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PRENATAL CORTICOSTEROIDS FOR REDUCING MORBIDITY AND MORTALITY AFTER PRETERM BIRTH

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

20/22

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PRENATAL CORTICOSTEROIDS FOR REDUCING MORBIDITY AND MORTALITY

Participants

- ✓ Dr Mary Ellen (Mel) Avery
- ✓ Sir Christopher Booth (2)
- ✓ Dr Peter Brocklehurst
- email dated 7/11/05 ✓ Sir Iain Chalmers
- Professor 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) ✓(2)
- ✓ Dr Ian Jones
- ✓ Professor Richard Lilford
- ✓ Professor Miranda Mugford
- ✓ Mrs Brenda Mullinger
- ✓ Professor Ann Oakley
- ✓ Dr Sam Richmond
- ✓ Dr Roger Vernier Jones
- ✓ Professor Dafydd Walters
- ✓ Mr John Williams

Among those attending the meeting:

Professor Richard Beard, Dr Sheila Duncan, Professor Abby Fowden, Dr Anita Magowska, Dr John Muir Gray, Ms Alison Macfarlane, Dr David Paintin, Professor Maureen Young

Apologies include:

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[†]Died 31 August 2004

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10/1/06

missing Crowley.

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Missing Chalmers x Crowley.

20/3/07

FIRST DRAFT
7 DECEMBER 2004

Participants

Dr Mary Ellen (Mel) Avery ✓
Sir Christopher Booth ✓
Dr Peter Brocklehurst ✓
Sir Iain Chalmers ✓
Professor Patricia Crowley ✓
Professor John Gabbay ✓
~~Professor Harold Gamsu~~*
Dr Gino Giussani ✓
Mrs Gill Gyte ✓
Dr Stephen Hanney ✓
Professor Jane Harding ✓
Dr John Hayward ✓
Dr Edmund Hey (Chair) ✓
Dr 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 ✓

*Died 2004

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

Reproduced by permission of Dr Ross Howie.

Prenatal Corticosteroids for Reducing Morbidity and Mortality After Preterm Birth

Reynolds L A, Tansey E M. (eds) (2005) *Wellcome Witnesses to Twentieth Century Medicine*, vol. 25. London: The Wellcome Trust Centre for the History of Medicine at UCL. xxii+150pp, 191mm x 234mm.

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In 1959 the New Zealand obstetrician Graham (Mont) Liggins began investigating mechanisms that triggered premature labour. Supported by the Wellcome Trust, he examined the effects of hormones on labour in sheep, and demonstrated co-incidentally that *in utero* corticosteroids accelerated fetal lung maturation. A randomized controlled trial (RCT) of prenatal corticosteroids in humans by Liggins and pediatrician Ross Howie, showed a reduction of respiratory distress syndrome in preterm babies. This Witness Seminar, chaired by Dr Edmund Hey, discussed the influence of Liggins' and Howie's 1972 paper announcing these results, and subsequent work by Avery and Kotas on induction of pulmonary surfactant in lambs. Other subjects included Crowley's 1981 systematic review of four RCTs; the low uptake of corticosteroids in practice until the Royal College of Obstetricians and Gynaecologists issued usage guidelines in 1992; trials to determine optimum drug, dose and number of courses; potential adverse effects; and cost–benefit analysis. Participants included Dr Mel Avery, Sir Iain Chalmers, Dr Patricia Crowley, the late Professor Harold Gamsu, Professor Jane Harding, Professor Richard Lilford, Professor Miranda Mugford, Professor Ann Oakley, Professor Dafydd Walters and Mr John Williams. Appendices from Liggins and Howie; Liggins' Wellcome Trust grant; and the protocol of the 1975 UK trial of betamethasone, complete the volume.

THE WELLCOME TRUST CENTRE FOR THE HISTORY OF MEDICINE AT UCL

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British Medical Journal (2002) **325**: 1119, review of the series

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23. The recent history of platelets in thrombosis and other disorders
24. Short-course chemotherapy for tuberculosis
25. Prenatal corticosteroids for reducing morbidity and mortality after preterm birth
26. Public health in the 1980s and 1990s: Decline and rise? (In Press)
27. Fifty years of cholesterol, atherosclerosis and coronary disease in the UK, 1950–2000 (In Press)
28. The development of physics applied to medicine in the UK, 1945–90 (In Press)

Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth

Witness Seminar – Tuesday 15th June, 2004

To be held in Franks I & II, Mezzanine Floor, The Wellcome Building, 183 Euston Road, London NW1 starting at 2.00pm

In the late 1960s, Graham (Mont) Liggins, a professor of obstetrics in Auckland, New Zealand, investigated parturition in sheep. He noticed that lambs born to ewes whose labour had been induced prematurely with corticosteroids had air in their lungs, which suggested that steroids might accelerate lung surfactant production. These observations were confirmed within a year, in the USA by De Lemos and Avery, who also reported that corticosteroid administration was associated with the appearance of surfactant in lamb lungs.

Liggins and a paediatric colleague, Ross Howie, began a statistically powerful randomised control trial (RCT) at the National Women's Hospital in Auckland, to assess whether administering corticosteroids to women expected to deliver preterm would reduce the associated neonatal morbidity and mortality. This yielded one of the most important discoveries in perinatal medicine. It showed that an inexpensive and widely applicable treatment resulted in a clinically and statistically highly significant reduction in morbidity and mortality among infants whose mothers had received steroids. Initially rejected by the *Lancet* the study was published in *Pediatrics* in 1972.

Several replications of the Liggins and Howie RCT during the 1970s and 1980s were statistically much less powerful than the original trial. As a result there was confusion and uptake of the treatment was very patchy. In 1989 the Irish obstetrician, Patricia Crowley published a systematic review and meta-analysis of the RCTs, which made crystal clear the strength of the accumulated evidence, and the discovery began to influence clinical practice. Partly because there was no commercial interest in this use of corticosteroids, uptake in clinical practice remained far from adequate, and steps were taken to address this situation. During the mid-1990s, clinicians in the UK began to be influenced by 'getting research into practice' initiatives and clinical guidelines prepared by the Royal College of Obstetricians and Gynaecologists, while a National Institutes of Health Consensus Conference was influential in the USA. Concurrently, the health economist Miranda Mugford, showed that prenatal steroids were highly cost-effective. The potential of Liggins and Howie's discovery began at last to be realised, nearly two decades after their report had been published. A recent analysis by Stephen Hanney and others judged that investment in all phases of this work – from animal research to the systematic review of RCTs – was one of the most striking examples of cost-effective payback from research.

Participants who hope to attend include

Dr Mary Ellen Avery, Professor Richard Beard, Dr Peter Brocklehurst, Professor Martin Buxton, Sir Iain Chalmers, Dr Patricia Crowley, Dr Sheila Duncan, Professor John Gabbay, Professor Harold Gamsu, Dr John Muir Gray, Mrs Gill Gyte, Dr Stephen Hanney, Professor Jane Harding, Dr John Hayward, Dr Roger Verrier Jones, Professor Richard Lilford, Professor Miranda Mugford, Mrs Brenda Mullinger, Professor Ann Oakley, Dr Sam Richmond, Professor Dafydd Walters, Mr John Williams, Professor Maureen Young

The meeting will be chaired by Dr Edmund Hey

Space is limited, so please contact Mrs Wendy Kutner if you wish to attend. The Wellcome Trust Centre for the History of Medicine at UCL, 24 Eversholt Street, London NW1 1AD. Tel: 020-7679-8106; Fax: 020-7679-8193; E-mail: w.kutner@ucl.ac.uk. www.ucl.ac.uk/histmed

Liggins tape in Harding presentation

History of Twentieth Century Medicine

UCL

ATTENDANCE LIST

Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth

Witness Seminar – Tuesday 15th June, 2004

Attending

✓ Alison Macfarlane
✓ Dr Mary Ellen Avery
✓ Mr Richard Barnett
— Professor Richard Beard
✓ Professor Sir Christopher Booth
✓ Dr Peter Brocklehurst
~~Professor Martin Buxton~~ hernia op tomorrow
✓ Sir Iain Chalmers
Dr Michael Chew
✓ Professor Patricia Crowley
✓ Dr Sheila Duncan
✓ Professor Abby Fowden
✓ Professor John Gabbay
✓ Professor Harold Gamsu
✓ Dr Gino Giussani
✓ Mrs Gill Gyte
✓ Dr Lesley Hall V2
✓ Dr Stephen Hanney
✓ Professor Jane Harding
✓ Dr John Hayward
✓ Dr Edmund Hey
✓ Professor Richard Lilford
✓ Dr Anita Magowska
Miss Kathryn Michaud
Dr Quen Mok —— apology received
✓ Professor Miranda Mugford
✓ Mrs Brenda Mullinger
✓ Professor Ann Oakley
✓ Dr David Paintin
✓ Dr Sam Richmond
✓ Dr Roger Verrier Jones
✓ Professor Dafydd Walters
✓ Dr Lise Wilkinson
✓ Mr John Williams
✓ Professor Maureen Young
Ian Jones, Publicity

staff

Dr Daphne Christie
Mrs Wendy Kutner
Mrs Lois Reynolds
Dr Tilli Tansey

Apologies

Dr Herbert Barrie
Professor Sir Robert Boyd
Professor Geoffrey Chamberlain
Dr Stuart Dalziel
Dr Clive Dash
Dr Pamela Davies
Professor Sir Liam Donaldson
Professor James Drife
Professor Peter Dunn
Dr Jonathan Grant
Dr John Muir Gray
Dr Selena Gray
Professor Aidan Halligan
Professor Mark Hanson
Dr Nick Hicks
Professor Ross Howie
Professor Frank Hytten
Professor Marc Keirse
Professor Sir Graham Liggins
Dr Jerold Lucey
Professor Sally MacIntyre
Dr Jonathan Mant
Ms Clare Matterson
Professor Jim Neilson
Professor Colin Normand
Dr Sandy Oliver
Professor Osmund Reynolds
Dr Cliff Roberton
Mr Martin Sexton
Dr Jean Smellie
Ms Barbara Stocking
Dr Peter Stutchfield
Dr Peter Williams
Professor Mark Walport
Professor Jonathan Wigglesworth

15 June 2004

WT01-2138/25k/9-2000/AW

To with Hts
(Transcription -)
names

ATTENDANCE LIST

Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth

Witness Seminar – Tuesday 15th June, 2004

Attending

Dr Mary Ellen Avery
Mr Richard Barnett
Professor Richard Beard
Professor Sir Christopher Booth
Dr Peter Brocklehurst
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Sir Iain Chalmers
Dr Michael Chew
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Dr Gino Giussani
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Dr Lesley Hall
Dr Stephen Hanney
Professor Jane Harding
Dr John Hayward
Dr Edmund Hey
Professor Richard Lilford
Dr Anita Magowska
Miss Kathryn Michaud
Dr Quen Mok
Professor Miranda Mugford
Mrs Brenda Mullinger
Professor Ann Oakley
Dr David Paintin
Dr Sam Richmond
Dr Roger Verrier Jones
Professor Dafydd Walters
Dr Lise Wilkinson
Mr John Williams
Professor Maureen Young

staff
Dr Daphne Christie
Mrs Wendy Kutner
Mrs Lois Reynolds
Dr Tilli Tansey

Liggins (recording)
Howie (Ltr)
Ian Jones (WT)

Apologies

Dr Herbert Barrie
Professor Sir Robert Boyd
Professor Geoffrey Chamberlain
Dr Stuart Dalziel
Dr Clive Dash
Dr Pamela Davies
Professor Sir Liam Donaldson
Professor James Drife
Professor Peter Dunn
Dr Jonathan Grant
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Professor Jonathan Wigglesworth

15 June 2004

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Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth

Witness Seminar – Tuesday 15th June, 2004

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~~Professor James Drife~~
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Professor Osmund Reynolds
Dr Cliff Roberton
Mr Martin Sexton
Dr Jean Smellie
Ms Barbara Stocking
Dr Peter Stutchfield
Dr Peter Williams
Professor Mark Walport
Professor Jonathan Wigglesworth

* main witness

37

10 June 2004

Awaiting replies
Dr Alison Hill, public health specialist, Oxford
Mr Derek Tacchi, retired obstetrician, Newcastle

Other suggestions
Mr Paul Donnai (Gamsu)
Professor Denys Fairweather (Walters)
Dr Alison Hislop (Walters)
Professor Richard Olver (Boyd, Walters)
Professor Rodney Rivers (Paintin)
Professor Charles Rodeck (Walters)
Professor Phillip Steer (Paintin)
Dr Saffron Whitehead
Professor Andrew Whitelaw (Gamsu)
Professor Charles Whitfield (Gamsu)

Send to Chalmers + Hey
Sent 8/6/04

ATTENDANCE LIST

Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth

Witness Seminar – Tuesday 15th June, 2004

Attending

Dr Mary Ellen Avery*
Professor Richard Beard
Dr Peter Brocklehurst*
Professor Martin Buxton
Sir Iain Chalmers*
Dr Michael Chew
Professor Patricia Crowley*
Professor James Drife
Dr Sheila Duncan ? flyer-let ✓
Professor Abby Fowden
Professor John Gabbay
Professor Harold Gamsu*
Dr Gino Giussani ? Flyer let –
Dr John Muir Gray
Mrs Gill Gyte
Dr Lesley Hall
Dr Stephen Hanney*
Professor Jane Harding*
Dr John Hayward
Dr Edmund Hey*
Professor Richard Lilford*
Dr Anita Magowska
Miss Kathryn Michaud
Dr Quen Mok
Professor Miranda Mugford*
Mrs Brenda Mullinger
~~Professor Colin Normand~~ ? flyer let ✓
Professor Ann Oakley
Dr David Paintin
Dr Sam Richmond
~~Mr Martin Sexton~~ ?
~~Dr Jean Smellie~~ ? flyer let –
Professor Dafydd Walters
Mr John Williams
Professor Maureen Young ? flyer let ✓
Dr Roger Vaman Soreg ?

* main witness

Ms Alison Macfarlane?

