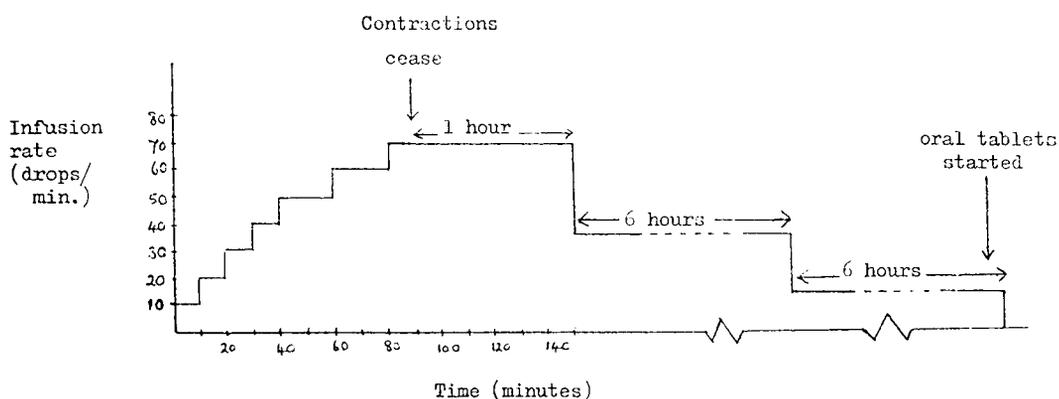


Figure 8: Example of salbutamol treatment

Records: Uterine contractions, maternal pulse rate and blood pressure and fetal heart rate will be monitored regularly (or prior to each change in salbutamol dose), until the maintenance infusion rate is reached; thereafter records will be made at 30-minute intervals until infusion is stopped.

Repeat therapy: If contractions become re-established during or after infusion treatment, the infusion will be increased or re-started at the previous one hour maintenance level and reduced as before at six hourly intervals.

Treatment will not normally be repeated on more than four occasions or after 36 weeks' gestation without the direction of the clinician concerned.

Specific queries regarding the use of salbutamol may be addressed to:—

Clinical Research Unit, Allen and Hanburys Research Ltd, Ware, Herts
Tel: Ware 3232 Ext 286

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Biographical notes*

Dr Mary Ellen (Mel) Avery

MD (b. 1927) was Thomas Morgan Rotch Professor of Pediatrics at Harvard Medical School, Boston, MA, and Physician-in-Chief, later Emeritus, at the Children's Hospital, Boston from 1974 to 1985. She received the Virginia Apgar Award from the American Academy of Pediatrics in 1991 and the John Howland Award from the American Pediatric Society in 2005. She served on the Board of Directors of the Burroughs Wellcome Fund from 1993 to 2001; has been a member of the National Academy of Sciences since 1994, and was President of the American Association for the Advancement of Science for 2003, and Chairman of its board in 2004. See Avery and Mead (1959); Avery (2000); Figure 5.

Sir Joseph Barcroft

Kt CBE HonFRSE HonFRCOG FRS (1872–1947) was Reader (1919) and Professor of Physiology (1926–37) in Cambridge, and was appointed by the Agricultural Research Council as Director of the Unit of Animal Physiology, Babraham, in 1941. His research

interests included studies of the properties of blood, especially blood gases and the oxygen-carrying function of haemoglobin, and studies on the physiology of the fetus. See, for example, Barcroft (1914, 1946). See also Roughton (1948–49).

Sir Christopher Booth

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

Dr Peter Brocklehurst

MBChB FRCOG MSc (Epidemiology) (b. 1962) trained in London as an obstetrician and gynaecologist, and an epidemiologist. He joined the National Perinatal Epidemiology

* Contributors are asked to supply details; other entries are compiled from conventional biographical sources.

Unit (NPEU), Oxford, as a research fellow in 1994, became consultant epidemiologist in 1996 and was appointed Director in 2002. See www.npeu.ox.ac.uk/npeu_home.php (visited 18 July 2005).

Sir Iain Chalmers

FRCPE FFPH FMedSci (b. 1943) has been Editor of the award-winning *James Lind Library* since 2003. He was Director of the UK Cochrane Centre in Oxford from 1992 to 2002 and Director of the National Perinatal Epidemiology Unit, Oxford, from 1978 to 1992. See www.jameslindlibrary.org/ (visited 2 June 2005).

Professor Archie Cochrane

CBE MBE FRCP FFCM (1909–88), medical scientist and epidemiologist, whose first clinical trial was conducted as a prisoner of war in Salonika. Following the war he was appointed to the Medical Research Council's Pneumoconiosis Research Unit in 1948. In 1960 he was appointed David Davies Professor of Tuberculosis and Diseases of the Chest at the Welsh National School of Medicine, Cardiff, becoming Director of the Epidemiology Research Unit there in 1961 until his retirement in 1974. His papers are available for study at the Cochrane Archive, Llandough Hospital, Penarth, Cardiff. See Cochrane (1976);

Cochrane [ALC] (1988). See also Ness *et al.* (2002).

Dr Patricia Crowley

FRCOG FRCPI (b. 1951) has been a consultant obstetrician gynaecologist at the Coombe Women's Hospital, Dublin, and Senior Lecturer at the Department of Obstetrics and Gynaecology, Trinity College Dublin since 1990.

Dr Clive Dash

MB ChB FFPM (b. 1940) graduated from the University of Birmingham and did postgraduate obstetrics with Professor Hugh McLaren in Birmingham, and has spent most of his professional life in clinical research within the pharmaceutical industry. He instigated and coordinated the UK trial of antenatal steroids in 1974 while working as a clinical research physician for Glaxo in the UK. Between 1985 and 1994 he worked for Squibb and Bristol-Myers Squibb. He has been an independent consultant in healthcare and pharmaceutical medicine since 1994, while continuing his clinical practice in thoracic medicine.

Professor Geoffrey Dawes

CBE FRCOG FRCP HonFACOG FRS (1918–96), qualified at Oxford in 1943, spent a year at Harvard in 1946. He was Director of the Nuffield Institute

for Medical Research, Oxford, from 1948 to 1985, and was Vice-President of the Royal Society, 1976–77. See Dawes (1968); Robinson (1997); Liggins (1998).

Professor John Gabbay

FFPHM (b. 1949) qualified in medicine at Manchester in 1974. After working on the social origins of medical knowledge for seven years at the University of Cambridge, he trained in public health and carried out qualitative research on NHS management and clinical audit in the 1980s. From 1992 until his retirement in 2004 he was Professor of Public Health and Director of the Wessex Institute of Health Research and Development at the University of Southampton, which houses the National Coordinating Centre for Health Technology Assessment, which he formerly directed. His recent research has focused on the implementation of evidence in clinical practice.

Professor Harold Gamsu

FRCP FRCPCH (1931–2004) graduated from the University of Witwatersrand in 1954. His training in paediatrics commenced there, and continued at the University of Sheffield and at the Cleveland Metropolitan General Hospital, Ohio. He was appointed as Wates Fellow at King's College Hospital, London, in 1965, becoming Reader in Neonatal

Paediatrics and Director of the Regional Neonatal Unit at King's in 1979, and in 1994 he was appointed Professor of Neonatology until his retirement in 1995, later Emeritus. He established the London Perinatal Group in the 1970s, later known as the Thames Regional Perinatal Group. See Gamsu *et al.* (2004).

Dr Dino Giussani

PhD (b. 1967) received his PhD in fetal medicine at UCL and has conducted postdoctoral work at the University of Chile and Cornell University. He was appointed university lecturer at the University of Cambridge in 1993; has been Director for Studies in Pre-clinical Medicine at Gonville and Caius College, Cambridge, since 2000; Fellow of the Lister Institute for Preventive Medicine, Cambridge, since 2001, and Reader in Developmental Cardiovascular Physiology and Medicine since 2004.

Mrs Gill Gyte

MPhil (b. 1948) has been an antenatal teacher with the National Childbirth Trust (NCT) since 1985. She was a volunteer worker on the NCT Research and Information Group from 1990 to 1997 and has been the Consumer Panel Coordinator for the Cochrane Pregnancy and Childbirth Group since 1997.

Dr Stephen Hanney

PhD (b. 1951) trained as a political scientist and has specialized in examining evaluation and policy making in higher education and research. Since 1993 he has worked with Professor Martin Buxton at the Health Economics Research Group, Brunel University, London, developing and applying techniques of assessing payback or benefits from health research.

Professor Jane Harding

ONZM DPhil FRACP FRSNZ (b. 1955) obtained her medical degree at the University of Auckland in 1978 and completed a DPhil in fetal physiology at the University of Oxford in 1982. After specialist paediatric training in New Zealand and a postdoctoral fellowship at the University of California at San Francisco, she joined the faculty of Medicine at the University of Auckland in 1989 and was appointed Professor of Neonatology in 1997. She works as a specialist neonatologist at the National Women's Hospital. She also heads the fetal physiology laboratory and is Deputy Director of the Liggins Institute at the University of Auckland. See Figure 3.

Dr John Hayward

FFPH (b. 1946) was in general practice for 16 years before re-training in public health. From

1994 to 1996 he led the Effective Care Project in maternity services for Camden and Islington Health Authority. He was Director of Public Health in Newham, London, from 2002 until 2005. See Hayward (2001).

Dr Edmund Hey

FRCP (b. 1934) trained as a respiratory physiologist in Oxford and worked for the MRC with Kenneth Cross, Geoffrey Dawes and Elsie Widdowson for some years before moving to Newcastle to get a grounding in paediatrics in 1968. He returned briefly to London in 1973 as a consultant to set up a respiratory intensive care service at Great Ormond Street Hospital, London, but returned to Newcastle in 1977 when the town's first neonatologist, Dr Gerald Neligan, died of leukaemia. Epidemiology, neonatal pharmacokinetics, and the conduct of controlled clinical trials have been his main research interests in recent years.

Professor Ross Howie

FRACP (b. 1933) has held various neonatal paediatric positions at National Women's Hospital and the University of Auckland, New Zealand, from 1962 until 1995. See Appendix 2; see also Figures 1 and 3.

Mr Ian Jones

(b. 1965) has at the Wellcome Trust since 1992 and Publisher since 2003.

Dr William ('Bill') Kitchen

AM MD FRACP FRACOG

(b. 1926) trained at the University of Melbourne Medical School and joined the Children's Hospital in 1953 as a Junior Resident, and was Research Registrar for a year under Drs Howard Williams and Charlo Anderson. Until 1965 he combined work as an outpatient physician at the Hospital with a private paediatric practice. In 1965 he was appointed to a full-time position as First Assistant (equivalent to Associate Professor) in both the University of Melbourne Department of Paediatrics and the Department of Obstetrics and Gynaecology, continuing in this post until 1991. See www.cshs.unimelb.edu.au/programs/jnmhu/witness/references1.html (visited 2 August 2005). See note 57.

Professor Sir Graham

(Mont) Liggins

Kt PhD FRCOG FRCSE FRS

(b. 1926) graduated in medicine at the University of Otago in 1949. He was appointed to a personal chair at the Postgraduate School of Obstetrics and Gynaecology, University of Auckland, in 1971, specializing in endocrinology

and fetal physiology. His most important discovery was that the time of birth was controlled by the fetus, not the mother. See Appendix 1; and Figures 1 and 3.

Professor Sir William Liley

KCMG FRS(NZ) (1929–83)

was trained at Otago University, New Zealand, did research under Professor John Eccles on neuromuscular transmission, switching to obstetrics at the Women's National Hospital, Auckland, from 1959 as a New Zealand Medical Research Council Senior Research Fellow, then at the Auckland University Medical School as Research Professor in Perinatal Physiology from 1969 until his death in 1983. His diagnostic procedure for rhesus haemolytic disease of the newborn was perfected so that he could predict which could remain in the uterus and which could not; he led the team that performed the first successful intrauterine transfusion, and he believed in the rights of the unborn child. See Hawgood (2005).