Apologies

Dr Herbert Barrie
Professor Sir Robert Boyd
Professor Geoffrey Chamberlain
Dr Stuart Dalziel
Dr Clive Dash
Dr Pamela Davies
Professor Sir Liam Donaldson
Professor Peter Dunn
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Witness Seminar – Tuesday 15th June, 2004

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Dr Michael Chew
~~Professor~~ Patricia Crowley*
Professor James Drife
Dr Sheila Duncan
Professor Abby Fowden
Professor John Gabbay
Professor Harold Gamsu*
Dr Gino ~~Guissani~~ GIUSSANI + to flyer?
Dr John Muir Gray
Mrs Gill Gyte
Dr Lesley Hall
Dr Stephen Hanney*
Professor Jane Harding*
Dr John Hayward
Dr Edmund Hey*
Professor Richard Lilford*
Dr Anita Magowska
Miss Kathryn Michaud
Dr Quen Mok
Professor Miranda Mugford*
Mrs Brenda Mullinger
~~Dr Colin Normand~~ + to flyer as attending
Professor Ann Oakley
Dr David Paintin
~~Professor Osmund Reynolds~~
Dr Sam Richmond
~~Mr Martin Sexton~~
~~Dr Jean Smellie~~ + to flyer?
Professor Dafydd Walters
Mr John Williams
Professor Maureen Young
Dr Roger Vernet Jones [? Alison Macfarlane?]
* main witness

Apologies

Professor Sir Robert Boyd
Professor Geoffrey Chamberlain
Dr Stuart Dalziel
Dr Clive Dash
Dr Pamela Davies
Professor Sir Liam Donaldson
Professor Peter Dunn
Dr Jonathan Grant + Nicola Hodos (NI)
Dr Selena Gray
Professor Aidan Halligan
Professor Mark Hanson
Professor Ross Howie
Professor Frank Hytten
Professor Marc Keirse
Professor Sir Graham Liggins
Dr Jerold Lucey
Professor Sally MacIntyre
Dr Jonathan Mant
Ms Clare Matterson
Professor Jim Neilson
Dr Sandy Oliver
Dr Cliff Roberton
Ms Barbara Stocking
Dr Peter Stutchfield
Dr Peter Williams
Professor Mark Walport
Professor Jonathan Wigglesworth

PBF

tt
DC
LR
WK

~~42~~ 7/6/04

37 9/6/04

3 June 2004

Awaiting replies
Dr Nick Hicks, public health specialist, Oxford
Dr Alison Hill, public health specialist, Oxford
Mr Derek Tacchi, retired obstetrician, Newcastle
Dr Roger Verrier Jones, retired paediatrician, Cardiff ✓ invite to attend

Other suggestions
Mr Paul Donnai (Gamsu)
Professor Denys Fairweather (Walters)
Dr Alison Hislop (Walters)
~~Professor Colin Normand~~ (Boyd)
Professor Richard Olver (Boyd, Walters)
Professor Rodney Rivers (Paintin)
Professor Charles Rodeck (Walters)
Professor Phillip Steer (Paintin)
Dr Saffron Whitehead
Professor Andrew Whitelaw (Gamsu)
Professor Charles Whitfield (Gamsu)

3 June 2004

ATTENDANCE LIST

Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth

Witness Seminar – Tuesday 15th June, 2004

Attending

✓ Dr Mary Ellen Avery*
✓ Dr Peter Brocklehurst*
✓ Professor Martin Buxton
✓ Sir Iain Chalmers*
✓ Professor Patricia Crowley*
✓ Professor James Drife
✓ Professor John Gabbay
✓ Professor Harold Gamsu*
✓ Dr John Muir Gray
✓ Mrs Gill Gyte
✓ Dr Stephen Hanney*
✓ Dr Edmund Hey*
✓ Professor Richard Lilford*
✓ Professor Miranda Mugford*
✓ Professor Ann Oakley
✓ Dr David Paintin
✓ Professor Osmund Reynolds
✓ Dr Sam Richmond
✓ Professor Dafydd Walters
✓ Professor Maureen Young

(20)

Apologies

Professor Sir Robert Boyd
Dr Pamela Davies
Professor Sir Liam Donaldson
Professor Peter Dunn
Professor Aidan Halligan
Professor Mark Hanson
Professor Frank Hytten
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Dr Jerold Lucey
Professor Sally MacIntyre
Dr Jonathan Mant
Professor Jim Neilson
Dr Cliff Roberton
Ms Barbara Stocking
Dr Peter Stutchfield
Dr Peter Williams
Professor Mark Walport

* main witness

rmroberts 21/4
cullendaas 26/4
Mike Laycock 26/4
WT nmeeboards 26/4 + Centre nmeeboards 26/4

e-mail notifications of meetings

20 April 2004

ATTENDANCE LIST

Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth

Witness Seminar – Tuesday 15th June, 2004

Attending

Dr Mary Ellen Avery*
Dr Peter Brocklehurst*
Professor Martin Buxton
Sir Iain Chalmers*
Professor Patricia Crowley*
Professor James Drife
Professor Harold Gamsu*
Dr Stephen Hanney*
Dr Edmund Hey*
Professor Miranda Mugford*
Dr David Paintin

Professor Osmund Reynolds

Apologies

Professor Sir Liam Donaldson
Professor Frank Hytten
Professor Marc Keirse
Professor Sir Graham Liggins
Dr Jerold Lucey
Dr Jonathan Mant
Ms Barbara Stocking

Awaiting replies

(Main Witnesses marked with *)
Prof Geoffrey Chamberlain, retired obstetrician, Cardiff
Dr Pamela Davies, retired paediatrician, London
Prof Peter Dunn, retired paediatrician, Bristol
Dr Jonathan Grant, RAND Europe, Cambridge
Dr Muir Gray, public health specialist, Oxford
Dr Selina Gray, public health specialist, Bristol
Dr Gill Gyte, formerly National Childbirth Trust, Poulton-le-Fylde
Dr Aidan Halligan, deputy chief medical officer, DH, London
Dr John Hayward, public health specialist, London
Dr Nick Hicks, public health specialist, Oxford
Dr Alison Hill, public health specialist, Oxford
Professor Richard Lilford*
Prof Sally Macintyre, medical sociologist, Glasgow
Prof Jim Neilson, obstetrician, Liverpool
Prof Ann Oakley, medical sociologist, London
Dr Sandy Oliver, formerly National Childbirth Trust, London
Dr Cliff Roberton, retired paediatrician, Cardiff
Dr Sam Richmond, paediatrician, Tyne and Wear
Mr Derek Tacchi, retired obstetrician, Newcastle
Dr Roger Verrier Jones, retired paediatrician, Cardiff
Prof Jonathan Wigglesworth, retired paediatrician, Cardiff
Mr John Williams, obstetrician, Chester

Witness Seminar: Prenatal corticosteroids – 15th June 2004

12/5/04 + Dr Sheila Duncan

Attending

Dr Mary Ellen Avery*
Professor Richard Beard
Dr Peter Brocklehurst*
Professor Martin Buxton
Sir Iain Chalmers*
Professor Patricia Crowley*
Professor James Drife
Professor John Gabbay
Professor Harold Gamsu*
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Professor Osmund Reynolds
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Professor Dafydd Walters
Mr John Williams
Professor Maureen Young

Apologies

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Professor Sally MacIntyre
Dr Jonathan Mant
Professor Jim Neilson
Dr Cliff Roberton
Ms Barbara Stocking
Dr Peter Stutchfield
Dr Peter Williams
Professor Mark Walport
Professor Jonathan Wigglesworth

Awaiting replies

Dr Stuart Dalziel, NZ (hard copy in post)	21/4	
Dr Selina Gray, public health specialist, Bristol	28/3	21/4
Professor Jane Harding, NZ (hard copy in post)	21/4(f)	22/4(e)
Dr John Hayward, public health specialist, London	19/3	21/4
Dr Nick Hicks, public health specialist, Oxford	25/3	21/4
Dr Alison Hill, public health specialist, Oxford	25/3	21/4
Dr Sandy Oliver, formerly National Childbirth Trust, London	19/3	21/4
Mr Derek Tacchi, retired obstetrician, Newcastle	25/3	21/4
Dr Roger Verrier Jones, retired paediatrician, Cardiff	25/3	21/4
Prof Jonathan Wigglesworth, retired paediatrician, Cardiff	19/3	21/4

Professor Jane Harding FRACP FRSNZ, Dept of Neonatology, University of Auckland, Private Bag 91029, Auckland, NEW ZEALAND (f) 00 649 3737497	Dr Stuart Dalziel, Research Fellow, Clinical Trials Research Unit, University of Auckland, Private Bag 92019, Auckland, NEW ZEALAND (f) 00 649 373 7481

(e) j.harding@auckland.ac.nz	
Dr Nick Hicks, Upper Dolcoppice Farm, Whitwell, Ventnor P038 20B	Dr Selina Gray FFPHM FRCP, Research & Development Directorate, Westward House, Lime Kiln Close, Stoke Gifford, BRISTOL BS34 8SR
Dr Sandy Oliver, Reader in Public Policy, Institute of Education, University of London 20 Bedford Way London WC1H 0AL	Dr Alison Hill, Buckinghamshire Health Authority, Vernley House, Gatehouse Road, Aylesbury HP19 8ET
Dr Roger Verrier Jones, FRCP Ed., FRCP, Hon. FRCPCH, Greenfields, Newport Road, St Mellons, Cardiff CB3 5TW	Mr Derek Tacchi TD FRCOG, 2 Oakfield Road, Gosforth, Newcastle upon Tyne NE3 4HS

Other suggestions (to be sent flyers today)

Mr Paul Donnai FRCOG, Dept of Obstetrics & Gynaecology, St Mary's Hospital, MANCHESTER M13 0JH (Consultant Obstetrician) **sb** Gamsu	Professor Denys Fairweather, 37 Lyndhurst Avenue, Mill Hill, LONDON NW7 2AD **sb** Walters
Dr Alison Hislop, Developmental Vascular Biology & Pharmacology Unit, Great Ormond Street Hospital NHS Trust, Great Ormond Street, LONDON WC1N 3JH **sb** Walters	Sir David Hull (Dept of Child Health, University of Nottingham) **sb** Sir Robert Boyd
Professor Richard Olver, Maternal & Child Health Sciences, Ninewells Hospital & Medical School, University of Dundee, Dundee DD1 9SY **sb** Boyd, Walters	Professor Colin Normand FRCP 23 St Thomas Street WINCHESTER Hampshire SO23 9JH **sb** Sir Robert Boyd
Professor Charles Rodeck, Department of Obstetrics & Gynaecology,	Professor Rodney Rivers, 53 Loftus Rd, London, W12 7EH

University College London Medical School, 86-96 Chenies Mews, LONDON WC1E 6HX **sb** Walters	(Paediatrician) **sb** Paintin
Professor Andrew Whitelaw FRCP FRCPCH, Neonatal Intensive Care Unit, Southmead Hospital, Southmead Road, Westbury-on-Trym, BRISTOL BS10 5NB **sb** Gamsu	Professor Phillip Steer, 48 Langley Ave, Surbiton, Surrey, KT6 4QR **sb** Paintin
Professor Charles Whitfield FRCP (Glas) FRCOG, 7 Grange Road, Bearsden, Glasgow G61 3PL **sb** Gamsu	

PROGRAMME

Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth

Witness Seminar – Tuesday 15 June 2004

History of Twentieth Century Medicine

UCL

Bearing in mind Sir Peter Medawar's view that 'the scientific paper is a fraud',[1] the purpose of this meeting is to get behind the published record of scientific achievement and to examine wider issues. Throughout, we want to ask the question 'Why did things happen the way they did?' For example, we hope to address questions such as: why particular projects were developed, by whom and in what institutional settings? What were the failures, the problems, the wrong directions and why did they happen? How was research funded and why? Who were the influential individuals and groups? (Sometimes, for example, it can be a lab technician, or someone who moved into or came from another field, who exerted tremendous influence at a particular period, but whose contribution is now overlooked.) We suggest some general outline themes below, to provide a structure to the meeting, and some participants have been asked to 'start the ball rolling' in each area. However this is a flexible scheme, and we want to encourage as many people as possible to participate, to explain what happened and why in the development of this field.

14.00 –16.00	**Introduction to the History of Twentieth Century Medicine Group, Witness Seminars and this meeting.**
	Chairman's introduction
	Presentation on behalf of Professor Mont Liggins and Professor Ross Howie
	From ewes and lambs to women and babies
	The systematic review of RCTs and the NIH consensus conference
	Cost-effective analyses
	The Cochrane Collaboration Logo
16.00-16.30 tea	
	Getting research into practice
	Assessing payback from research
	Recent and current research on prenatal corticosteroids
18.00 finish	**To be followed by informal drinks**

To be held in Franks I & II, Mezzanine Floor, The Wellcome Building, 183 Euston Road, London NW1 2.00pm – 6.00pm

[1]Medawar P. (1990) Is the scientific paper a fraud? In Pyke D. (ed.) *The Threat and the Glory: Reflections on Science and Scientists*. Oxford: Oxford University Press, 228–33.

6 May 2004

PROGRAMME

Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth

Witness Seminar – Tuesday 15 June 2004

History of Twentieth Century Medicine

UCL

Bearing in mind Sir Peter Medawar's view that 'the scientific paper is a fraud',[1] the purpose of this meeting is to get behind the published record of scientific achievement and to examine wider issues. Throughout, we want to ask the question 'Why did things happen the way they did?' For example, we hope to address questions such as: why particular projects were developed, by whom and in what institutional settings? What were the failures, the problems, the wrong directions and why did they happen? How was research funded and why? Who were the influential individuals and groups? (Sometimes, for example, it can be a lab technician, or someone who moved into or came from another field, who exerted tremendous influence at a particular period, but whose contribution is now overlooked.) We suggest some general outline themes below, to provide a structure to the meeting, and some participants have been asked to 'start the ball rolling' in each area. However this is a flexible scheme, and we want to encourage as many people as possible to participate, to explain what happened and why in the development of this field.

14.00 –16.00	**Introduction to the History of Twentieth Century Medicine Group, Witness Seminars and this meeting.**	Dr Daphne Christie
	Chairman's introduction	Dr Edmund Hey
	Presentation on behalf of Professor Mont Liggins and Professor Ross Howie	Professor Jane Harding
	From ewes and lambs to women and babies	Dr Mary Ellen Avery
	The systematic review of RCTs and the NIH consensus conference	Professor Patricia Crowley
	Cost-effective analyses	Professor Miranda Mugford
	The Cochrane Collaboration Logo	Sir Iain Chalmers
16.00-16.30 tea		
	Getting research into practice	Professor Richard Lilford
	Assessing payback from research	Dr Stephen Hanney
	Recent and current research on prenatal corticosteroids	Dr Peter Brocklehurst
18.00 finish	**To be followed by informal drinks**	

To be held in Franks I & II, Mezzanine Floor, The Wellcome Building, 183 Euston Road, London NW1 2.00pm – 6.00pm

[1]Medawar P. (1990) Is the scientific paper a fraud? In Pyke D. (ed.) *The Threat and the Glory: Reflections on Science and Scientists*. Oxford: Oxford University Press, 228–33.

Start the ball rolling Uts + noname programme 13 May '04 (DC)

DRAFT PROGRAMME

Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth

Witness Seminar – Tuesday 15 June 2004

Bearing in mind Sir Peter Medawar's view that 'the scientific paper is a fraud',[1] the purpose of this meeting is to get behind the published record of scientific achievement and to examine wider issues. Throughout, we want to ask the question 'Why did things happen the way they did?' For example, we hope to address questions such as: why particular projects were developed, by whom and in what institutional settings? What were the failures, the problems, the wrong directions and why did they happen? How was research funded and why? Who were the influential individuals and groups? (Sometimes, for example, it can be a lab technician, or someone who moved into or came from another field, who exerted tremendous influence at a particular period, but whose contribution is now overlooked.) We suggest some general outline themes below, to provide a structure to the meeting, and some participants have been asked to 'start the ball rolling' in each area. However this is a flexible scheme, and we want to encourage as many people as possible to participate, to explain what happened and why in the development of this field

14.00 –16.00	**Introduction to the History of Twentieth Century Medicine Group, Witness Seminars and this meeting.**	Dr Daphne Christie
	Chairman's introduction	Dr Edmund Hey [named prog] [+supper] NO Newcastle Spa Tyne
	Presentation on behalf of Professor Mont Liggins and Professor Ross Howie	Professor Jane Harding 13/5 ✓ NZ, London * [+ hotel + supper]
? Howie	**From ewes and lambs to women and babies**	Dr Mary Ellen Avery 13/5 ✓ No [+ Hotel + supper] Boston / London *
	The systematic review of RCTs and the NIH consensus conference	Professor Patricia Crowley 13/5 ✓ Dublin [+ Hotel ? + supper] ?
	Cost-effective analyses	Professor Miranda Mugford 13/5 ✓ Norwich + supper
	The Cochrane Collaboration Logo	Sir Iain Chalmers ✓ 13/5 Oxford 13/5 [named prog + supper] Yes
16.00-16.30 tea		
	Getting research into practice	Professor Richard Lilford 13/5 ✓ Birmingham + Supper
	Assessing payback from research	Dr Stephen Hanney 13/5 ✓ (Uxbridge) (birthday) ? supper NO
	Recent and current research on prenatal corticosteroids	Dr Peter Brocklehurst ✓ 13/5 Oxford ? supper
18.00 finish	**To be followed by informal drinks**	3/6 Professor Maureen Young [SUPPER]

To be held in Franks I & II, Mezzanine Floor, The Wellcome Building, 183 Euston Road, London NW1 2.00pm – 6.00pm

[1] Medawar P. (1990) Is the scientific paper a fraud? In Pyke D. (ed.) *The Threat and the Glory: Reflections on Science and Scientists*. Oxford: Oxford University Press, 228–33.

Start the Ball Rolling

6 May 2004

PROGRAMME

Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth

Witness Seminar – Tuesday 15th June 2004

brief outline

14.00 –16.00	**Introduction to the History of Twentieth Century Medicine Group, Witness Seminars and this meeting.**	Dr Daphne Christie
	Chairman's introduction	Dr Edmund Hey (Chair)
	From ewes and lambs to women and babies	Dr Mary Ellen Avery
	The systematic review of RCTs and the NIH consensus conference	Professor Patricia Crowley
	Cost-effective analyses	Professor Miranda Mugford
	The Cochrane Collaboration Logo	Sir Iain Chalmers
16.00-16.30 tea		
	Getting research into practice	Professor Richard Lilford
	Assessing payback from research	Dr Stephen Hanney
	Recent and current research on prenatal corticosteroids	Dr Peter Brocklehurst
18.00 finish	**To be followed by informal drinks**	

To be held in Franks I & II, Mezzanine Floor, The Wellcome Building, 183 Euston Road, London NW1 2.00pm – 6.00pm

28 April 2004

DRAFT PROGRAMME

Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth

Witness Seminar – Tuesday 15 June 2004

Bearing in mind Sir Peter Medawar's view that 'the scientific paper is a fraud',[1] the purpose of this meeting is to get behind the published record of scientific achievement and to examine wider issues. Throughout, we want to ask the question 'Why did things happen the way they did?' For example, we hope to address questions such as: why particular projects were developed, by whom and in what institutional settings? What were the failures, the problems, the wrong directions and why did they happen? How was research funded and why? Who were the influential individuals and groups? (Sometimes, for example, it can be a lab technician, or someone who moved into or came from another field, who exerted tremendous influence at a particular period, but whose contribution is now overlooked.) We suggest some general outline themes below, to provide a structure to the meeting, and some participants have been asked to 'start the ball rolling' in each area. However this is a flexible scheme, and we want to encourage as many people as possible to participate, to explain what happened and why in the development of this field.

14.00 –16.00	**Introduction to the History of Twentieth Century Medicine Group, Witness Seminars and this meeting.**	Dr Daphne Christie
	Chairman's introduction	✓Dr Edmund Hey Newcastle Spartyne
	Presentation on behalf of Professor Mont Liggins and Professor Ross Howie	Professor Jane Harding NZ, London *
	From ewes and lambs to women and babies	✗ Dr Mary Ellen Avery Boston / London *
	The systematic review of RCTs and the NIH consensus conference	✗ Professor Patricia Crowley Dublin
	Cost-effective analyses	✓Professor Miranda Mugford Norwich
	The Cochrane Collaboration Logo	✓Sir Iain Chalmers Oxford
16.00-16.30 tea		
	Getting research into practice	✓ ✗ Professor Richard Lilford Birmingham
	Assessing payback from research	Dr Stephen Hanney ✗ (Uxbridge) ✗
	Recent and current research on prenatal corticosteroids	✓ Dr Peter Brocklehurst ✗ Oxford
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To be held in Franks I & II, Mezzanine Floor, The Wellcome Building, 183 Euston Road, London NW1 2.00pm – 6.00pm

[1] Medawar P. (1990) Is the scientific paper a fraud? In Pyke D. (ed.) *The Threat and the Glory: Reflections on Science and Scientists*. Oxford: Oxford University Press, 228–33.

6 May 2004

Witness Seminar:
Prenatal Corticosteroids
15th June 2004
Professor Ross Howie

Draft only: for Wellcome Trust Centre seminar, London, 15 June 2004

Prenatal glucocorticoids in preterm birth: a paediatric view of the history of the original studies

Ross N Howie
Auckland, New Zealand
2 June 2004

Distributed at meeting 15/6/04

Firstly my warmest greetings to Mel Aver
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least as a major public health problem. If
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in the year 2004, I would have replied tha
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storage after a recent house move) or to v
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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 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.

Witness Seminar:
Prenatal Corticosteroids
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Prenatal glucocorticoids in preterm birth: a paediatric view of the history of the original studies

Ross N Howie
Auckland, New Zealand
2 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 [1] 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. Which only goes to show how naïve 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 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.

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. In my medical school years (1952-6) I never heard the word 'perinatal' [2], and the outlook the word implied was in many places some time in the future.

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. 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 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 keeping them away from 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 (?127 days): 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. 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. It is complex partly because of the variety of causes 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: one 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 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. 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 recognise 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 United States of America, punch cards were used in their last Presidential election. 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 Organisation, 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 followup studies. ('Long-term' to us then meant to 6 years. The 30-year followup 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 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.

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 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 followup 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.

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. 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 followup studies with WHO, 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). 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 20th century. In New Zealand it improved possibly more than most due to a remarkable nation-wide 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 [3]) fell by nearly 80%, from 34.6 per 1000 births in 1950 to 7.4 in 1990. Steroid therapy was a welcome advance during this time, but it would be hard to attribute to it more than a small 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 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). Examples: 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.

Acknowledgments

It needs to be said of both 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 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.

Notes and references

1. Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid therapy for the prevention of the respiratory distress syndrome in premature infants. Pediatrics 1972; 50: 515-525

2. On the history of the word 'perinatal', I 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 3. 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.

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

Wellcome Trust. Witness Seminar, June 25th, 2004.

The use of steroids before birth to reduce the morbidity and mortality associated with preterm birth.

[1] The original version of the Cochrane Logo showing a meta-analysis of 7 trials of the use of antenatal steroids. 1992.

[2] The version of Patricia Crowley's meta-analysis of 12 trials, as published in *Effective Care in Pregnancy and Childbirth*, OUP, 1989. (See also Table 45.3 below.)

[3] The version of Patricia Crowley's meta-analysis of data from 15 trials as presented at the *NIH Consensus Development Conference,* in Bethesda, on February 28th, 1994. The trials are explicity listed in descending order of quality.

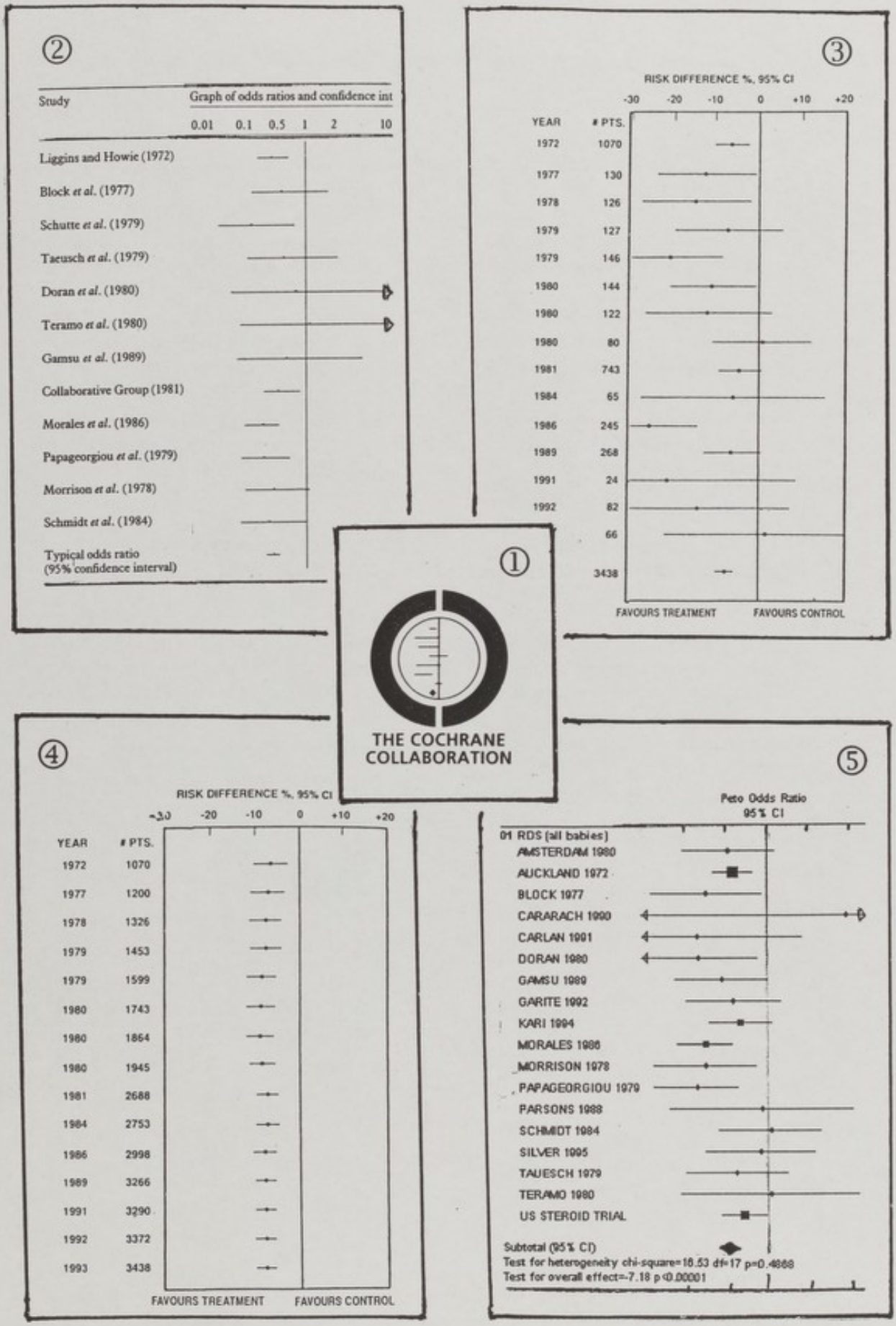
[4] A cumulative meta-analysis of the same 15 trials as in [3] incorporating each trial in turn by date of publication, taken from Jack Sinclair's commentary on the NIH Conference presentation, as published in July 1995 in the *American Journal of Obstetrics and Gynecology* 1995;173;335-44..

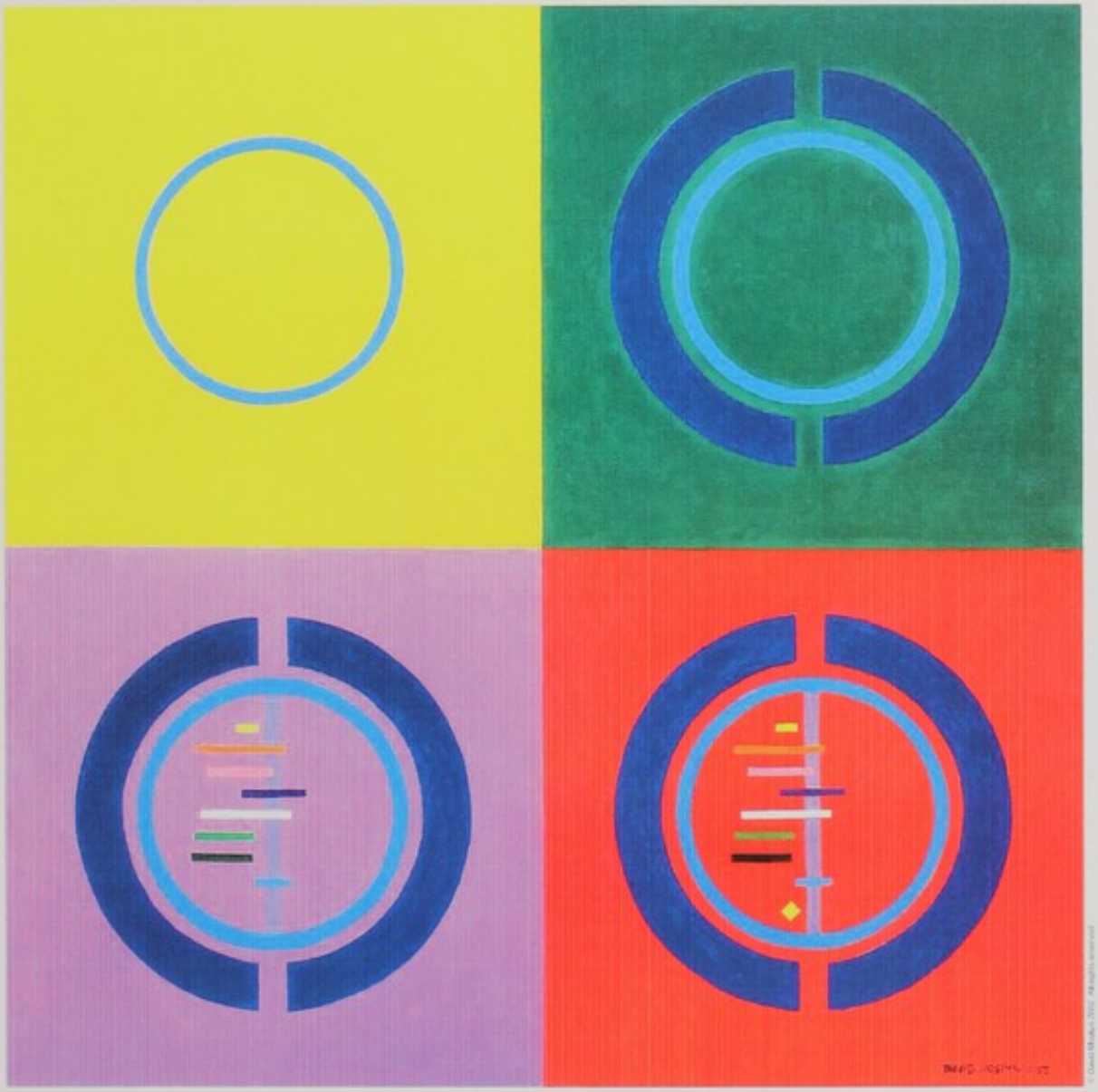
[5] The current version of Patricia Crowley's meta-analysis with data from 18 trials, as it appears in the latest version of the *Cochrane Library*, 2004 (CD000065).