Professor Richard Lilford

PhD FRCOG FRCP FFPH

(b. 1950) was Consultant Obstetrician and Gynaecologist to Queen Charlotte's Hospital, London, before moving to the University of Leeds in 1984

as Professor of Obstetrics and Gynaecology and Chairman of the Epidemiology Research Institute (1991–5). He has been Professor of Clinical Epidemiology and Head of the Division of Primary Care, Occupational Health and Public Health in the Medical School of the University of Birmingham since 2004. He is also the Director of the Patient Safety Research Programme for the Department of Health in England and is Director of Research Methods Programme, for NHS R&D.

Sir Peter Medawar

OM FRS (1915–87) was Jodrell Professor of Zoology and Comparative Anatomy at University College London from 1951 to 1962. He shared the 1960 Nobel Prize in Physiology or Medicine with Macfarlane Burnet for the discovery of acquired immunological tolerance. Between 1962 and 1971 he was Director of the National Institute for Medical Research at Mill Hill, London, remaining on its scientific staff until 1984. See Mitchison (1990).

Professor Miranda Mugford

DPhil (b. 1950), an economist and health services researcher, joined the National Perinatal Epidemiology Unit at the University of Oxford in 1981. She has been Professor of Health Economics in the School

of Medicine and Health Policy and Practice at the University of East Anglia (UEA), since 1997 and Chair of Convenors of the Campbell and Cochrane Collaboration Economics Methods Group. Her special interest lies in methods used in economic evaluations, especially how methods for systematic review of literature can be incorporated into economic evaluation techniques. See Macfarlane and Mugford (1984).

Mrs Brenda Mullinger

BSc (b. 1949), graduated from the University of Southampton. She was a clinical research associate in the UK (Glaxo, 1972–81) and Canada (Squibb, 1982–85). Working with Dr Clive Dash in the 1970s she coordinated the UK trial of antenatal steroids for the prevention of RDS [Gamsu *et al.* (1989)]. She subsequently moved into medical writing and editing, working as an independent freelance [see for example, Mullinger (1995)] before joining a healthcare communications agency. Most recently she has been a postgraduate research coordinator for the European School of Osteopathy, Maidstone, Kent.

Professor Ann Oakley

PhD (b. 1944) joined the National Perinatal Epidemiology Unit, University of Oxford, as Consultant

in 1979, becoming a Wellcome Research Fellow the following year, and was appointed Senior Research Officer in 1983. She moved to the Thomas Coram Research Unit, University of London, in 1985 as Deputy Director. She has been Director of the Social Science Research Unit at the University of London Institute of Education since 1990 and Professor of Sociology and Social Policy there since 1991. She has been involved in health services research for many years, and has a particular interest in the evaluation of social interventions, methodology and the experiences of health service users.

Dr Sam Richmond

FCRP FRCPC (b. 1949) graduated MB BS at Newcastle upon Tyne in 1972, and has worked for various non-governmental organizations in maternal child health in North Africa and Arabia from 1974 before returning to Newcastle in 1979 to train in paediatrics and neonatology. He has been a consultant neonatologist at Sunderland Royal Hospital since 1988. His research interests include the epidemiology of fetal abnormalities, neonatal screening and resuscitation at birth.

Professor Leonard Strang

MD FRCP (1925–97) trained in the University of Newcastle and joined the Department of Paediatrics at UCL in 1963. His main research interest in clinical paediatrics was in the adaptation of the fetal lung to breathing air. He was President of the Neonatal Society from 1981 to 1984 and received the James Spence Medal of the Royal College of Paediatrics and Child Health. See Boyd (2000).

Sir Alexander (Alec) Turnbull

Kt CBE MD FRCOG (1925–90) was the third Nuffield Professor of Obstetrics and Gynaecology, University of Oxford, from 1973 until his retirement in 1990, later Professor Emeritus; and Honorary Consultant Obstetrician and Gynaecologist for the Oxfordshire Health Authority from 1973 to 1990. He qualified at Aberdeen University in 1947, was appointed Senior Lecturer and Honorary Consultant Obstetrician and Gynaecologist at the University of Dundee from 1957 to 1961; and with Sir Dugald Baird at the University of Aberdeen from 1961 to 1966. In 1966 he moved to the chair of obstetrics and gynaecology and Honorary Consultant Gynaecologist at the Welsh National School of Medicine, Cardiff, as well as advising the Welsh Hospital Board in obstetrics

and gynaecology from 1966 to 1973. He was Adviser in Obstetrics and Gynaecology from 1975 to 1986 to Sir Henry Yellowlees and Sir Donald Acheson as Chief Medical Officer at the Department for Health and Social Security (DHSS). He served on many committees, such as the MRC's Clinical Research Board, 1969–72; the Lane Commission (1973, on which the 1967 Abortion Act was based), 1971–73; and the Medical Education Subcommittee of the University Grants Committee, 1973–83. In 1990 he received the Eardley Holland Medal from the Royal College of Obstetricians and Gynaecologists, London. See I Z M (1990).

Dr Roger Verrier Jones

FRCP FRCP(Ed) Hon FRCPC (b. 1934) trained at Cambridge and University College Hospital, London, in 1961, his house jobs included Senior House Officer at the Hospital for Sick Children, Great Ormond Street, London. He was Consultant Paediatrician at St David's Hospital, Cardiff, from 1969 until his retirement in 1999.

Professor Dafydd Walters

FRCP FRCPC (b. 1947) has been Professor of Child Health at St George's Hospital Medical School, London, since 1994. He trained at UCL taking degrees in physiology

and medicine. He worked later at University College Hospital Medical School in general paediatrics and neonatology from 1974 to 1994, as well as undertaking research into the maturation of the fetal lung. For a short time he worked with Professor John Clements at the Cardiovascular Research Institute (CVRI) in San Francisco, California, on pulmonary surfactant composition. He was Chairman of the Executive of the Physiological Society for 2002–04 and has been chairman of the Historical and Archives Committee of the Physiological Society since 2004.