The outcome under consideration in all these analyses is the reduction in the proportion of babies showing symptoms of respiratory distress syndrome (RDS) after birth, except for the Cochrane logo, which shows effect on early neonatal mortality

Table 45.3 Effect of corticosteroids prior to preterm delivery on respiratory distress following optimal treatment

Study	EXPT		CTRL		Odds ratio	Graph of odds ratios and confidence intervals
	n	(%)	*n*	(%)	(95% CI)	0.01 0.1 0.5 1 2 10 100
Liggins and Howie (1972)	16/182	(8.79)	37/156	(23.72)	0.32 (0.18–0.58)	
Block *et al.* (1977)	4/36	(11.11)	6/29	(20.69)	0.48 (0.13–1.86)	
Schutte *et al.* (1979)	0/22	(0.00)	6/25	(24.00)	0.12 (0.02–0.66)	
Taeusch *et al.* (1979)	2/15	(13.33)	7/28	(25.00)	0.50 (0.11–2.30)	
Doran *et al.* (1980)	1/18	(5.56)	1/13	(7.69)	0.71 (0.04–12.35)	
Teramo *et al.* (1980)	1/38	(2.63)	1/42	(2.38)	1.11 (0.07–18.08)	
Gamsu *et al.* (1989)	1/131	(0.76)	2/137	(1.46)	0.53 (0.06–5.18)	
Collaborative Group (1981)	14/151	(9.27)	29/144	(20.14)	0.42 (0.22–0.80)	
Morales *et al.* (1986)	16/64	(25.00)	31/48	(64.58)	0.20 (0.09–0.42)	
Papageorgiou *et al.* (1979)	6/29	(20.69)	19/32	(59.38)	0.21 (0.08–0.57)	
Morrison *et al.* (1978)	3/49	(6.12)	8/45	(17.78)	0.33 (0.09–1.15)	
Schmidt *et al.* (1984)	4/26	(15.38)	8/19	(42.11)	0.26 (0.07–0.99)	
Typical odds ratio (95% confidence interval)					0.31 (0.23–0.42)	


②
Study
Graph of odds ratios and confidence int
0.01 0.1 0.5 1 2 10
Liggins and Howie (1972)
Block et al. (1977)
Schutte et al. (1979)
Taeusch et al. (1979)
Doran et al. (1980)
Teramo et al. (1980)
Gamsu et al. (1989)
Collaborative Group (1981)
Morales et al. (1986)
Papageorgiou et al. (1979)
Morrison et al. (1978)
Schmidt et al. (1984)
Typical odds ratio
(95% confidence interval)
③
RISK DIFFERENCE %, 95% CI
-30 -20 -10 0 +10 +20
YEAR # PTS.
1972 1070
1977 130
1978 126
1979 127
1979 146
1980 144
1980 122
1980 80
1981 743
1984 65
1986 245
1989 268
1991 24
1992 82
66
3438
FAVOURS TREATMENT
FAVOURS CONTROL
①
THE COCHRANE
COLLABORATION
④
RISK DIFFERENCE %, 95% CI
-30 -20 -10 0 +10 +20
YEAR # PTS.
1972 1070
1977 1200
1978 1326
1979 1453
1979 1599
1980 1743
1980 1864
1980 1945
1981 2688
1984 2753
1986 2998
1989 3266
1991 3290
1992 3372
1993 3438
FAVOURS TREATMENT
FAVOURS CONTROL
⑤
Peto Odds Ratio
95% CI
01 RDS (all babies)
AMSTERDAM 1980
AUCKLAND 1972
BLOCK 1977
CARARACH 1990
CARLAN 1991
DORAN 1980
GAMSU 1989
GARITE 1992
KARI 1994
MORALES 1986
MORRISON 1978
PAPAGEORGIOU 1979
PARSONS 1988
SCHMIDT 1984
SILVER 1995
TAUESCH 1979
TERAMO 1980
US STEROID TRIAL
Subtotal (95% CI)
Test for heterogeneity chi-square=16.53 df=17 p=0.4868
Test for overall effect=-7.18 p<0.00001



The Cochrane Logo

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. Ten years later, on leaving the Cochrane Collaboration, Iain commissioned David to produce a painting to illustrate how the Cochrane Logo had been conceptualised and created. In doing so, Iain wished to express his gratitude to his colleagues in the UK Cochrane Centre, Update Software, and the international Cochrane Collaboration.

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 controlled trials of a simple and inexpensive treatment to reduce problems experienced by premature babies. (The reason that 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 studies in 1991!)

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 a treatment, which was 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 health care. The Cochrane Collaboration was established to do something about this unsatisfactory state of affairs (www.cochrane.org).

The painting is to hang in the Cochrane Collaboration Secretariat, which is currently based in the Summertown Pavilion in Oxford, U.K. It was in this building that the international Cochrane Collaboration was inaugurated at the first Cochrane Colloquium in October 1993.

Witness Seminar:
Prenatal Corticosteroids
15th June 2004
Professor Miranda Mugford

Figure 1
Matrix linking effectiveness and cost

EFFECTIVENESS decreasing

COST increasing	1	2	3	4
A	✓	✓		?
B	✓	✓×	×	?
C		×	×	?
D	?	?	?	?

✓ = recommended experimental treatment
X = recommended control
✓X= neutral
? = not enough evidence
□ = judgement required

Compared with control treatment, experimental treatment is:

1. more effective
2. of equal effectiveness
3. less effective
4. insufficient evidence to judge

A. less costly
B. of equal cost
C. more costly
D. insufficient evidence to judge

From Vale, Donaldson: Cochrane economics workshop material

Witness Seminar:
Prenatal Corticosteroids
15th June 2004
Professor Richard Lilford

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The Leeds University maternity audit project

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Abstract

Objectives. To measure levels of and changes in compliance with evidence-based recommendations in obstetrics in the UK. To identify barriers to and factors associated with compliance.

Design. A quantitative case-note audit for 1988 and 1996, and a qualitative interview study of key staff.

Setting. Twenty maternity units, selected at random from all UK units

Subjects. Fifty consecutive cases of pre-term delivery (PTD), Caesarean section (CS), instrumental delivery (ID), and perineal repair (PR) operations in each period in each unit. The lead clinician, midwifery manager, a senior midwife, neonatologist, and middle-grade obstetrician in each unit.

Main outcome measures. Maternal steroid use in PTD, antibiotic use in CS, use of the ventouse (vacuum extractor) rather than forceps as instrument of first choice for ID, and use of polyglycolic acid (PGA) sutures for PR in each time period. Facilities for implementing, staff attitudes to, and the degree of planning to follow each recommendation.

Main results. The median proportion of ventouse as instrument of first choice in each unit was 8% (range 0–32%) in 1988, rising to 64% (range 0–98%) in 1996. PGA use for PR was 0% (range 0–30%) in 1988, and 72% (range 0–100%) in 1996. Steroid use for eligible PTD was median 0% (range 0–23%) in 1988, rising to 82% (range 63–95%) in 1996. Antibiotic use for CS was 7% (range 0–25%) rising to 84% (range 10–100%) in 1996. There was no relationship between unit size, type of unit, facilities, staff attitudes or degree of planning, and compliance with the recommendations, nor was the level of adherence to one standard typically correlated with adherence to the others. However, there was a positive correlation ($R = 0.6$, $P < 0.005$) between local availability of the Cochrane database of perinatal trials and unit compliance with the audit standards in the latter time period.

Conclusions. We have documented a massive shift in practice in line with the evidence, although many units still have substantial room for improvement. About 2000 wound infections, 200 deaths due to prematurity, nearly 8000 women in pain from catgut sutures, and 1500 cases of severe perineal trauma from forceps remain preventable. The reasons why units vary remain obscure, although the qualitative interviews often revealed local factors such as key enthusiastic staff. There was no sign of evidence being positively driven into practice by any systematic managerial process. The relationship between Cochrane availability and high-standard care may be simply a marker of commitment to the evidence, but it remains plausible that if senior staff make Cochrane available for their juniors, audit compliance improves.

Keywords: audit, clinical standards, evidence-based care, pregnancy

In the UK, agreement on what constitutes evidence-based care for pregnancy and childbirth is relatively advanced because of the efforts of the National Perinatal Epidemiology Unit in Oxford, UK, which has collected and disseminated evidence from randomized controlled trials since the 1980s. Systematic reviews have been published in books [1,2], and computer databases [3] are widely available through the Cochrane collaboration. These form the basis of a range of guidelines produced by the Royal College of Obstetricians and Gynaecologists (RCOG). However, the recommended practices may have been only patchily implemented. Allegedly, only one in five women in the UK received steroids prior to

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pre-term delivery less than 8 years ago [4], although it was not clear what proportion had a contraindication or insufficient time to administer them. If such claims are true of such a well-publicized recommendation, compliance with others might be even lower. Unfortunately, these data are based on small studies that did not measure eligibility adequately, and which may be out of date, and routine data are inadequate to check today's figures precisely.

If compliance is low those responsible for quality of care should takes steps to improve it. In the UK this would to a large extent be the role of those with a responsibility for the newly introduced function of clinical governance. However, the best methods for translating evidence into practice are unclear, as evidenced by a recent review, which identified no less that 44 systematic reviews of 102 different studies of methods to do this [5]. The main conclusion was that dissemination activities by themselves were rarely effective, there were no 'magic bullets', and a diagnostic analysis identifying barriers to change should precede interventions to effect change. The first part of this project was to provide up-to-date estimates of rates of compliance with evidence-based recommendations and to measure changes over time. The second part of the project comprises such a diagnostic analysis, albeit undertaken after many of the recommendations had been circulated.

Methods

Four audit standards underwritten by evidence-based recommendations were selected for study.

(1) For perineal injury, polyglycolic acid sutures (Dexon or Vicryl) should be used for repair of both the deep layers and skin.
(2) All women undergoing Caesarean section should receive prophylactic antibiotics.
(3) All women expected to deliver pre-term (<34 weeks [6]) should be administered corticosteroids.
(4) The ventouse (a vacuum cup attached to the baby's head) should be the instrument of first choice for operative vaginal delivery, in preference to the obstetric forceps.

These topics were selected largely for practical reasons, namely that cases could be easily ascertained from the statutory labour-ward record book. Some topics such as use of postnatal anti-D immunoglobulin for Rhesus prophylaxis were excluded because compliance was already documented to be very high [6]. Others, such as use of external cephalic version for breech presentation or the offer of induction post-term, would have required review of all or most records because few units keep a computer or paper record of cases with mal-presentation or post-maturity, and would therefore have been very expensive. We also intended to examine one further audit standard, which emerged after submission of the protocol, namely that all women with eclampsia should be treated with magnesium sulphate. However, eclampsia is so uncommon that only a few cases could be studied opportunistically, and results demonstrating a massive and rapid change of practice have already been reported elsewhere [7].

Twenty maternity units were selected at random from a full list of those in England and Wales held by the RCOG. All hospitals initially selected agreed to participate. Units were classified as teaching and non-teaching hospitals, and their number of annual deliveries was recorded.

We measured compliance with each audit standard for two periods, the years 1988 and 1996. The study began during 1998, while 1996 was the most recent year for which delivery records were unlikely to still be in use. 1988 was the latest year before the randomized trial evidence became widely available to obstetricians with publication of the book *Effective Care in Pregnancy and Childbirth* in 1989 [1]. Although individuals may have been aware of the evidence before that date, and some units may have achieved high compliance by accident, no systematic efforts to disseminate evidence had been made at that time. The actual evidence, in terms of published randomized controlled trials, on which the RCOG recommendations were based did not alter substantially between 1988 and 1996 for any of the standards studied. For example, although there was evidence for the effectiveness of steroids as early as 1972 [8] many review articles and textbooks regarded this as inconclusive until Crowley's review in 1990 [9]. The RCOG promulgated national guidelines in 1992.

We identified an audit clerk in each unit and invited them to Leeds for 2 days of training. The purpose of the study and the clinical justification for each audit standard were explained. Each clerk brought two sets of notes for each topic from their own hospital, for each of which they and another clerk independently completed an audit data form. The results were compared and checked by two of the authors (JGT or RJL) and the form design was modified in response to advice from the clerks about availability and accuracy of local data. Each clerk then completed five finalized audit forms from standard notes for each audit standard, which were checked before starting the project.

Each clerk identified 50 sets of records of Caesarean deliveries, deliveries before 34 completed weeks, and operative vaginal deliveries from each time period from the delivery register. The latter 50 records were used to assess both the instrument of first choice for the operative delivery and the suture material used for perineal repair. Suitable records were identified by simultaneously searching forward and backwards from the first of June in each index year until 50 cases were identified.

For the ventouse, suture material, and antibiotic use at Caesarean section audit, the clerks were able to classify records unambiguously with little difficulty. Any record of administration at the appropriate time was regarded as evidence that antibiotics or steroids had been given, even if a drug prescription chart could not be found. A more elaborate system was required to assess whether patients who had delivered before 34 weeks had been eligible for steroids and whether there had been, in prospect, sufficient time for them to act. If steroids had been given at all, the cases was classed as 'audit standard met'. Otherwise patients either admitted

with a diagnosis of pre-term labour for more than 3 hours or delivered electively were classed as 'eligible and not given steroids'. This is a conservative algorithm in that some people in whom delivery appears imminent may not deliver as soon as expected. Patients admitted with a diagnosis of pre-term labour less than 3 hours before delivery or in whom pre-term labour was never diagnosed were classed as 'not eligible for steroids'. For example, a woman admitted with abdominal pain and a closed cervix, with a reasonable diagnosis of urinary infection or non-specific pain, who nevertheless went on to deliver precipitously would be classed as ineligible. All the latter cases, and a one in 10 subset of those in whom the audit standard was met, were reviewed independently by one of three experienced clinicians. Any disagreements were reviewed again by one of the authors (JGT) and a final classification was made.

The result was a level of compliance with each of the four audit standards for each unit at each time period. Finally, a hospital level of audit compliance for each time period was calculated as the mean of each of these four standards.

The research assistant interviewed five people from each unit [the medical director or senior obstetric consultant, the unit manager (who may have been a midwife or administrator), the paediatrician with most responsibility for neonatal care, a clinically active midwife, and a middle grade obstetrician]. The aim was to measure the degree to which respondents had moved along the continuum of the 'theory of implementation intentions' [10,11]. This suggests that behavioural change can be divided into two phases, an intention/motivation phase and an implementation phase.