Mr John Williams

FRCOG (b. 1945) was Consultant Obstetrician and Gynaecologist at the Countess of Chester Hospital, Chester, from 1980 to 2005, formerly Senior Registrar (Lecturer) at the University College Hospital of Wales, Cardiff, from 1977 to 1979.

Dr Peter Williams

CBE FRCP (b. 1925) was a Medical Officer on the headquarters staff of the MRC from 1955 to 1960. He joined the Wellcome Trust in 1960 and was its Director from 1965 to 1991 and the Director of the Wellcome Institute for the History of Medicine from 1981 to 1983.

Professor Maureen Young

PhD (b. 1915) graduated in physiology from Bedford College for Women, where she worked from 1933 to 1938. She spent two years at a London Blood Transfusion Unit at the beginning of the Second World War and returned to teach at Bedford. Later she was one of the first women to join the staff of the Physiology Department at St Thomas' Hospital Medical School, London, after the war. She worked at the hospital for 36 years; later she was invited to join a research unit in Professor Philip Rhodes' Department of Gynaecology, and was given a personal chair in Perinatal Physiology in 1975. She was one of the founder members of the Neonatal Society and was President from 1984 to 1987. See Christie and Tansey (eds) (2001).

Index: Subject

- 1975 UK study *see* UK multicentre trial (Gamsu *et al.*, 1989), 45, 103–8
- ACTH *see* adrenocorticotrophic hormone
- Adelaide, Australia, 44
- adrenal gland, 47, 86, 87, 106
- adrenocorticotrophic hormone (ACTH), 8, 86
- adverse effects of corticosteroids
- adrenal, 47
 - cardiovascular, 47–8
 - general concerns, 19, 29–30, 46, 79, 80–1
 - hazards, 29, 30
 - maternal, 41, 63, 64
 - neurological, 32, 42, 79
- alkaline phosphatase, 5
- American College of Obstetricians and Gynecologists, 34, 72
- American Journal of Obstetrics and Gynecology*, 44, 76, 77
- amnion, rupture, 35, 42–4, 105
- amniotic fluid testing, 30, 33, 105
- animal research, 4, 11, 39–40, 46
- see also* mice, rabbits, sheep
- antenatal *see also* prenatal
- Antenatal Steroids for Term Elective Caesarean Section *see* ASTECS trial
- antibiotics, at parturition, 41, 60, 66, 67, 105; *see also* ORACLE trial
- Archives of Disease in Childhood*, 50, 80
- archiving clinical trial data, 45, 46–7
- Association for the Improvement in Maternity Services, 41
- ASTECS (Antenatal Steroids for Term Elective Caesarean Section) trial, 80; *see also* funding
- Auckland Hospital Board, 15, 95
- Auckland Medical Research Foundation, 95
- Auckland trial of corticosteroids (Liggins and Howie, 1972)
- blood pressure, 48
 - citation analysis, 70
 - design and execution, 9–11, 12–14, 16–18, 81, 82, 86–7, 91–5
 - follow-up studies, 12, 16–17, 19, 22, 82–3, 92–3
 - funding, 13, 20–1, 92, 95, 97
 - gender effects, 26, 38–40
 - neurological effects, 42
 - publications arising from, 23, 33, 101–2
 - reactions to, 11–12, 33, 36, 87–8, 89, 98
 - ruptured membranes, 43–4
- Auckland, University of, New Zealand, 95
- audit, 60–1, 64–8
- Australia
- clinical trials, 78, 79
 - steroid use, 27, 70, 79
- Barcroft Symposium, 43
- β -agonist as a tocolytic, 17
- betamethasone (9- α fluoro-16- β methyl prednisolone)
- Auckland trial, 12–13, 81
 - compared to dexamethasone, 76–7
 - gender specific, 38–40
 - hazards, 29–30
 - meta-analysis, systematic review, 24

- betamethasone (cont.)
 - NIH recommendations, 27
 - review, vs dexamethasone, 76
 - UK trial (betamethasone 21 phosphate, *Betnesol*, Glaxo Laboratories Ltd), 31, 82, 103–8
 - see also* pharmacology
- ‘Betnesol’ *see* betamethasone
- bibliometric analysis, 70
- Bird ventilator, 15
- blobograms, 28 (Figure 4), 65–6
- blood pressure, 48
- BMJ see British Medical Journal*
- brain, effects on
 - adverse, 32, 42, 79
 - long-term, 80–1, 92–3
 - protective, 32–3, 73, 79
- breech presentation, 66–7
- British Association of Perinatal Medicine, 58
- British Journal of Obstetrics and Gynaecology*, 26, 34, 54
- British Medical Journal (BMJ)*, 36, 50, 58, 67, 80
- British National Formulary*, 81
- British Perinatal Mortality Survey, 90
- British United Provident Association (BUPA), 59
- Brunel University, London, 69
- bubble test *see* Clements’ shake test
- BUPA *see* British United Provident Association

- caesarean section
 - antibiotic use, 66, 67
 - steroid use, 80
- Camden and Islington Health Authority, London, 64–8
- Canada, clinical trials, 59, 78
- Canadian Paediatric Society, 59
- Cape Town, South Africa, 30

- cardiotocography (fetal heart rate monitoring), 53
- cardiovascular system
 - antenatal steroids and, 47–8
 - treatment of heart attack, 60
- cerebral palsy, 79
- cervical cancer, 16
- Chester, 34
- Christchurch, New Zealand, 9, 19, 20
- citation analysis, 70
- Clements’ shake test, 30
- Clinical Negligence Scheme for Trusts (CNST), 62
- clinical trials
 - currently recruiting (2004), 29, 44–5, 78–9
 - difficulties in performing, 40–1, 78–9, 81
 - long-term follow-up, 16–17, 77, 80–3
 - repeated courses of treatment, 29, 78–9
 - reviews and meta-analyses, 22–9, 45, 52–7, 62
 - Wellcome Trust’s attitude to funding, 56–7
 - see also* Auckland trial; Collaborative Group on Antenatal Steroid Therapy; Dublin trial; UK multicentre trial; Ten Centre study; OSIRIS; ORACLE; Jobe and Soll (2004); Canada, clinical trials;
- CNST *see* Clinical Negligence Scheme for Trusts
- Cochrane Collaboration, 52, 56, 93
 - logo, 28, 54–6, 57
 - Reviews, 18, 27, 54
- Cochrane Pregnancy and Childbirth Database of Perinatal Trials*, 26, 27