The interview was divided into two parts. In the first part, respondents were asked if there was a unit policy for each topic, and the responses classified as no policy, unclear if there is a policy, unclear if the policy follows the guidelines, policy differs from the guidelines, or policy follows the guidelines. The following questions concerned respondent's knowledge of and attitudes towards evidence-based practice and the Cochrane collaboration, and towards the four specific study guidelines. Information on the local availability of the Cochrane database was also collected. If respondents were unfamiliar with the content of a recommendation, that information was provided before attitudes were sought. Respondents were asked if they supported the recommendation for their unit. Knowledge was coded according to pre-specified criteria. For example, correct statements included mentioning that the Cochrane collaboration searched for evidence systematically, only (or predominantly) included evidence from randomized trials, and gave the correct weight to each trial. Attitudes and intentions were classed as positive, negative, or unclear/uncertain. Access was coded as full for individuals if they had access to the database on the maternity unit. Otherwise, respondents were coded as having limited or no access. The hospital level of access was the proportion of respondents in that unit reporting full access. Similar calculations were performed for other relevant variables.

The second phase of the interview covered the extent to which implementation had actually occurred. Respondents were asked if any explicit attempts to change practice had been made, and if so, what these had been. Had any guidelines been written, had any formal attempt been made at dissemination, or had any co-ordinated action to implement the unit policy been taken? At unit level, having an explicit policy was taken as evidence of intention to follow a recommendation.

The interviews were audiotaped, transcribed, and coded using standard methods of content analysis employed in social surveys [12]. For each question, data from the full sample were used to devise the coding frame, and individual responses classified accordingly. Numeric codes were then assigned to the classified data for the purposes of quantitative analysis. The audit and interview results were analysed using SPSS. The outcome variable was always compliance with the audit standard in the second time period (1996), either for each standard individually or aggregated by unit as appropriate. First the relationship of teaching/non teaching and size of unit (continuous variable) to this outcome was tested in a single regression analysis. Subsequent analyses consisted of simple Pearson correlations, except for those involving proportions of respondents, when a non-parametric test (Spearman) was used.

Results

The level of compliance with each audit standard is shown for each unit over the two time periods in Figures 1–4. The median proportion of ventouse as the instrument of first choice in each unit was 8% (range 0–32%) in 1988, rising to 64% (range 33–98%) in 1996. Polyglycolic acid suture use for perineal repair was 0% (range 0–30%) in 1988, and 72% (range 0–100%) in 1996. Steroid use for eligible pre-term delivery was median 0% (range 0–23%) in 1988, rising to 82% (range 63–95%) in 1996. Antibiotic use for Caesarean section was 7% (range 0–25%) rising to 84% (range 10–100%) in 1996. The weak positive correlation between 1988 and 1996 scores can be seen from the figures. As change scores (improvement in compliance) were highly correlated with final scores, only the latter are used as outcome measures in the analyses reported below. The correlation between scores for different standards varied. For example, in 1996, there was a weak positive correlation between compliance with the audit standards for instrumental delivery and steroid use ($R = 0.46$, $P = 0.04$, two tailed) and between the perineal suture and antibiotic standard for the same time period ($R = 0.51$, $P = 0.02$). Neither of these was predicted in advance. Otherwise, there were no other significant correlations among 14 comparisons, and the above significance tests would be rendered non-significant if an appropriate adjustment were made for multiple comparisons. There was no difference between the 1996 compliance rates for teaching or non-teaching hospitals ($P = 0.97$), and no relationship between compliance and the size of the hospital ($P = 0.32$).

There were 88 taped interviews. In the latter time period (1996) only six units had half or more respondents reporting full access to the Cochrane database. There was a positive relation between average unit compliance with the four audit

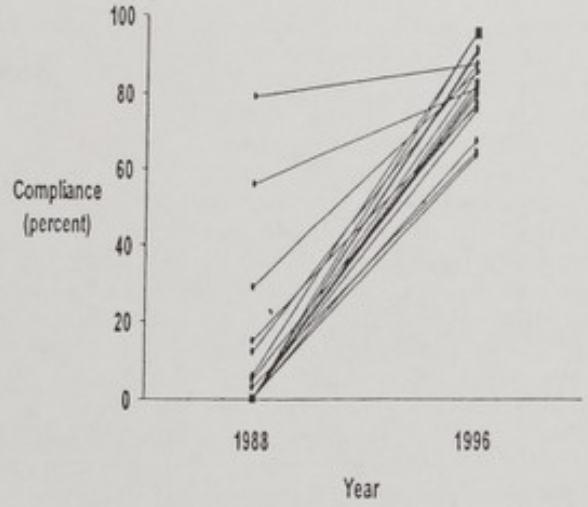

Figure 1 The rate of compliance with the steroid use standard in each unit for each time period.

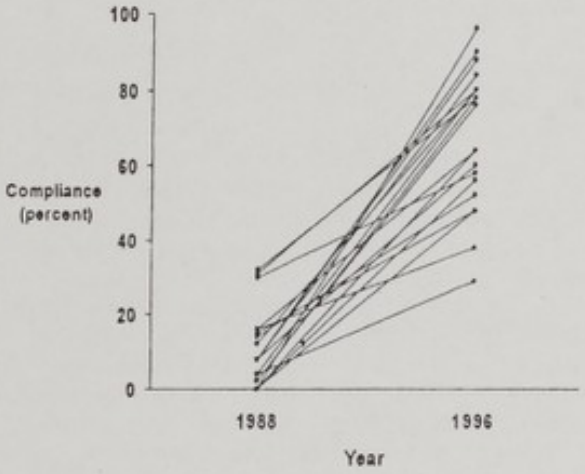

Figure 2 The rate of compliance with the instrumental delivery standard in each unit for each time period.

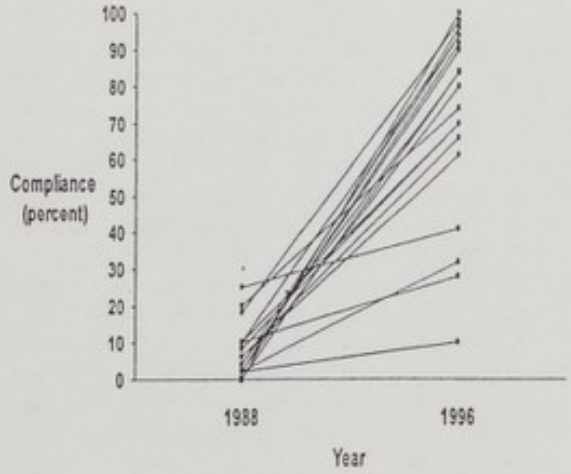

Figure 3 The rate of compliance with the antibiotic standard in each unit for each time period.

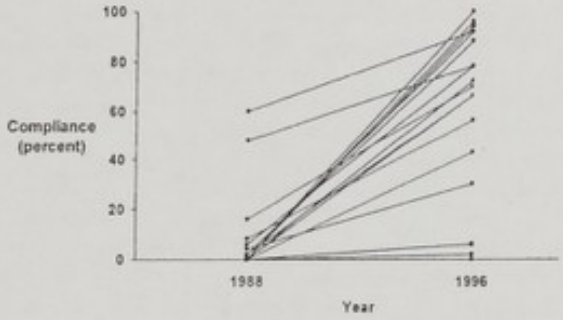

Figure 4 The rate of compliance with the suture material standard in each unit for each time period.

standards and the proportion of respondents reporting full access (rho = 0.6, $P < 0.005$). Attitudes towards Cochrane were generally favourable (64/88 clearly positive attitudes), but knowledge about the methodology was poor (only 29/88 respondents were able to make two or more correct statements about this). Neither the proportion of staff with favourable attitudes nor the proportion with knowledge about the methodology correlated with audit compliance.

At an individual level, the relationships between attitudes, knowledge and access were complex. Although a greater proportion of those with positive (27/64) than negative (2/24) attitudes to the Cochrane collaboration had full access (chi-square = 7.59, $P = 0.006$), those with positive attitudes did not have better knowledge (20/64) than those with negative ones (9/24). Furthermore, those with full access did not have better knowledge (6/29) than those with more limited access (23/59). The trend was, if anything, in the opposite direction. Staff seniority may explain these patterns. Access was higher in senior than junior staff (20/39 versus 9/49; $P = 0.002$), but knowledge was lower (8/39 versus 21/49; $P = 0.047$).

Senior and junior staff were just as likely to have positive attitudes (28/39 versus 36/49), but in senior staff, the majority (18/28) of those with positive attitudes had full Cochrane access, whereas this was true for only a minority of more junior staff (9/36; $P = 0.004$). The two people with negative attitudes who had full Cochrane access were also both seniors.

It was possible to obtain information on awareness of specific recommendation content, and the source of that awareness, in 80 of the 88 interviews. Some managers, for example, did not have a clinical background, and preferred not to comment on what they perceived as clinical matters, and some paediatricians preferred not to comment on the antibiotic use and suture material standards. Awareness was high for the steroid recommendation (79/80), but far from complete for the ventouse (66), suture (58) and antibiotics (56) recommendations. Respondents reported having heard about the different recommendations from a variety of sources. Nine people mentioned the RCOG in connection

with the ventouse recommendation, and six, two, and three in connection with the steroid, suture, and antibiotic recommendations, respectively. The numbers of individuals mentioning directorate/departmental sources were three, five, five, and four, for the same four standards, respectively. Other sources of information included preparation for examinations, clinical practice, the research literature, and audit meetings.

Expressed attitudes to the individual recommendations were generally favourable: antibiotics 49 favourable versus four unfavourable, steroids 84 versus two, sutures 61 versus three, and ventouse 58 versus nine. There was no correlation between unit level respondents average attitude (negative mark for unfavourable attitude) and compliance with each audit standard (instrumental delivery $R = 0.023$, perineal suture material $R = 0.13$, antibiotics $R = 0.32$, steroid use $R = 0.29$). The apparently favourable attitudes to the ventouse were accompanied by qualifying remarks in 27/58 cases, which may partly explain the overall low compliance with this standard even in 1996. The numbers of qualifying remarks for the other recommendations were 11/61 for suture material, 8/49 for antibiotics, and 5/84 for steroids.

The proportion of respondents reporting that their unit had written guidelines in accord with the standards varied by standard (steroids 72/88; ventouse 12/70 plus eight reporting a guideline differing from the audit standard; suture material 35/70 plus one guideline differing from the standard; antibiotics 42/70 plus one differing from the standard. Note that paediatricians were only asked about the steroid recommendation). Units with higher proportions of respondents reporting suture material guidelines also had higher compliance with the suture material standard (rho = 0.47, $P = 0.035$), but for the other standards there was no relation between having written guidelines and compliance with audit standards.

There was little evidence of systematic planning to implement any recommendations in any units. Relatively few units had made any explicit attempt to disseminate the policies, or designed an implementation strategy and facilitated adoption of the policy by, for example, sending people on training courses, buying new equipment, or ensuring that only the appropriate materials were available. The figures were:

(1) Ventouse – 1/20 units had disseminated guidelines but none had taken co-ordinated managerial action.
(2) Steroids – 7/20 disseminated and none actioned further.
(3) Suture material – 5/20 disseminated and 4/20 actioned.
(4) Antibiotics – 7/20 disseminated and none actioned.

In one of the four sites where a suture policy had been actioned, only a minority of respondents believed that their unit had a suture policy, so there were only three instances out of a possible 80 where a successfully disseminated policy and an action plan occurred together. None of the actions or lack thereof correlated with recommendation compliance, but the numbers were small.

Discussion

We have shown a dramatic rise in adherence to the four evidence-based recommendations over the 8 years since 1988. It is not possible to say how much of this resulted directly from the assembly of the evidence by the Cochrane collaboration and its forerunners, and how much from various dissemination activities such as the RCOG audit guidelines or the National Health Service (NHS) audit programme. Nevertheless, it is clear that over a relatively short time period, obstetricians and midwives have altered their practice in response to evidence. It is no longer possible to claim that only 20% of eligible women are receiving steroids. However, adherence rates are still below 100% in many units, and in some units considerably below this level. As a result, large numbers of women and babies are receiving substandard care in the UK NHS.

This improvement in adherence to recommendations is despite the fact that few units have access to the Cochrane database, have prepared or disseminated guidelines, or have taken any active steps to implement recommendations. The explanation for the range of unit compliance levels remains unexplained. With one exception, none of the knowledge attitudinal, or behavioural characteristics, which we recorded for each unit, explained the difference. The exception was access to the Cochrane database. This may mean that access to the database is causing high compliance, but it is more likely that access is a marker of a type of staff or organizational characteristic, which goes with the following of evidence-based recommendations. A plausible interpretation of these data is that senior people with positive attitudes to Cochrane arrange access to the database for themselves and, to a lesser extent, for their staff. At unit level, there were no sites in which junior people had access but senior people did not, so essentially, the units in which a greater proportion of staff had full Cochrane access were the ones in which access was available to some junior as well as senior staff.

Essentially, senior staff arranging access to Cochrane for their juniors correlates with high levels of compliance. This is plausibly a causative relation.

The shortfall in compliance with the recommendations in the latter time period is all the more important because we took considerable care to ensure that legitimate reasons for non-compliance such as admission in advanced labour, were excluded. We also ensured that we classified the choice of instrument as correct if the ventouse was used as first choice but delivery was completed with another instrument. This means that any residual shortfall is likely to be genuine, although our algorithm on steroid use is conservative. Our algorithm would have underestimated the steroid administration shortfall to eligible women since those eligible women in whom steroids were omitted but who did not go on to deliver prematurely, would not be classed as a failure to adhere to the standard.

The specific shortfall in steroid use after legitimate reasons for non-prescription has been identified as similar to that seen in thrombolytic therapy after acute myocardial infarction. In Europe only 36% of such patients receive thrombolysis, but

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Review

Corticosteroids in pregnancy: the benefits outweigh the costs

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INTRODUCTION

Since 1972 four prospective controlled trials have demonstrated that antepartum glucocorticoid treatment reduces the incidence of respiratory distress syndrome (Table I). When respiratory distress syndrome does occur following antenatal glucocorticoid treatment its severity is reduced, with a lower requirement for mechanical ventilation (Papageorgiou *et al.*, 1979; Tauesch *et al.*, 1979). There is also a decreased incidence of associated intraventricular haemorrhage (Block *et al.*, 1977; Tauesch *et al.*, 1979). The ultimate effect is an increased survival of preterm infants (Table II).

A number of other substances have been claimed to stimulate lung maturation. These include thyroxine, cyclic AMP and prolactin (Gross, 1979). Intravenous isoxsuprine also appears to affect the production and release of surfactant (Van Iddekinge and Hughes, 1977). While the search continues for a more specific agent to accelerate pulmonary maturation, corticosteroids remain the only treatment of proved efficacy. There is, of course, concern over the potential hazards of corticosteroids administered antenatally. The two main areas for discussion are the potential effect of steroids on neurological development and their effect on immune competence.