- Collaborative Group on Antenatal Steroid Therapy (NIH, 1981; follow-up, 1984), 22, 25, 26, 36–8, 82
 follow-up studies, 22, 46
 unblinding, problem with, 82
- Columbia Presbyterian Medical School, New York, US, 6
- communications theory, 61, 71
- compensation awards, 74–5
- Confidential Enquiries into Maternal Deaths, Reports on* (Department of Health, various years), 64
- consent, 16–17, 87
- consensus *see* NIH Consensus Conference
- continuous positive airway pressure (CPAP), 15, 94
- convulsions, 53
- cord serum, 30, 82
- cortisol
 lung maturation, 9, 85, 87
 premature labour, 8, 86, 87
- corticosteroids *see* Auckland trial;
 betamethasone; dexamethasone;
 pharmacology
- cortisone acetate, 13, 82
- cost–benefit analysis, 48–9, 50–2, 69–72, 75
- CPAP *see* continuous positive airway pressure
- Data Monitoring Committee, US, 79
- data
 processing, 26, 45, 65–6, 92
 retention, 43–4, 45–6, 46–7, 85
 sharing and preservation, 47
- Department of Health
 funded evidence-based guidelines, 59
 Confidential Enquiries into Maternal Deaths, Reports on, 64
- dexamethasone (9- α fluoro-16- α methyl prednisolone), 27, 76–7
 review, vs betamethasone, 76
- diffusion of innovation, 61, 71
- dosage regimes for prenatal corticosteroids
 Auckland trial, 30
 NIH recommendation, 27
 UK trial, 31, 104, 105
 single course, 29, 30, 42, 46, 77–8
 multiple course, 42, 46, 76–80
- Dublin trial, 23, 53–4
- eclampsia, 60, 61
- Economic and Social Research Council, 47
- Economic and Social Data Service, University of Essex, 47
- economics *see* funding;
 health economics
- ECV *see* external cephalic version
- ‘Effective Care in Labour and Delivery’, 25
- Effective Care in Pregnancy and Childbirth* (Chalmers *et al.*, eds, 1989), 25, 26, 27, 41, 57, 65, 75
- Effective Care Project, 65
- Effectiveness and Efficiency: Random reflections on health services* (Cochrane, 1972), 52
- Effectiveness and Satisfaction in Antenatal Care* (Enkin and Chalmers, eds, 1982), 25
- efficacy data, 24, 25, 28, 35
- epistemology, 61–2, 63, 70, 71, 74
- ethanol, 16–17
- ethical issues, 14, 16–17, 25, 31, 40, 41, 87; *see also* Senior Medical Staff Committee; Data Monitoring Committee
- ethnicity, 26, 39

- evidence-based medicine, 52–4, 56–68, 93
- Exosurf (surfactant), 37
- external cephalic version (ECV), 66–7
- Federation of American Societies for Experimental Biology, 6
- fetal lung maturation *see* lung maturation
- fetal monitoring, 53–4
- fetal physiology, 39
- follow-up studies
 - Auckland trial, 12, 16–17, 19, 22, 82–3, 92–3
 - need for more, 29, 77, 80–1
 - NIH trial, 22, 46
 - UK trial, 45
- formulation, betamethasone, 12–13, 76–7, 81–2
- funding
 - ASTECS trial, 80
 - Auckland follow-up, 12, 92
 - Howie, 92, 95
 - lack of, 13, 78
 - Liggins, 8, 13, 20–1, 86, 97–9
 - NPEU, 54
 - RCTs by the Wellcome Trust, 56–7
 - Wellcome Trust grant to Liggins, 97–9
- gender, 26, 38–40
- gestational age
 - Auckland trial, 17–18
 - indication for steroid use, 27, 80
 - UK trial, 31, 32
- Getting Research Into Practice and Purchasing (GRIPP), 50–1
- Glaxo Laboratories Ltd
 - Auckland trial, 12–13, 87
 - UK trial, 31, 45, 82
- glucocorticoids, 4–10, 12, 17, 30–3, 47–8,
 - GRIPP *see* Getting Research Into Practice and Purchasing
 - guidelines on prenatal corticosteroid use, 27, 57–61, 64–8, 71–2
 - gurus, 63, 74
 - haemolytic disease of the newborn, 90, 95
 - Hammersmith Hospital, London, 23, 24
 - Harvard University, US, 32
 - hazards *see* adverse effects
 - health economics
 - cost–benefit analysis, 48–9, 50–2, 69–72, 75
 - insurance, 62
 - neonatal intensive care, 14–15, 49, 51–2
 - salary costs, 51–2
 - surfactant, 37, 50, 51
 - see also* funding
 - heart attack, 60
 - Hollerith machine, 92
 - hyaline membrane disease *see* respiratory distress syndrome
 - hypophysectomy, 21–2, 86
 - implementation
 - epistemological change, 61–2, 63, 70, 71, 74
 - guidelines, 27, 57–61, 64–8, 71–2
 - reasons for slow uptake, 22, 23, 30–1, 33–7, 48, 67, 68–9
 - use of systematic reviews, 52–7, 63, 64, 71–2
 - user influence, 66, 68, 73–4, 75
 - see also* prescribing practice
 - Index Medicus see* Medline®
 - innovation, 61, 71
 - insulin, 17
 - insurance, 62

- intensive care, neonatal, 14–15, 49,
51–2, 90–1, 93–4
- intestine, maturation of, 5
- intraventricular haemorrhage (IVH),
32, 73
- Irish Perinatal Society, 23
- Jobe and Soll (2004), 76
- Johns Hopkins University, Baltimore,
Maryland, US, 5
- John Radcliffe Hospital, Department
of Obstetrics and Gynaecology,
Oxford, 63
- Journal of Obstetrics and
Gynaecology*, 24
- Journal of Obstetrics and Gynaecology
of the British Empire* (later *British
Commonwealth*), 34
see also *British Journal of Obstetrics
and Gynaecology*
- labour
antibiotic use, 41, 60, 66, 67, 105
control of onset, 8, 16–17, 85–6, 97
inhibitor *see* tocolytic
premature *see* premature labour
tocolytic, 16–17, 23–4, 69, 103–8
use of salbutamol, 17, 103–8
- lambs *see* sheep
- Lancet*, 36, 41, 54, 58, 87
- legal issues, 74–5
- lung disease, long-term costs, 75
- lung maturation
animal studies, 5–6, 9, 10–11,
19–20, 85, 91, 97
bubble test, 30
humans, 6, 20, 25, 85, 87
- magnesium, 60, 61
- Markle Foundation, 5
- Maternal Fetal Medicine Unit
Network, US, 79
- Maternity Services Liaison Committee
(MSLC), Camden and Islington
Health Authority, London, 65–6
- maturation of fetal lungs *see*
lung maturation
- Medical Research Council (MRC),
UK, 3, 47, 78
- Medical Research Council of New
Zealand, 95, 98
- medico–legal issues, 74–5
- Medline®, 52, 90, 101
- Melbourne, Australia, 27
- meta-analysis, 26, 28, 45, 52–7, 77, 93
- mice, 5, 6
- Middlesex Hospital Medical School,
London, 52
- mortality
maternal, 64
neonatal, 15, 24, 25, 36, 72, 93, 94
WHO definition, 94
- mothers
effect of steroids on, 41, 63, 64
influence on policy, 66, 68, 73–4
- MRC *see* Medical Research Council
- MSLC *see* Maternity Services Liaison
Committee
- multiple courses of steroids, 29, 42,
44, 46, 77–9
- National Childbirth Trust (NCT),
41, 73
- National Institute for Health and
Clinical Excellence (NICE),
UK, 62
- National Institutes of Health
(NIH), US
Avery and, 5
Collaborative Group on Antenatal
Steroid Therapy (1981), 25, 26,
36–7, 38, 82
follow-up studies, 22, 46
Consensus Conference (1994), 27,
58, 72

- National Maternity Hospital, Dublin, 23, 53–4
- National Perinatal Epidemiology Unit (NPEU) (Oxford), 25, 45, 49, 54, 75, 78
- National Women's Hospital, Auckland, NZ, 14–15, 16, 89–90, 94–5
- Liggins and Howie at, 8, 85, 95
- Senior Medical Staff Committee, 32, 34
- size and influence, 89–90
- NCT *see* National Childbirth Trust
- negligence, defence against, 62, 74–5
- neonatal intensive care, 10, 14–15, 49, 51–2, 90–1, 93–4
- neonatal mortality, 15, 24, 25, 36, 72, 93, 94
- neurology *see* brain, effects on
- New Zealand
- clinical trials *see* Auckland trial
 - funding of research, 21, 95, 98
 - neonatal intensive care, 10, 14–15, 94
 - steroid use, 70, 79
- NICE *see* National Institute for Health and Clinical Excellence
- NIH *see* National Institutes of Health
- NPEU *see* National Perinatal Epidemiology Unit, Oxford
- Nuffield Institute for Medical Research, John Radcliffe Hospital, University of Oxford, 39
- Liggins' visit (1970), 40
- nurses, 51–2
- Observer*, 61
- obstetricians and paediatricians, 11, 32, 33–4, 90
- Open Study of Infants at High Risk of or with Respiratory Insufficiency – the Role of Surfactant (OSIRIS) Collaborative Group (1992), 37, 68
- opinion leaders, 63, 74
- ORACLE trial, 41
- OSIRIS study *see* Open Study of Infants at High Risk of or with Respiratory Insufficiency – the Role of Surfactant (OSIRIS) Collaborative Group
- Oxford Database of Perinatal Trials, 25, 26, 27, 49; *see also Effective Care in Pregnancy and Childbirth*
- Oxford Regional Health Authority, 50–1
- Paediatric Society, New Zealand, 6
- paediatricians and obstetricians, 11, 32, 33–4, 90
- parturition *see* labour;
- premature labour
- Pediatrics*, 48
- perinatal
- origin of the word, 90
 - perinatal mortality, 15, 24, 25, 36, 72, 93, 94
- periventricular leukomalacia (PVL), 32–3
- Perth (Australia) group, 42, 46, 79
- pharmacology
- betamethasone, 12–13, 76–7, 81–2
 - dexamethasone, 76
 - see also* adverse effects
- physiology, fetal, 39
- pituitary gland, removal *see* hypophysectomy
- placebo, 12–13, 82, 87
- prelabour rupture of fetal membranes *see* ORACLE trial
- premature infants
- intensive care, 14–15, 49, 51–2, 90–1, 93–4
 - postnatal steroids, 6, 32, 80
- prenatal steroids
- morbidity reduction, 24, 31, 32–3, 35, 73, 79, 94