ANIMAL STUDIES

Administration of glucocorticoids to neonatal rats impairs growth and later neurological function (Schapiro *et al.*, 1970; Cotterrell *et al.*, 1972; Howard and Granoff, 1968). The neonatal rat brain is considered by some to be at an analogous stage of development to that of the fetal brain in the third trimester. However, all biological effects of steroid hormones are related to the dose and duration of treatment. Extrapolation of data from the neonatal rat to the human fetus is valid only if the dose of corticosteroid administered is similar. The dose of corticosteroid recommended for pregnant women by Howie and Liggins (1977) is 12 mg of betamethasone given over a 24-hour period. Assuming that betamethasone is twenty-five times more potent than cortisol (Haynes and Larner, 1975), the dose of cortisol per kilogram of body weight required to cause a reduction in brain weight and depression of cell division in the neonatal rat (Cotterrell *et al.*, 1972) is twenty-five times greater than Howie and Liggins' (1977) recommended dose. Similar calculations indicate that Schapiro's (1970) 0·5 mg dose of cortisol to the neonatal rat is analogous to a dose of 200 mg of betamethasone to the pregnant woman. No relevant animal experiments have been reported where the dose of corticosteroid is comparable to that recommended for the pregnant human.

HUMAN NEONATAL STEROID THERAPY

Human neonates have been exposed to large doses of corticosteroids in unsuccessful attempts to treat respiratory distress syndrome. In Fitzhardinge *et al.*'s (1974) series the dose of cortisol was up to five times higher than the equivalent dose of betamethasone recommended by Howie and Liggins (1977). At one year of age the treated infants had a similar developmental quotient to the controls, although they did appear to have an increased incidence of abnormalities of muscle tone and mild electroencephalographic abnormalities suggestive of a lower seizure threshold. This apparent effect did not reach the usual level of statistical significance.

Cord blood estimations of glucocorticoid activity following antenatal betamethasone treatment are in the physiological stress range, while all the adverse effects reported in both animals and humans occur after pharmacological doses (Ballard and Ballard, 1976). Similarly, cord blood and neonatal sampling has shown that the glucocorticoid levels required for prenatal lung maturation are no higher than the levels seen in an untreated human neonate suffering from respiratory distress syndrome (Ballard and Ballard, 1976; Avery, 1977).

HUMAN FOLLOW-UP STUDIES

The long term follow-up of infants exposed to corticosteroids *in utero* is the ultimate test of the safety of antenatal corticosteroid therapy. The first 318 children treated by Liggins and Howie (1972) have been followed up to the age of four years and to date developmental and psychometric assessment has failed to demonstrate any significant differences between the treated and control groups (Howie and Liggins, 1977). Further assessment of these infants at the age of seven is being conducted but has not yet been reported.

THE RISK OF INFECTION

Antenatal steroid administration is associated with a theoretical risk of depressing the immune response and increasing the susceptibility of both mother and fetus to infection. Howie and Liggins (1977) failed to demonstrate any increase in neonatal pneumonia following antenatal betamethasone therapy, even when the membranes were ruptured for 48 hours or more. In their series prophylactic antibiotics were administered in the presence of prolonged rupture of the membranes. Tauesch *et al.* (1979) showed an apparent increase in maternal infection in dexamethasone-treated patients with prolonged rupture of the membranes. The increase in neonatal infection was not statistically significant. In Tauesch's opinion the risk of respiratory distress syndrome, even following

Table I. Incidence of respiratory distress syndrome as percentages of live preterm births

	Maturity (weeks)	*Betamethasone-treated group* (Per cent)	*Control group* (Per cent)	*Difference*
Liggins and Howie (1972)	24–37	4	24	$P < 0{\cdot}002$
Block *et al.* (1977)	<37	10	27	$P < 0{\cdot}05$
Papageorgiou *et al.* (1979)	25–34	18	58	$P < 0{\cdot}005$
Tauesch *et al.* (1979)	<36	13	30	$P = 0{\cdot}085$

Table II. Perinatal mortality rates as percentages of preterm* births

	Betamethasone-treated group (Per cent)	*Control group* (Per cent)	*Difference*
Liggins and Howie (1972)	6	18	$P < 0{\cdot}02$
Block *et al.* (1977)	8	13	$P < 0{\cdot}05$
Papageorgiou *et al.* (1979)†	0	19	$P < 0{\cdot}02$

*The maturity is that cited in Table I.
†Early and late neonatal deaths.

prolonged rupture of the membranes, outweighed the risk of infection. In a controlled trial of corticosteroid therapy in patients, less than 34 weeks with prolonged rupture of the membranes, asymptomatic bacterial colonization of the infant was increased but there was no significant difference in infectious morbidity (Kappy *et al.* 1979).

CONCLUSION

Respiratory distress syndrome of the newborn is a potentially lethal disease. Antenatally administered glucocorticoids alone have been proved to reduce the incidence and severity of the disease. The recommended treatment elevates the fetal plasma corticosteroids only to the high physiological range. Adverse effects on the developing brain have been reported in animals and humans treated neonatally with pharmacological doses of corticosteroid. These doses, per kilogram, were from 5 to 300 times that which the human mother and fetus receive with antenatal betamethasone therapy (Ballard and Ballard, 1976). Follow-up of infants treated with antenatal betamethasone has failed to reveal any abnormality to date (Howie and Liggins, 1977).

A small increase in infectious morbidity has been reported (Taeusch *et al.*, 1979) in patients with prolonged rupture of the membranes. This effect may be abolished by antibiotic prophylaxis (Howie and Liggins, 1977) and does not alter the increase in survival of preterm infants following antenatal betamethasone therapy (Howie and Liggins, 1977).

The hazards of antenatal steroid therapy are mainly theoretical and are outweighed by the potential benefits for the infant delivered between 26 and 34 weeks. Finally, it is worth noting that Howie and Liggins (1977) demonstrated identical results with 12 and 24 mg dose schedules of betamethasone. As any potential adverse effects are likely to be dose-related, the lower dose is obviously preferable. The point made by Sachs (1981) that whenever possible the need for steroid therapy should be verified by determining the lecithin–sphingomyelin ratio before the drugs are given, is clearly sound.

Acknowledgement

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PROFESSOR ERICA WACHTEL

The British Society for Clinical Cytology has opened a Memorial Fund to commemorate Professor Erica Wachtel, who died in June this year. Erica Wachtel was Emeritus Professor of Gynaecological Cytology in the University of London, a post which she held at the Institute of Obstetrics and Gynaecology, Hammersmith Hospital. Professor Wachtel was one of the foremost in the development of clinical cytology in Britain and she had an international reputation for her research and teaching of the subject.

It is intended that the income from the Memorial Fund should be used either for an Erica Wachtel Lecture to be given by an invited speaker at the Annual Scientific Meeting of the British Society for Clinical Cytology or for a Travel Fellowship.

Donations to the fund are invited. They should be payable to 'The Erica Wachtel Memorial Fund' and sent to Dr K. J. Randall, Hon. Treasurer, British Society for Clinical Cytology, Pathology Department, Orpington Hospital, Orpington, Kent BR6 9JU. Covenant forms are available from the Hon. Treasurer.

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Changing medical practice: The strange case of the prenatal steroids

[summary]
Why did it take 20 years for a treatment that saved premature babies' lives to be widely adopted?

[main text]
In biomedical science, discovery is supposed [commonly believed?] to lead inexorably to application and changes in medical practice. But things are rarely this simple. The use of prenatal steroids is a case in point. It is an undeniable medical 'success story', but an examination of its history, discussed at a recent Witness Seminar'*, raises troubling questions about how research is translated into practice and benefits people.

The basics

The story begins in the late 1960s, when [the obstetrician] Graham ('Mont') Liggins returned to New Zealand from the USA, with a Wellcome Trust grant to study pregnancy and birth in sheep. Liggins had the idea that the fetus might be producing something that triggered premature labour, possibly steroid hormones. He set about testing the effects of different steroids on pregnancy.

As so often happens in science, serendipity then intervened. Liggins routinely carried out post-mortems, and he noticed a striking difference in the lungs of two fetal sheep. As Liggins's co-worker Ross Howie describes:

> "I still remember the excitement I felt [...] 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."

An infant's underdeveloped lungs left it gasping for air – respiratory distress that could be fatal or caused permanent brain damage, typically cerebral palsy. Many [necessray?] people [doctors? Medical researchers? were trying to extend pregnancy, to give the infant lungs more time to develop. But what if steroids could accelerate development of the fetal lungs? A baby born prematurely would then have a much greater chance of survival.

So chance was only part of the story. As Pasteur noted, "Fortune favours the prepared mind," and Liggins immediately realized his chance discovery had clinical potential.

While Liggins had stumbled on the effect of steroids by chance, other [s scientists] were specifically looking [for ways] to promote lung maturation. One such person was Mel Avery from the USA. She was invited to give a paper at a conference in Christchurch, [New Zealand] "the most boring paper I ever gave," she suggests disarmingly. Over coffee, Liggins told her about his sheep results. Avery was astounded. "She couldn't get back to the States fast enough," recalled Liggins.

As it happened, Christchurch was the ideal place for the research to progress. Liggins was eager to try clinical studies, and he needed to work with a clinician. [this inaccurate - suggests Liggins not a clinician – he needed to work with another specialist, such as a paediatrician] At the time, Ross Howie was the only paediatrician in the whole of New Zealand who could artificially respirate premature babies. The two set about designing a clinical trial to test the effects of a single injection of steroids in mothers undergoing premature labour – a conceptually simple randomised controlled trial, half the mothers getting steroids, half a placebo.

Within a few months (an unthinkably short time now), the trial had begun. The results were crystal clear. More babies were surviving and staying healthy in the treated group. Prenatal steroids were working [ref].

Given that the new treatment was saving babies' lives, one might have expected a rapturous reception for the results. But nothing of the sort happened. The *Lancet* rejected the paper. Ross Howie recalled the reaction of the Royal College of Obstetricians and Gynaecologists in 1972: "They didn't want to know".

Not that the work was completely ignored. Avery and others began similar studies, in experimental animals and humans. A large trial was coordinated by the US National Institutes of Health.

Dissemination

Working in Dublin at the time was a young obstetrician, Patricia Crowley. Just as the steroid work was breaking, a premature baby in her care died due to respiratory distress. She became an early convert to steroid treatment and began collecting papers published on the topic (a laborious manual process in those pre-database days). She published a review in a new publication, the *Journal of Obstetrics and Gynaecology*, a cost–benefit analysis of prenatal steroids (an approach she puts down to the fact she was dating an economist at the time) [ref].

She soon realized that this approach was too *ad hoc*, and needed to be done systematically to be of real value. At the same time, Iain Chalmers in Oxford was growing convinced of the need for systematic reviews of the literature, to inform clinical practice. He had grown increasingly alarmed at the number of medical calamities that could have been avoided had already published knowledge been applied.

Chalmers established the Cochrane Collaboration to promulgate 'evidence-based medicine', particularly evidence derived from randomised controlled trials. Moreover, the concept of 'meta-analysis' had emerged in the mid-1970s, a way of pooling data from multiple trials; by themselves, clinical trials (particularly small ones) may throw up spurious associations.

Crowley led the systematic review of prenatal steroid use, covering eight large trials. Again, the results could not have been clearer: steroids had a reproducible beneficial effect. A graphic representation of this study became the Cochrane Centre's logo.

[will probably have to cut the following two paras]
Even financial analyses backed up the use of steroids. The health economist Miranda Mugford ~~trained as an economist, turning to health economics as the field began to emerge in the late 1970s. With a placement student from York, James Piercy, she attempted to~~ quantifyied the financial costs of ~~increased~~ steroid use. ~~The figures~~ She revealed a win–win scenario: as well as clinical benefits, the treatment would save money, as there would be fewer sick babies to treat[ref].

~~Yet even T~~this study received a lukewarm reception. ~~At seminars, e~~Eminent clinicians tended to downplay the research, while health service accountants ~~simply~~ said cost savings wcould not be realized – paediatricians would ~~simply~~ spend the money in other ways.

Finally, things began to accelerate. In Birmingham in 198?, Professor Richard Lilford(?) was a convert to evidence-based medicine. He suggested to the board [is this the right word? Council? Research board?] of the Royal College of Obstetricians and Gynaecologists that it should promote good practice by producing clinical guidelines. To his surprise, they agreed. He and colleagues ~~drew together a group that spent a long day~~ trawlinged through a database on perinatal medicine established in Oxford. They ~~group~~ proposed 21 guidelines, in order of ~~clarity of~~ benefit. Number 2 in the list were prenatal steroids.

The guidelines seemed to do the trick. Published in 198?, almost overnight they led to a huge change in clinical practice. Bizarrely, though, doctors not only took up steroids but began using higher or multiple doses, without any evidence that this was effective or safe (several trials are currently assessing the effects of multiple steroid doses).

Lessons

Thise fascinating tale of ~~the~~ prenatal steroids raises ~~all kinds of~~ several questions about biomedical science and its translation into practice. It is often cited as evidence of the benefits of animal research, ~~— it originated with Liggins's observations in sheep. It~~ and is also an example of the clinical payback of 'basic' research [ref]. Yet it also raises questions about how scientific information is used.

Why did it take so long for such a valuable treatment to be accepted? A previous Witness Seminar [ref which one?] had highlighted the fact that the location of the research – New Zealand – had lessened its impact: how could key research come from such a backwater?

Perhaps Liggins and Howie could have done more to publicize their work. Howie was very cautious, arguing that decisions should never be based on one trial and that more research was needed. Pharmaceutical interests may also have been significant; companies were more interested in new drugs to prolong pregnancy, not in the use of a non-patentable therapy.

Some of ~~T~~the later research was also damaging, often being of poor quality or raising issues in animals that obscured the findings in people. (Steroid biology is complicated, and some findings in animals seem to apply to humans and some do not.) Perhaps most problematic was the US NIH study, particularly its subgroup analysis, which suggested, for example, that prenatal steroids had no benefits for Caucasians. Re-analysis of the Liggins and Howie data failed to confirm this anomaly.

Undoubtedly, clinicians' own experience had a huge impact. In the 1980s, for example, two hospitals in Cardiff had diametrically opposite approaches~~, one having seen~~ [does a hospital 'see for itself'?] ~~for itself the benefits of prenatal steroids in a series of local case studies. ,And~~ ~~A~~as mmmm described, clinicians may be strongly influenced by their experience. In his study of the use of ~~five~~ perinatal guidelines in three East London hospitals ~~in East London~~, he found markedly different take up of a difficult technique to manoeuvre babies in the womb [ref]. ~~If~~ ~~c~~Clinicians who had experienced a baby's death~~, they~~ were highly resistant to its use, whatever the published evidence ~~might~~ saidy. It is easy to see why death of a premature baby to a mother given steroids might sway a clinician's mind away from the treatment.

The turning point seems to have been the systematic reviews and the clinical guidelines. The evidence had always been in the literature but the sheer mass of papers was obscuring it. The meta-analysis and production of clinical guidelines gave doctors an authoritative source on which to base their clinical decisions.

Perhaps there are other lessons. The value of challenging orthodoxy: most people believed ~~it was~~ the mother's physiology ~~that~~ controlled the time of childbirth; Liggins insisted it was the fetus. The negative impact that poor science, no matter how well motivated, can have on important medical issues: bad science is worse than no science. The detrimental effect of scientific snobbery: how could the colonies produce anything significant? And finally, interdisciplinary turf warfare undoubtedly played a part too: obstetricians and paediatricians did not always talk to one another, and the latter saw their professional territory being invaded.

**The Witness Seminar, Prenatal corticosteroids for reducing morbidity and mortality associated with preterm birth, was held at the Wellcome Trust on 15 June 2004.*

Box: Ethical issues

One interesting feature of the steroids research is the speed at which it went from an observation in animals to a clinical trial. Medical and research ethics procedures were quite different in the 1970s. The trial protocol was approved by the hospital's medical board (essentially, its top doctors); ethics committees did not exist. One reason Liggins wanted to move so fast was because ~~he knew~~ other studies were being planned at the hospital, and he needed to get in first.

Mothers gave verbal consent to the trial. Professor Jane Harding, who works in Mont Liggins's old office and is coordinating a 30-year follow-up of the original babies, believes they all took part willingly. She has traced 75 per cent of the original group, and although some mothers cannot remember taking part in the trial (possibly because ethanol was often ~~used~~ given to delay birth ~~parturition!~~), the response has been overwhelmingly positive. Many mothers have coerced [is this appropriate word? Urged?] their offspring to get involved [not clear what their 'involvement' is], grateful that the trial may have saved their baby's life.

Box: For the record

Although carried out 30 years ago, the Liggins and Ross study stands out as one of the finest pieces of clinical research ever carried out. The randomised controlled trial was relatively new when the study began, but it was planned and carried out with meticulous care and attention. It remains the largest study ever carried out on prenatal steroids.

Interestingly, the original data sheets were also kept. Hence, whenever new findings have questioned some aspect of the treatment, Professor Harding has been able to go back to the original data and re-analyse – as with the subgroup analysis and when the use of steroids was claimed to be problematic under particular clinical circumstances [ref].

Systematic archiving of data sources remains an important issue today. A Medical Research Council working party is currently examining the issue in the UK.

Witness Seminar:

Prenatal Corticosteroids
Tuesday 15th June 2004

TRAVEL/HOTEL/SUPPER list

(main witnesses in bold)

name	travel	supper	hotel
Dr Mary Ellen Avery	**Boston**	yes	no hotel
Dr Peter Brocklehurst	**Oxford**	~~yes~~ NO	
Professor Sir Iain Chalmers	**Oxford**	yes	
Professor Patricia Crowley	**Dublin**	no	no hotel
Dr Stephen Hanney	Uxbridge	no	
Professor Jane Harding	**NZ**	yes	Ibis 14th, 15th, late dep 16th
Dr Edmund Hey	**Newastle u T**	no	
Professor Richard Lilford	**Birmingham**	yes	
Professor Miranda Mugford	**Norwich**	yes	
Dr Daphne Christie		yes	
Dr Tilli Tansey		~~yes~~ NO	
Professor Maureen Young		yes	

Simon's corrections 31/8/05.

MEETING: Prenatal Corticosteroids for Reducing Morbidity and Mortality DATE OF PUBLICATION November 2004

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Gamsu died: 31 Aug 2004.

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Dr Mary Ellen AVERY.	7/12/04	22/12/04	"	no corrections		10/8/05	emails 29+30/8/05	7/9/05	16/9/05 to			
✓ Sir Christopher Booth	7/12/04					10/8/05	31/8/05	31/8/05	no corr	no further copy		
Dr Peter Brocklehurst	7/12/04			10/3/05	25-6-05 7/6/05	10/8/05						
✓ Sir Iain Chalmers	7/12/04	20/12/04	20/12/04		1-2/6/05	10/8/05	15/8/05	15/8/05	29/9/05			
Professor Patricia Crowley	7/12/04			9/6/05 changes 19/7/05		10/8/05	neg 29/9					
✓ Professor John Gabbay	7/12/04	13/1/05	13/1/05		1/6/05	10/8/05	2/9/05	5/9/05	no corrects			
✓ Professor Harold Gamsu*	7/12/04				1/6/05	10/8/05	5/9/05	5/9/05	27/9/05			
✓ Dr Gino Giussani	7/12/04					10/8/05	9/9/05	9/9/05	21-22/9/05.			
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Professor Jane Harding	7/12/04	9/1/05	9/1/05		7-8/6/05	10/8/05	4/9/05	5/9/05	27/9/05			
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Dr Edmund Hey (Chair)	7/12/04	14/12/04	15/12/05		10/6/05		9/9/05	9/9/05	22/9/05			
Dr Ian Jones	7/12/04	3rd Reminder										6/7/05
Professor Richard Lilford	7/12/04 30/6/05	28/6/05	28/6/05	10/6/05 21/7/05	30/6/05		neg 29/9					
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Dr Sam Richmond	7/12/04	28/6/05	28/6/05	9/6/05	28/6/05							
Dr Roger Verrier Jones	7/12/04						neg 29/9					
✓ Professor Dafydd Walters	7/12/04				2/6/05		5/9/05	5/9/05	27/9/05			
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Dash, Clive (Dr) – Gamsu Repair, sent dec via Mullinger. Rec'd 21/7/05. Email 10/1/05; edited 2/6/05 / Rec'd 9/9/05; ed 21/9/05

Liggins. Slide rec'd + returned 21/6/05. edited 2/6/05; permission to reproduce, 25/8/05; ack 1/9/05.

Howie rec'd 6/1/05 edited 8/6/05.

NB. Williams' changed address 1/9/05; Hardie Δ to bag #; 4/9/05.

Crowley – no reply initial contacted / on Chalmers. 11/7/05: new email: patc@indigo.ie, no reply 26/7/05.

Rec'd Dash 1995 protocol for App 4: Tillmanky on A3 21/9/05

MEETING: Prenatal Corticosteroids for Reducing Morbidity and Mortality **DATE OF PUBLICATION** November 2005

Edited by DC and TT

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Dr. Mary Ellen Avery	7/12/04	chase 9/6/05										
Sir Christopher Booth	7/12/04	✓	✓						✓			
Dr Peter Brocklehurst	7/12/04	chased 8th+13th										
Sir Iain Chalmers	7/12/04	20.12.04	✓	~2/6/05				N	N/A			
Professor Patricia Crowley	7/12/04	chase 9/6/05										
Professor John Gabbay	7/12/04	✓	✓	asked to cancel 9/6/05					✓			
Professor Harold Gamsu*	7/12/04			D. E D					WIFE			
Dr Gino Giussani	7/12/04	✓	✓	9/6/05					✓			
Mrs Gill Gyte	7/12/04	✓	✓	10/6/05					✓			
Dr Stephen Hanney	7/12/04	✓	✓						✓			
Professor Jane Harding	7/12/04	~~chase~~ 19.1.05	✓	7/6/05					✓			
Dr John Hayward	7/12/04	✓	✓	8/6/05					✓			
Dr Edmund Hey (Chair)	7/12/04	✓	✓	9/6/05					✓			
Dr Ian Jones	7/12/04	chase 14/6/05										
Professor Richard Lilford	7/12/04	chase 14/6/05										
Prof Miranda Mugford	7/12/04	✓	✓	1/6/05					✓			
* Mrs Brenda Mullinger	7/12/04	✓	✓	1/6/05					✓			
Professor Ann Oakley	7/12/04	✓	✓	2/6/05					✓			
Dr Sam Richmond	7/12/04	chase 14/6/05										
Dr Roger Verrier Jones	7/12/04	chase 14/6/05										
Professor Dafydd Walters	7/12/04	✓	✓	2/6/05					✓			
Mr John Williams		20.12.04	✓	2/6/05				✓	✓			

Mullinger checking Gamsu's contribution.

*Died 31/8/2004 - ltr 5/1/05 → Gamsu's wife

LR: started 1/6/05 merging docs - 3:3 (2/6/05); Liggins et al 1973, Fig 9, scanned + added.

copyright checked 8/6/05

Howie, ucd 7.1.05.

Dezee. (11/1/05) - late Harold Gamsu ✓ added most notes 4/6/05

Liggins (ucd note 19.1.05 + reprint) - edited 2/6/05 ✓ Fig 1 added 2/6/05.

Mugford (qualifications?) (d.o.b.)?

email for 10/6/05:

Richmond — sam.richmond@ncl.ac.uk

Vernier Jones

Chase

Avery ✓ WT + email

" ✓

A 9/6/05 Crowley ✓

14/6/05 Ian Jones WT ✓

Lilford ✓ + pubmed

Richmond ✓

Jones ✓

✓ 14/6/05

8/6/05

Prof Dr Mark Harrison

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Hanne Jalbert

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Hilary Marland

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✓Birmingham
Bud Arnold

✓Manchester (see above)

✓Oxford (see above)

To: Tailor Ms Gita,Somji Ms Mohsina,Scovell Ms Sally,Kutner Mrs Wendy
From: Bragg Miss Sally
Cc:
Bcc:
Subject: Wellcome changes
Attachment:
Date: 03/09/98 16:30

New Wellcome Unit - officially opens 01 October:

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Ms Becky Fitt (Administrator): 01603 593878
r.fitt@uea.ac.uk
Dr Brian Dolan: 01603 592095
Dr Rhodri Hayward (from 01/04/99)

Cambridge Unit - only existing staff (closes 30/09/99) Andy Cunningham & Harmke Kamminga.

Oxford Unit until 30/09: Jane Lewis has left. From 01 October these people only:
~~Dr Maureen Malowany~~ (Montreal)
Dr Mary Dobson (~~Acting~~ Director from now) Tel - 01865 - 274602
Dept
Ms Diana Sibbick (Administrator)
Prof Nancy Leys Stepan (Sen Res Fellow)
Wellcome Unit for the Hist of Medicine
in Tropical Medicine & Infectious Diseases
address remains same otherwise

Other moves from Oxford on 01/10
Paul Weindling to Oxford Brookes(don't have address)
Maggie Pelling to Dept Modern Hist, Uni of Oxford
(don;t have address)

Mark Jackson moves from Manchester Unit on 01/10 to:
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hold
[JH attending + 3 nts accom +100]

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June
14, 15, 16 → 6pm
Flows
+ £100

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Witness Seminar: 'Origins of Neonatal Intensive Care'
27th April, 1999

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Professor Albert Aynsley-Green Institute of Child Health University of London 30 Guilford Street LONDON WC1N 1EH	**C**	Professor Aynsley-Green	Aynsley-Green	reynolds			
Dr Denis Azzopardi 21 Summerlands Avenue LONDON W3 6EW		Dr Azzopardi	Azzopardi	reynolds			
Dr Herbert Barrie 3 Burghley Avenue New Malden SURREY KT3 4SW	**B**	Dr Barrie	Barrie	reynolds	**28/1/99**	**1/2/99 yes ack 18/2 (1)**	
Professor David Baum Institute of Child Health Royal Hospital for Sick Children St Michael's Hill BRISTOL BS2 8BJ	**A**	Professor Baum	Baum	reynolds	**28/1/99**	**4/2/99 yes (1)**	with Tizard in Oxford
Professor Richard Beard Dept of Obstetrics & Gynaecology St Mary's Hospital Medical School LONDON W2 1PG	**C**	Professor Beard	Beard	reynolds			Obst. Doyenne of foetal monitoring on the London clinical scene and introduced it to Mary's in 1970/71. Made his career on it. Hard line foetal monitroing chap. very very keen on it. Became a bogey man to some of the natural childbirth movement. Linked to Philip Steer

Witness Seminar: 'Origins of Neonatal Intensive Care'
27th April, 1999

Dr Simon Bignall Consultant Neonatalogist St Mary's Hospital LONDON W2 1NY		Dr Bignall	Bignall	Rivers	**21/4**	**21/4 (e)**	
Professor Roland Blackwell Dept of Medical Physics & Bio-Engineering University College London First Floor Shropshire House 11-20 Capper Street LONDON WC1E 6JA	**B**	Professor Blackwell	Blackwell	reynolds	**28/1/99**	**16/2/99 yes ack 22/2 (1)**	Physicists
Miss Anthea Blake Chief Nurse The Obstetric Hospital University College London Hospitals Huntley Street LONDON WC1	**B**	Miss Blake	Blake	reynolds	**28/1/99**	**12/2/99 yes ack 18/2 (1)**	Senior Nurse at Neonatal Unit, UCH, Huntley St - was there when the unit started - (w) asked for more nurses' names (25/2) **a.blake@academic.uclh.nthames.nhs.uk** **(t) 0171 387 9300 x 8679** **bleep 5822**
Professor Robert Boyd FRCP Principal's Office St George's Hospital Medical School Cranmer Terrace LONDON SW17 0RE	**A**	Robert	Boyd	reynolds	**26/1/99**	**4/2/99 yes**	**suggested as Chair 3rd (& by reynolds) Old boy of UCL Paediatrics** **(t) 0181 725 5008**

Witness Seminar: 'Origins of Neonatal Intensive Care'
27th April, 1999

Dr Elizabeth Bryan The Multiple Births Foundation Queen Charlotte's & Chelsea Hospital Goldhawk Road LONDON W6 0XG		Dr Bryan	Bryan	reynolds			(pre-)
Professor Neville Butler International Centre for Child Studies 86 Cumberland Road Hotwells BRISTOL BS1 6UG		Professor Butler	Butler	reynolds			
Mr E.B. Cady Dept of Medical Physics & Bio-Engineering University College London First Floor Shropshire House 11-20 Capper Street LONDON WC1E 6JA	C	Mr Cady	Cady	reynolds			Physicist
Professor Alexander Campbell FRCP 34 Woodburn Crescent ABERDEEN AB15 8JX	C	Professor Campbell	Campbell	reynolds			
Professor Stuart Campbell 34 Corfton Road LONDON W5 2HT		Professor Campbell	Campbell	reynolds			Obst. St. George's (came to obst. ultrasound) One of the founders of obstetric ultrasound.