- mortality reduction, 24, 25, 36,
72, 93
see also respiratory distress syndrome
- premature labour
antibiotic use, 41, 60
causes, 8, 86
difficulties in prediction, 42, 44–5,
46, 79–80
prevention, 16–17, 23–4, 69, 105,
107–8
- prenatal steroids *see* Auckland trial;
betamethasone; dexamethasone;
pharmacology; premature infants
- prescribing practice
1970s–1980s, 27, 31–2, 37
1990s to current day, 26–7, 41–2,
71–2, 77–8
audit, 60, 61, 66
reasons for slow uptake, 22, 23,
30–1, 33–7, 48, 67, 68–9
repeated courses, 29, 42, 46, 77–8
see also implementation
- Preterm Labour Study Group
(RCOG), 23
- prolonged rupture of fetal membranes,
35 (Table 4)
- PROM *see* prolonged rupture of fetal
membranes
- protocol, 16–17; 103–8
- psychology, 79, 92–3
- public health, 48–52, 64–5
- publishing, problems with getting
papers accepted, 44, 50, 65,
67–8, 87
poor quality of papers, 3, 34
- PubMed *see* Medline®
- pulmonary oedema, 69
- punch cards, 92
- PVL *see* periventricular leukomalacia
- Qualidata *see* Economic and Social
Data Service
- Quality of Health Care*, 65
- Queen Charlotte's Hospital,
London, 59
- rabbits, 9, 97
- race *see* ethnicity
- randomized controlled trials (RCT)
see clinical trials
- RCOG *see* Royal College of
Obstetricians and Gynaecologists
- RCT (randomized controlled trials)
see clinical trials
- RDS *see* respiratory distress syndrome
- regulatory issues, 40, 77, 81
- repeated courses of steroids, 29, 42,
44, 46, 77–9
- respiratory distress syndrome (RDS)
as cause of death, 15, 23, 90
gender differences, 39
treated vs untreated, 24, 31, 35,
73, 97
ventilation for, 15, 73
- rhesus factor, 90
- Ross Conference on Pediatric Research,
29, 33, 40
- Royal College of Obstetricians and
Gynaecologists (RCOG)
guidelines, 27, 57–9, 64, 71, 88
Howie and, 11
President's Newsletter, 59
Preterm Labour Study Group, 23
survey of steroid use, 36, 37
- Royal Free Hospital, UCL, London, 65
- Ruakura Agricultural Research Station,
New Zealand, 11, 86
- rupture of fetal membranes, 35,
42–4, 105
- S-curve of innovation diffusion, 61, 71
- safety *see* adverse effects
- salbutamol (*Ventolin*, Allen &
Hanburys Ltd), 17, 105, 107–8

- San Francisco (US) group, 14, 15
 scientific method, 3–4, 39–41
 retaining data, 43–4, 45, 47
 see also publishing, problems with
 Senior Medical Staff Committee,
 National Women’s Hospital,
 Auckland, 32, 34, 87
 70th Ross Conference on Pediatric
 Research *see* Ross Conference on
 Pediatric Research
 sex (gender), differential effects of
 corticosteroids on, 26, 38, 39, 40
 sheep
 fetal hypophysectomy, 21–2
 fetal lung development, 5–6, 9,
 10–11, 19–20, 85, 91, 97
 side-effects *see* adverse effects
 skunk cabbage, 85
Social Science and Medicine, 69
 Society of Obstetricians,
 New Zealand, 5
 South Africa, 30, 67
 St David’s Hospital, Cardiff, 34–6,
 63, 64
 St Louis, Missouri, US, 5
 statistics, 53, 65–6
 streptokinase, 60, 64
 Stutchfield *et al.* (2005), 80
 sulphatase deficiency, placental, 98
 sulphide preservatives, 81
 surfactant, 9–10, 18, 20, 36, 50, 59,
 72–3, 87
 Avery and Kotas discovery, 9, 97
 bubble or shake test, 30
 clinical trials, 18, 37
 cost, 37, 51
 Dawes and, 40
 function, 9
 induction by steroids, 85, 87, 97
 see also Canadian Paediatric
 Society; Exosurf; OSIRIS; health
 economics
 suturing, 60, 66–7
 systematic reviews, 26–7, 32–4, 42,
 44, 48, 50, 53–9, 63, 71–5
 TEAMS *see* Trial of the Effects of
 Antenatal Multiple courses of
 Steroids
 Ten Centre Study, UK, 37
 Third Programme (BBC Radio), 3
 30-year-old Auckland trial subjects,
 16–17
 thrombolytic drugs, 60, 64
 tocolytic, 16–17, 23–4, 69, 105,
 107–8
 ethanol, 16–17
 β -agonist, 17
 Trial of the Effects of Antenatal
 Multiple courses of Steroids
 (TEAMS), 78
 triplets, 78
 twins
 animal studies, 10–11, 19–20, 91
 human, 77, 78
 type 2 error, 53
 UK
 attitude to Liggins and Howie’s
 work, 11, 33, 36, 87–8
 clinical trials, 22–9, 45, 52–7, 62;
 see also UK multicentre trial; Ten
 Centre Study
 steroid use, 27, 31–2, 37, 70–1, 72
 UK Data Archive, 47
 UK multicentre trial of betamethasone
 phosphate in the prevention of
 RDS (Gamsu *et al.* 1989; also
 called 1975 UK study)
 design, 12, 17, 32, 82, 103–8
 follow-up studies, 45
 recruitment problems, 31–2, 68–9
 Université de Paris, 30

- University of California at Davis,
 - veterinary school, 8, 21, 86
- University College Hospital, London,
 - 5, 65
- University Hospital of Wales, 34
- uptake of prenatal corticosteroids *see*
 - also* implementation; prescribing practice
- USA
 - clinical trials, 79
 - steroid availability, 77
 - veterinary school, 8, 21, 86
 - see also* Collaborative Group on Antenatal Steroid Therapy; National Institutes of Health
- ventilation of neonates, 10, 15, 73,
 - 90–1, 94
- ventouse, 58, 60
- Veratrum californicum*, 85
- veterinary school *see* USA
- vicryl rapide, 66
- Wellcome Trust
 - archiving clinical trial data, 47
 - attitude to RCTs, 56–7
 - bibliometric analysis, 70
 - funding Liggins, 8, 20–1, 86, 97–9
 - Witness Seminar on ‘Origins of Neonatal Intensive Care in the UK’, 36, 52
- Whittington Hospital, London, 65
- WHO *see* World Health Organization
- women in science, 23
- World Health Organization (WHO),
 - 12, 15, 92, 93, 95
 - definition of perinatal mortality, 94