Witness Seminar: 'Origins of Neonatal Intensive Care'
27th April, 1999

Professor GVP Chamberlain FRCS FRCOG Sycamores Llanmadoc Gower SWANSEA SA3 1DB		Professor Chamberlain	Chamberlain	reynolds			Obst. St. George's
Professor Malcolm Chiswick FRCP St Mary's Hospital Whitworth Park MANCHESTER M13 0JH	**B**	Professor Chiswick	Chiswick	reynolds	**28/1/99 30/3**	**1/4/99 no (e)**	
Professor Forrester Cockburn CBE 53 Hamilton Drive GLASGOW G12 8DP	**A**	Professor Cockburn	Cockburn	reynolds	**25/3/99**	**31/3/99 no**	
Linda Collins			Collins	reynolds			Nurse
Professor Richard Cooke FRCP Institute of Child Health Royal Liverpool Childrens Hospital Alder Hey LIVERPOOL L12 2AP	**B**	Professor Cooke	Cooke	reynolds	**28/1/99**	**29/1/99 yes (e) ack 18/2 (3)**	

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Dr Beryl Corner FRCP Flat 4 Chartley The Avenue Sneyd Park BRISTOL BS9 1PE	**B**	Dr Corner	Corner	reynolds	**28/1/99**	**2/2/99 yes ack 18/2 (2)**	(pre-) recommended by Ghislaine Lawrence - v. helpful re Science Museum display extremely elderly (85?) Pre-intensive care useful for background Has spent her entire working life in neonatal intensive care. Set up the first unit in this country in Bristol soon after the second world war. Dealt with Good quads (born 48 and survived in her unit)
Dr Kathleen Costeloe FRCP Homerton Hospital Homerton Row LONDON E5 6SR	**C**	Dr Costeloe	Costeloe	reynolds			
E. Cowan C (PCH Bk)	**C**		Cowan	reynolds			
Dr Pamela Davies FRCP The Garden Flat 22 Warrington Crescent LONDON W9 1EL	**B**	Dr Davies	Davies	reynolds	**28/1/99**	**1/2/99 yes ack 18/2 (1)**	(follow-up)
Emeritus Professor John Davis FRCP Four Mile House 1 Cambridge Road Great Shelford CAMBRIDGE CB2 5JE	**A**	Professor Davis	Davis	reynolds w-smith	**28/1/99**	**8/2/99 yes ack 18/2 (2)**	(pre-)

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Professor David Delpy FRS Dept of Medical Physics & Bio-Engineering University College London First Floor Shropshire House 11-20 Capper Street LONDON WC1E 6JA	**A**	Professor Delpy	Delpy	reynolds	**28/1/99**	**29/1/99 yes (e) ack 18/2 (4)**	Others: Physicists: David Delpy - came to NMR meeting (infra-red imaging)
Dr Cecil Drillien FRCP 6 Abbey Mews North Berwick E. Lothian EH39 4BT	**B**		Drillien	reynolds	**28/1/99 30/3**		(? OK follow-up) **no travel ltr sent yet**
Dr Lilly Dubowitz FRCP 25 Middleton Road LONDON NW11 7NR	**B**	Dr Dubowitz	Dubowitz	reynolds	**28/1/99**	**16/2/99 yes ack 22/2 (1)**	(follow-up)
Professor Victor Dubowitz FRCP 25 Middleton Road LONDON NW11 7NR + wife Lilly ?	**B**	Dr Dubowitz	Dubowitz	reynolds	**28/1/99**	**5/3/99 yes (e) ack 10/3 (1)**	
Dr Anthony Ducker Meadowbank 265 London Road Rainham Mark Gillingham KENT ME8 6YS		Dr Ducker	Ducker	reynolds			
Professor Peter Dunn FRCP Dept of Child Health Southmead Hospital BRISTOL BS10 5NB	**A**	Professor Dunn	Dunn	reynolds w-smith	**28/1/99**	**29/1/99 ack 18/2 no 15/4**	**(1) modified**

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Dr Geoffrey Durbin FRCP 73 Cotton Lane Mosley BIRMINGHAM B13 9SE	**C**	Dr Durbin	Durbin	reynolds	**25/3/99**	**29/3 yes (leaving 5pm) (1)**	(t) 0121 627 2689 (Sec. B'ham Women's Hospital)
Sister Caroline Dux UCLH Trust Neonatal Unit Gower Street LONDON WC1		Sister Dux	Dux	christie	**29/3**	**Yes (dc) (1)**	
Professor David Edwards FRCP Dept of Paediatrics & Neonatal Medicine Royal Postgarduate Medical School Hammermsith Hospital Du Cane Road LONDON W12 0NN	**A**	Professor Edwards	Edwards	reynolds	**28/1/99**	**22/2/99 yes ack 25/2 (1)**	Ex UCL
Professor Janet Eyre FRCP 27 The Grove Gosforth NEWCASTLE UPON TYNE NE3 1NE	**C**	Professor Eyre	Eyre	reynolds			
Professor Denys Fairweather 37 Lyndhurst Avenue Mill Hill LONDON NW7 2AD	**A**	Professor Fairweather	Fairweather	reynolds	**28/1/99**	**1/2/99 yes ack 18/2 (1)**	Obst. **strongly recommended (reynolds)**
Professor Alistair Fielder Birmingham & Midland Eye Hospital Church Street BIRMINGHAM B3 2NS		Professor Felder	Felder	reynolds			(eyes)

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Dr David Field FRCP Neonatal Unit Leicester Royal Infirmary Maternity Hospital LEICESTER Leicestershire LE1 5WW		Dr Field	Field	reynolds			
Professor Peter Fleming Institute of Child Health Royal Hospital for Sick Children St Michael's Hill BRISTOL BS2 8BJ		Dr Fleming	Fleming	reynolds			in charge of unit at Bristol (see Corner) of that tradition
Professor John Forfar MC FRCP 9 Ravelston Heights Ravelston House Park EDINBURGH EH4 3LX	**C**	Professor Forfar	Forfar	reynolds			(pre-)
Professor Harold Gamsu FRCP 26 Calton Avenue Dulwich LONDON SE21 7DE	**B**	Professor Gamsu	Gamsu	reynolds	**28/1/99**	**12/2/99 yes ack 18/2 (1)**	**Phone/fax no. in South Africa: 00 272 1439 1301** (tel UK) 020 8693 9920
Dr Gillian Gandy 21 Nightingale Avenue CAMBRIDGE CB1 4SG	**B**	Dr Gandy	Gandy	reynolds	**28/1/99**		
Dr Jonathan Grant PRISM		Jonathan	Grant	tt	**2/3/99**	**2/3/99 yes (1) modified**	
Professor Anne Greenough FRCP Dept of Child Health King's College Hospital Medical School Denmark Hill LONDON SE5 9RT	**C**	Professor Greenough	Greenough	reynolds			

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Professor Henry Halliday FRCP Regional Neonatal Unit Royal Maternity Hospital Grosvenor Road BELFAST BT12 6BB	**C**	Professor Halliday	Halliday	reynolds			(N I)
Dr Patricia Hamilton FRCP Dept of Child Health St George's Hospital Lanesborough Wing Cranmer Terrace LONDON SW17 0RE	**C**	Dr Hamilton	Hamilton	reynolds	**25/3/99**	**26/3/99 yes**	
Professor Frank Harris CBE Faculty of Medicine University of Leicester PO Box 138 Maurice Shock Medical Sciences Bldg University Road LEICESTER LE1 9HN		Professor Harris	Harris	gordon			**suggested as Chairman 1st**
Professor David Harvey FRCP Queen Charlotte's & Chelsea Hospital Goldhawk Road LONDON W6 OXG	**B**	Professor Harvey	Harvey	reynolds	**28/1/99**	**15/3 yes (t) 15/3 ack (1)**	**(t) 0181 383 3270**
Dr Edmund Hey FRCP 51 Alwinton Terrace NEWCASTLE UPON TYNE NE3 1UD	**B**	Dr Hey	Hey	reynolds	**28/1/99 (3)**	**yes (undated letter) 25/3 ack 7/4 no**	

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Dr Peter L. Hope FRCP Special Care Nursery John Radcliffe Hospital Headington OXFORD OX3 9DU	**C**	Dr Hope	Hoffe	reynolds	**25/3/99**	**30/3 yes (t) (leaving 5pm)**	(t) 01865 221356
Professor Sir David Hull FRCP Oak House 3 Lanark Close Wollaton Park NOTTINGHAM NG8 1BQ	**B**	Sir David	Hull	reynolds	**28/1/99**	**1/4/99 yes (t) (3)**	**(t) 0115 978 3479 a/p message left 30/3**
Dr Antony Kaiser FRCP Dept of Neonatology St Thomas's Hospital Lambeth Palace Road LONDON SE1 7EH		Dr Kaiser	Kaiser	reynolds			
Dr Gary Katz 6 Oakhill Avenue Hampstead LONDON NW3 7RE		Dr Katz	Katz	reynolds			
Dr Anthony de Lacey Costello FRCP Centre for International Child Health Division of Public Health Institute of Child Health 30 Guilford Street LONDON WC1N 1EH	**C**	Dr de Lacey Costello	Lacey Costello	reynolds			

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Professor Malcolm Levene FRCP Dept of Paediatrics & Child Health D Floor Clarendon Wing Leeds General Infirmary Belmont Grove LEEDS LS2 9NS	**B**	Professor Levene	Levene	reynolds	**28/1/99**	**2/2/99 yes (will have to leave early to attend another mtg) ack 18/2 (1)**	
Dr Sheila Lewis FRCP Dept of Paediatrics North Middlesex Hospital Sterling Way LONDON N18 1QX	**C**	Dr Lewis	Lewis	reynolds			(husband was K. Cross)
Dr Anthony Lipscomb FRCP Paediatric Dept St John's Hospital Wood Street CHELMSFORD CM2 9BG	**B**	Dr Lipscomb	Limscomb	reynolds	**28/1/99 (1)**	**8/4/99 no (t)**	
Dr Ian Lister Cheese FRCP Dept of Health Wellington House Room 414 133-155 Waterloo Road LONDON SE1 8UG	**C**	Dr Lister Cheese	Lister Cheese	reynolds			Administrator at Dof H Civil Servant DHSS
Dr Ben Lloyd FRCP Dept of Paediatrics Royal Free Hospital Pond Street Hampstead LONDON NW3 2QG	**B**	Dr Lloyd	Lloyd	reynolds	**28/1/99**	**29/1/99 yes (e) ack 18/2 (1)**	writing history

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Professor Alan Lucas FRCP MRC Childhood Nutrition Research Centre Institute of Child Health 30 Guilford Street LONDON WC1N 1EH	**C**	Professor Lucas	Lucas	reynolds			
Dr Aidan MacFarlane FRCP Dept of Public Health & Health Policy Oxfordshire District Health Authority Richards Building Old Road Headington OXFORDSHIRE OX3 7LF		Dr MacFarlane	MacFarlane	reynolds			(edpid)
Professor Neil Marlow FRCP Dept of Child Health University Hospital Queens Medical Centre NOTTINGHAM NG7 2UH		Professor Marlow	Marlow	reynolds			
Professor Garth McClure			McClure	reynolds			(N I)
Professor Neil McIntosh FRCP Dept of Child Life and Health University of Edinburgh 20 Sylvan Place EDINBURGH Lothian EH9 1UW	**B**	Professor McIntosh	McIntosh	reynolds	**2/2/99**	**10/2/99** **yes** **ack 18/2** **(3)**	

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Professor Alexander McNeish FRCP St Bartholomew's & Royal London School of Medicine & Dentistry Turner Street LONDON E1 2AD		Professor McNeish	McNeish	gordon			**suggested as Chair 2nd**
Dr David Milligan FRCP Newcastle Neonatal Service Ward 35 Leazes Wing Royal Victoria Infirmary NEWCASTLE UPON TYNE NE1 4LP		Dr Milligan	Milligan	reynolds			
Professor Anthony Milner FRCP Academic Dept of Paediatrics Guy's, King's & St Thomas' School of Medicine 4th Floor North Wing Block St Thomas' Hospital Lambeth Palace Road LONDON SE1 7EH	**B**	Professor Milner	Milner	reynolds	**28/1/99**	**10/2/99** **yes** **ack 18/2 (1)**	
Professor Ross Mitchell FRCP Craigard Abertay Gardens Broughty Ferry DUNDEE, Tayside DD5 2RR	**B**	Professor Mitchell	Mitchell	reynolds	**28/1/99**	**29/1/99** **yes** **ack 18/2 (3)** **Ibis (no)** **supper (yes)**	(pre-) Gave a Founders Lecture to British Association of Perinatal medicine

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? Archie Norman			Norman	reynolds			
Professor Colin Normand FRCP 23 St Thomas Street WINCHESTER Hampshire SO23 9JH	**B**	Professor Normand	Normand	reynolds	**28/1/99**	**23/2/99 yes ack 25/2 (1)**	(pre-) **His wife, Dr Jean Smellie also attending**
Miss Mae Nugent UCLH Trust Neonatal Unit Gower Street LONDON WC1		Miss Nugent	Nugent	Christie		**23/4 yes**	
Dr Chris O'Callaghan Dept of Child Health University of Leicester Faculty of Medicine Robert Kilpatrick Clinical Sciences Building Leicester Royal Infirmary PO Box 65 LEICESTER LE2 7LX		Chris	O'Callaghan	tt		**25/3 yes (t) (3)**	
Professor Thomas Oppé CBE FRCP 2 Parkholme Cottages Fife Road Sheen Common LONDON SW14 7ER	**B**	Professor Oppé	Oppé	reynolds	**28/1/99**	**29/1/99 yes (t) ack 18/2 (1)**	(pre-) Great paediatrician at Mary's very well known. Active in 60s 70s 80s
Dr Richard Pearse FRCP Jessop Hospital for Women Leavygreave Road SHEFFIELD Yorkshire S3 7RE	**B**	Dr Pearse	Pearse	reynolds	**28/1/99**		

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Professor Peter O.D. Pharoah Dept of Public Health University of Liverpool Muspratt Laboratory LIVERPOOL L69 3GB		Professor Pharoah	Pharoah	reynolds			(epid) - Liverpool, invited to MRC Epidemiology meeting
Dr Melanie Pollitzer Paediatric Dept Royual Berkshire Hospital London Road READING, Berkshire RG1 5AN		Dr Pollitzer	Pollitzer	reynolds			
Professor Janet Rennie FRCP Royal Hospital for Sick Children Yorkhill GLASGOW G3 8SJ	**C**	Professor Rennie	Rennie	reynolds			Dundee ?
Professor Osmund Reynolds CBE FRS 72 Barrowgate Road Chiswick LONDON W4 4QU	**A**	Professor Osmund Reynolds	Reynolds	tt	**28/1/99**	**Yes**	Co-ordinator (t) **0181 994 3326**
Dr Rodney Rivers FRCP Dept of Paediatrics Division of Paediatrics, Obstetrics & Gynaecology Imperial College School of Medicine Norfolk Place LONDON W2 1PG	**B**	Dr Rivers	Rivers	reynolds	**28/1/99**	**4/2/99 yes (t)** **ack 18/2 (1)**	

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Dr Clifford Roberton Sea Cottage Lower Harrapool Broadford ISLE OF SKYE IV49 9AQ	**A**	Dr Roberton	Roberton		**28/1/99**	**3/2/99 no**	
Professor Roger Robinson FRCP 60 Madeley Road Ealing LNDON W5 2LU		Professor Robinson	Robinson	reynolds			
Professor Charles Rodeck Dept of Obstetrics & Gynaecology University College London Medical School 86-96 Chenies Mews LONDON WC1E 6HX		Professor Rodeck	Rodeck	reynolds			Obst. Also gave Founders Lecture in 1994 on less invasive prenatal diagnosis
Dr Simon Roth Barnet General Hospital Wellhouse Lane Barnet Hertfordshire EN5 3DJ		Dr Roth	Roth	reynolds			
Professor N. Rutter FRCP Dept of Child Health Queen's Medical Centre NOTTINGHAM Notts NG7 2UH		Professor Rutter	Rutter	reynolds			
Professor Jon Scopes FRCP 3 Chestnut Avenue Hampton Middlesex TW12 2NY	**A**	Professor Scopes	Scopes	reynolds	**28/1/99** **30/3**	**1/4/99 no** **(t)** **died**	**died**