Index: Names

Biographical notes appear in bold

- Anderson, Anne, 25
 Avery, Mary Ellen (Mel), 4–6, 9, 19–20, 20, 23, 29–30, 31, 32, 39, 40, 46, 85, 89, **129**
- Ballard, Phil, 14, 30
 Ballard, Roberta, 14, 30
 Barcroft, Sir Joseph, 5, **129**
 Barker, David, 93
 Barron, Don, 5
 Becroft, David, 95
 Bernard, Claude, 91
 Bonham, Dennis, 90
 Booth, Sir Christopher, 20, **129**
 Braunholtz, David, 59
 Brocklehurst, Peter, 41–2, 46, 72, 75–81, 81–2, **129–30**
 Buckingham, Sue, 6
 Burri, P H, 30
 Butler, Neville, 90
 Buxton, Martin, 69
- Carey, Harvey, 90, 95
 Caughey, Sir Harcourt, 95
 Chalmers, Sir Iain, 8, 18–19, 25, 35, 39–40, 47, 49, 52–7, 64, 73, 85, 93, **130**
 Clayton, Sir Stanley, 34
 Clements, John, 14
 Cochrane, Archie, 52, **130**
 Cross, Kenneth, 3
 Crowley, Patricia, 22, 23–9, 32–3, 36–7, 41, 42, 52, 53, 65, 73, 74–5, 93, **130**
 Crowther, Caroline, 44
- Dalziel, Stuart, 18, 82, 93
 Dash, Clive, 11, 12, 17, 31, 32, 45, 76, 80, **130**
- Dawes, Geoffrey, 39, 40, **130–1**
 deLemos, R A, 85
 Dezoete, Anne, 16
 Donaldson, Sir Liam, 58
 Dukes, Peter, 47
 Duley, Lelia, 60, 61
 Duncan, Sheila, 54
- Gabbay, John, 19, 20, 63, **131**
 Gamsu, Harold, 16, 45, 46, 52, 68–9, 82, **131**
 Giussani, Dino, 47–8, **131**
 Glass, Gene, 53
 Grant, Adrian, 49
 Grant, Jonathan, 69
 Gregory, George, 94
 Gross, N C, 61
 Gyte, Gill, 17, 41, 73, **131**
- Hanney, Stephen, 21, 36, 69–72, **132**
 Harding, Jane, 7–8, 9–14, 16–17, 18, 19, 20–1, 22, 33, 42–4, 44–5, 46, 48, 73, 82–3, 93, **132**
 Hawkins, Denis, 24
 Hayward, John, 48–9, 64–8, **132**
 Henley, Wilton, 95
 Hewison, Jenny, 59
 Hey, Edmund, 3–4, 6–7, 12, 13, 18, 21, 22–3, 29, 37, 40–1, 41, 44, 45, 46, 49, 51, 52, 57, 59, 68, 73, 75, 80, 81, 82, 83, **132**
 Hollins, Margaret, 95
 Howie, Ross, 6, 7, 9, 10–11, 12, 15, 16, 18, 22, 30, 33, 38, 43, 70, 76, 87, 89–95, **132**
 Huppi, Petra, 32
 Hytten, Frank, 54

- Jobe, Alan, 76
 Jones, Ian, 20, **133**

 Keirse, Marc, 58
 Kettle, Christine, 66
 Killam, A P, 40
 Kitchen, William (Bill), **133**
 Kitterman, Jo, 14
 Knight, David, 43
 Kotas, R V, 97

 Laurie, Ray, 95
 Liggins, Sir Graham (Mont), 4, 6, 7,
 8–9, 10, 12, 13, 14, 18, 20–1, 30,
 33, 40, 43, 70, 82, 85–8, 89,
 97–9, **133**
 Liley, Sir William (Bill), 8, 85, 90, **133**
 Lilford, Richard, 14, 30–1, 46–7,
 57–62, 71, 72, **133–4**

 MacArthur, Barton, 16, 92
 Macfarlane, Alison, 49
 Matthews, Jack, 90
 McMichael, Sir John, 98
 McPherson, Klim, 53
 Medawar, Sir Peter, 3–4, **134**
 Moog, Florence, 5
 Moore, T D, 40
 Mostyn, David, 55
 Mugford, Miranda, 14, 49–51, 52,
 63–4, 69, 72, 75, **134**
 Mullinger, Brenda, 16, 31–2, 45,
 69, **134**

 Newnham, John, 42, 46

 Oakley, Ann, 15–16, 74, **134–5**

 Page, Lesley, 59
 Paintin, David, 54
 Pattle, Richard, 30, 31
 Peckham, Sir Michael, 54

 Phillips, Leo, 91
 Piercy, James, 50, 63
 Popper, Karl, 3
 Pritchard, Steve, 52

 Richards, Martin, 53
 Richmond, Sam, 37–8, 39, **135**
 Robertson, Cliff, 34, 36, 38
 Robinson, Michael, 59
 Rodgers, Anthony, 93
 Rogers, Everett, 61, 71
 Rudbecke, Birgitta, 75
 Ryan, B, 61

 Sachs, Ben, 24
 Sayers, Sue, 94
 Simmons, Sir Stanley, 57
 Sinclair, Jack, 59
 Smith, Clement, 5
 Soll, Roger, 76
 Stewart, John, 95
 Stocking, Barbara, xxi–xxii, 73
 Strang, Leonard, 5, **135**
 Stutchfield, Peter, 80

 Thornton, Jim, 58, 59
 Tooley, Bill, 14
 Turnbull, Sir Alec, 63–4, **135–6**

 Verrier Jones, Roger, 34–6, 63, 64, **136**

 Walters, Dafydd, 17, 18, 40, **136**
 Watkins, John, 3
 Watt, Ian, 59
 Williams, Alan, 50
 Williams, John, 34, 62, 63, **136**
 Williams, Peter, 86, 98, 99, **136**

 Young, Maureen, 5, **137**

Key to cover photographs

Front cover, top to bottom

Dr Edmund Hey, Chair

Dr Mary Ellen (Mel) Avery

Professor Jane Harding

Sir Iain Chalmers

Back cover, top to bottom

Professor Harold Gamsu[†]

Dr Patricia Crowley

Professor Miranda Mugford

Dr Roger Verrier Jones

[†]Died 31 August 2004

